# CONTENTS

## ORAL PRESENTATIONS

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plenary Session 1</td>
<td>Host-Pathogen Interactions</td>
<td>4</td>
</tr>
<tr>
<td>Plenary Session 2</td>
<td>Vaccine Studies from the Asia/Pacific</td>
<td>6</td>
</tr>
<tr>
<td>Plenary Session 3</td>
<td>Epidemics, Outbreaks and Emergency Settings</td>
<td>11</td>
</tr>
<tr>
<td>Plenary Session 4</td>
<td>Indigenous Populations World-Wide</td>
<td>13</td>
</tr>
<tr>
<td>Plenary Session 5</td>
<td>The Lung</td>
<td>15</td>
</tr>
<tr>
<td>Plenary Session 6</td>
<td>Pneumonia and Prevention in Adults</td>
<td>18</td>
</tr>
<tr>
<td>Plenary Session 7</td>
<td>Genomics and Transmission</td>
<td>21</td>
</tr>
<tr>
<td>Plenary Session 8</td>
<td>New Vaccines and New Trials</td>
<td>27</td>
</tr>
<tr>
<td>Parallel Session 1</td>
<td>Vaccine Impact and Serotype Replacement</td>
<td>31</td>
</tr>
<tr>
<td>Parallel Session 2</td>
<td>Diagnosis and Treatment</td>
<td>41</td>
</tr>
<tr>
<td>Parallel Session 3</td>
<td>Host and Environment</td>
<td>49</td>
</tr>
<tr>
<td>Parallel Session 4</td>
<td>Interaction with Viruses and other Bacteria</td>
<td>57</td>
</tr>
<tr>
<td>Parallel Session 5</td>
<td>Global Pneumonia Control and Vulnerable Populations</td>
<td>66</td>
</tr>
<tr>
<td>Parallel Session 6</td>
<td>Infant Disease and Protection</td>
<td>74</td>
</tr>
<tr>
<td>Parallel Session 7</td>
<td>Microbiology</td>
<td>83</td>
</tr>
<tr>
<td>Parallel Session 8</td>
<td>Immunology</td>
<td>91</td>
</tr>
<tr>
<td>Parallel Session 9</td>
<td>Epidemiology and Mathematical Modelling</td>
<td>99</td>
</tr>
</tbody>
</table>

## E-POSTER SPOTLIGHT PRESENTATIONS

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-poster Spotlight session 1</td>
<td></td>
<td>107</td>
</tr>
<tr>
<td>E-poster Spotlight session 2</td>
<td></td>
<td>117</td>
</tr>
<tr>
<td>E-poster Spotlight session 3</td>
<td></td>
<td>129</td>
</tr>
<tr>
<td>E-poster Spotlight session 4</td>
<td></td>
<td>141</td>
</tr>
<tr>
<td>E-poster Spotlight session 5</td>
<td></td>
<td>150</td>
</tr>
<tr>
<td>E-poster Spotlight session 6</td>
<td></td>
<td>164</td>
</tr>
</tbody>
</table>

## POSTERS

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis and Treatment</td>
<td>174</td>
</tr>
<tr>
<td>Epidemics, Outbreaks and Emergency Settings</td>
<td>202</td>
</tr>
<tr>
<td>Epidemiology and Mathematical Modelling</td>
<td>207</td>
</tr>
<tr>
<td>Genomics and Transmission</td>
<td>281</td>
</tr>
<tr>
<td>Global Pneumonia Control and Vulnerable Populations</td>
<td>310</td>
</tr>
<tr>
<td>Host and Environment</td>
<td>334</td>
</tr>
<tr>
<td>Host-Pathogen Interactions</td>
<td>344</td>
</tr>
<tr>
<td>Immunology</td>
<td>369</td>
</tr>
<tr>
<td>Indigenous Populations World-Wide</td>
<td>383</td>
</tr>
<tr>
<td>Infant Disease and Protection</td>
<td>394</td>
</tr>
<tr>
<td>Interaction with Viruses and other Bacteria</td>
<td>414</td>
</tr>
<tr>
<td>Microbiology</td>
<td>420</td>
</tr>
<tr>
<td>New Vaccines and New Trials</td>
<td>464</td>
</tr>
<tr>
<td>The Lung</td>
<td>491</td>
</tr>
<tr>
<td>Pneumonia and Prevention in Adults</td>
<td>493</td>
</tr>
<tr>
<td>Vaccine Impact and Serotype Replacement</td>
<td>532</td>
</tr>
<tr>
<td>Vaccine Studies from the Asia/Pacific</td>
<td>666</td>
</tr>
</tbody>
</table>
ORAL PRESENTATIONS
PLENARY 1: HOST-PATHOGEN INTERACTIONS

ISPPD-0128
A NOVEL ENDODEOXYRIBONUCLEASE ASSOCIATED WITH THE EXTRACELLULAR VESICLES FROM STREPTOCOCCUS PNEUMONIAE DEGRADES NEUTROPHIL EXTRACELLULAR TRAPS

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Background and Aims:

During pneumococcal pneumonia there is production of proinflammatory cytokines, and recruitment of innate and adaptive immune cell types. It is believed that alveolar macrophages eliminate pneumococci in the initial stages of the infection and neutrophils are recruited following increase in pneumococcal burden. Neutrophils kill the bacterial pathogen primarily by phagocytosis and restrict the spread of infection by entrapping the pathogen in neutrophil extracellular traps (NETs). NETs are a meshwork of chromatin studded with antimicrobial peptides. One of the strategies utilized by pneumococci to evade host innate immune response involves the release of nuclease(s) to degrade NETs. The aim of the study was to characterize novel nuclease(s) released by pneumococci. In-gel DNase activity assay performed using pneumococcal secretome revealed the presence of 3 bands. Mass spectrometric and bioinformatic analyses led to the identification of a potential extracellular nuclease (eDNase). Recombinant eDNase was purified to homogeneity from Escherichia coli inclusion bodies. Unlike most nucleases eDNase does not require divalent cations for its activity; the activity was however enhanced slightly in their presence. eDNase can digest DNAs with different topologies including double-stranded plasmid DNA. eDNase was found to be associated with pneumococcal extracellular vesicles (EVs). NETs released by activated human neutrophils were efficiently degraded by secretome, recombinant eDNase, and EVs from wildtype but not from eDNase deficient pneumococci. eDNase deficient pneumococci exhibited decreased bacterial burden, lung pathology and virulence in a murine sepsis model. Our data suggests a potential role for eDNase in evasion of the innate immune system.
PLENARY 1: HOST-PATHOGEN INTERACTIONS

ISPPD-0688
FURTHER UNDERSTANDING OF PATHOGENESIS AND HOST IMMUNITY IN PNEUMOCOCCAL MENINGITIS

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Background and Aims:

Streptococcus pneumoniae is documented as the major etiological agent of bacterial meningitis, in industrialised and developing settings. However the exact mechanisms underlying host immune responses and pathogenesis of pneumococcal meningitis remain to be fully elucidated. Our study aims to elucidate host immunity and host-pathogen interactions using pneumococcal disease mouse models and state-of-the-art imaging.

Methods:

Using a newly established meningitis mouse model and 2-photon intravital imaging, we explored the translocation kinetics of pneumococci from the nasopharynx to the meninges, capturing the dynamics of immune cells in pneumococci-challenged mice. Through comparative genomics, a defined set of key virulence factors was identified. Mutant pneumococci deficient for these factors were generated in different serotype backgrounds and assessed for their colonisation and invasive properties.

Results:

Our results support the exciting finding that the translocation of S. pneumoniae to the CNS occurs through hematogeneous and non-hematogeneous routes, and highlight the novel finding, that the olfactory system is not only an entry path to the CNS, but also represent a hideout for pneumococci such as serotype 1, 5 and 7F. Using a nasopharynx-to-meninges translocation mouse model, we were able to demonstrate that a transient neutrophil-dominant immune response occurs within the dural meninge as a prompt response to pneumococcal invasion. This was concomitant with the recruitment and/or activation of dendritic cells within 12 hours of infection.

Conclusion

Our study suggests that a non-hematogeneous route of infection, involving the olfactory system, should not be neglected when designing anti-pneumococcal strategies, and provides novel insight into the mechanisms of host immunity during pneumococcal meningitis.
PLENARY 2: VACCINE STUDIES FROM THE ASIA/PACIFIC

ISPPD-0141

USING NASOPHARYNGEAL CARRIAGE SURVEILLANCE IN CHILDREN HOSPITALISED WITH PNEUMONIA TO DETERMINE THE PNEUMOCOCCAL CONJUGATE VACCINE COVERAGE REQUIRED FOR INDIRECT IMMUNITY IN MONGOLIA

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Background and Aims:

Pneumococcal conjugate vaccines (PCVs) prevent disease through both direct protection of vaccinated individuals, and indirect protection of unvaccinated individuals through reduction of nasopharyngeal (NP) carriage and transmission of vaccine-type pneumococci. While the indirect effects of PCV vaccination are well described, the PCV coverage required to achieve the indirect effects is unknown. We will investigate this using hospital-based NP pneumococcal carriage surveillance established alongside a phased introduction of a 2+1 schedule and catch up to 2 years of age of PCV13 in Mongolia.

Methods:

Surveillance commenced in November 2015 and includes children aged 2-59 months admitted to participating hospitals with pneumonia. PCV13 status is obtained from written records. An NP swab is collected according to guidelines and pneumococci detected using lytA qPCR, with positives serotyped by microarray. We will compare risk of PCV13 carriage among under-vaccinated cases (indirect effects) by subdistrict level PCV13 coverage, determined using administrative data.

Results:

Prior to PCV13 introduction, monthly trends in overall and vaccine-type pneumococcal carriage among a random sample of cases remained stable, despite seasonal variation in pneumonia admissions (figure). Currently, PCV13 coverage among children 12-23 months old is 44.1%. However coverage by subdistrict ranges from 18.0%-59.6%.
Conclusion

As PCV13 coverage increases, we hypothesise that PCV13 carriage will decline in vaccinated and under-vaccinated individuals. These results will inform vaccine policy makers about the PCV coverage required to maximise the effects of PCV.
PLENARY 2: VACCINE STUDIES FROM THE ASIA/PACIFIC

ISPPD-0280
A COMPREHENSIVE PNEUMOCOCCAL VACCINE IMPACT ASSESSMENT IN NEPAL
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Background and Aims:

Pneumococcus is one of the most common organisms causing invasive bacterial disease among under-five children in Nepal. We initiated a comprehensive programme, to assess the impact of pneumococcal conjugate vaccine (PCV10), which was introduced in 2015 using a unique 2+1 schedule. This abstract presents an overview of our impact programme.

Methods:

Nasopharyngeal swabs were collected from healthy children and from hospitalized children with pneumonia. Immunogenicity of the Nepal PCV schedule (6week-10week-9month) was assessed against the WHO schedule (6week-14week-9month). Administrative data are being collected to assess changes in syndrome-specific hospitalization rates and economic impact of pneumococcal disease on families. Surveillance of childhood invasive pneumococcal disease is ongoing.

Results:

A total of 5176 healthy children (3662 from urban, 1514 from rural community) and 938 hospitalized children with pneumonia were enrolled. Prior to vaccine implementation pneumococcal carriage was observed in 65% (1247/1905) of urban children, 82% (495/600) of rural children and 34% (320/938) of hospitalized children with pneumonia. Following PCV10 introduction, vaccine-type pneumococcal carriage declined by 37%, 63% and 51% in these groups respectively.

The Nepal PCV immunisation schedule was found to be non-inferior to the standard WHO schedule after the 9-month booster dose. Health expenditures for hospitalized child with pneumonia or sepsis were found to be economically catastrophic for 43% of poorest Nepali families.

Conclusion

These data show early evidence of a substantial impact of PCV10 introduction on vaccine-type pneumococcal carriage and by inference, vaccine-type disease. The potential for the programme to relieve economic crises for families can further improve the health of Nepali children.
TEMPORAL ASSOCIATION OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE INTRODUCTION WITH ALL-CAUSE, SEVERE, HYPOXIC AND RADIOLOGICAL PNEUMONIA HOSPITALISATIONS IN CHILDREN AND ELDERLY IN FIJI: A TIME-SERIES ANALYSIS


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Background and Aims:

Fiji introduced 10-valent pneumococcal conjugate vaccine (PCV10) as 3+0 schedule with no catch up in October 2012. We evaluated impact of infant immunisation (PCV10) on hospitalisations due to all-cause, severe or very severe, hypoxic and radiological pneumonia in children <5y and adults ≥55y in Fiji.

Methods:

Data from 2007-2015 were extracted from national hospitalisations database for three main hospitals in Fiji according to ICD-10 codes J10.0-18.9, J21 and J22 for all-cause pneumonia admissions in <5 years and those ≥55 years. From one main hospital, medical records and chest radiographs were reviewed to reclassify pneumonia and bronchiolitis in children <2 years as hypoxic, severe/very severe or radiographic pneumonia as per WHO (2005) definitions. To estimate changes in admissions associated with PCV10 and adjust potential changes in hospitalisations due to other reasons, we performed time series analysis using synthetic control method. We adjusted missing data using multiple imputations.

Results:

All-cause pneumonia declined significantly among children aged 2-4y old, by 37% (95%CI: 22%, 49%). There was evidence of decline among 2-23m olds, but pneumonia epidemic during post-PCV made it difficult to assess the magnitude. No evidence of decline among adults. Very severe/severe pneumonia, hypoxic pneumonia and radiological pneumonia among children age 2-23m showed declines of 35% (95% CI: 14%, 51%), 35% (95% CI: 11%, 53%) and 28% (95% CI: 5.3%, 46%) respectively.

Conclusion

We found temporal association between PCV10 and decline in pneumonia in children <5years. First study in Asia-Pacific to estimate PCV impact and fill gaps in literature on PCV10 impact and 3+0 schedules.
PLENARY 2: VACCINE STUDIES FROM THE ASIA/PACIFIC

ISPPD-0487
IMMUNOGENICITY AND MEMORY B CELL RESPONSE POST-BOOSTER AND AT 18 MONTHS OF AGE FOLLOWING ALTERNATIVE PNEUMOCOCCAL VACCINATION STRATEGIES IN VIETNAM

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Background and Aims:

Infant vaccination against *Streptococcus pneumoniae* dramatically reduces pneumococcal disease. Two pneumococcal conjugate vaccines are licensed (PCV10 and PCV13), but as these are expensive for developing countries, evidence for alternative cost-effective schedules are needed. To address this question, we conducted a head-to-head PCV trial of 1,200 infants in Ho Chi Minh City, Vietnam.

Methods:

Infants were randomised to receive PCV10 at 2,3,4 and 9m (3+1 schedule), 2,3,4m (3+0), 2,4 and 9m (2+1) or 2 and 6m (1+1). Another group of infants received PCV13 at 2,4 and 9m. Blood samples were collected one month post-booster and at 18m, with measurement of serotype-specific IgG and memory B-cell numbers. Data is presented for 930 infants post-booster (7-10m) and 231 infants at 18m.

Results:

The 3+1 PCV10 group produced higher IgG for most serotypes compared to 3+0 and 2+1 groups. The 1+1 schedule also produced IgG responses to most serotypes although the 3+1 and 2+1 schedules were superior. PCV13 produced higher IgG to 7/10 shared serotypes compared to PCV10, while PCV10 produced higher IgG for 18C,19F. At 18m, IgG levels were lower but the trend was consistent with post-booster response; PCV13 responses were similar to PCV10 except for serotypes 6A,19A (PCV13 higher) and 14,18C (PCV10 higher). Memory B-cell numbers were similar between the 3+1 and 3+0 schedules and between PCV10 and PCV13 except serotype 1 (PCV10 higher). The B cell analysis at 18m is ongoing.

Conclusion

Analysis of final study results including OPA will be undertaken in early 2018.
PLENARY 3: EPIDEMICS, OUTBREAKS AND EMERGENCY SETTINGS

ISPPD-0233
RECURRENT OUTBREAKS OF VACCINE-TYPE PNEUMOCOCCAL MENINGITIS IN GHANA FIVE YEARS AFTER INTRODUCTION OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE
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Background and Aims:

Increases in pneumococcal meningitis were reported from the northern regions in Ghana in 2016 and 2017 despite introduction of 13-valent pneumococcal conjugate vaccine (PCV13) in 2012 using a 3-dose schedule (6, 10, and 14 weeks). We describe the epidemiology of pneumococcal meningitis across two meningitis seasons in Ghana.

Methods:

WHO standard definitions were used to identify suspected meningitis cases in the Upper West and Northern regions. Clinical and laboratory data were collected for each case. Cerebrospinal fluid (CSF) specimens underwent pneumococcal identification and serotyping using polymerase chain reaction (PCR). Confirmed pneumococcal meningitis was defined as detection of pneumococcus by PCR, culture, or latex agglutination from a CSF specimen collected from December 2015-March 2017. Annual age-specific pneumococcal meningitis incidence was calculated adjusting for suspected meningitis without confirmatory testing performed.

Results:

Among 153 pneumococcal meningitis cases, 137 (89.5%) were serotyped; 100 (73.0%) were PCV13-type and 85 (62.0%) were serotype 1. Persons aged ≥5 years accounted for 96.7% (148/153) of cases. Adjusted-annual pneumococcal meningitis incidence per 100,000 population was 1.80 in children <5 years and 10.57 and 10.45 in adults and 30-59 and ≥60 years, respectively. Comparing the 2015-2016 and 2016-2017 seasons, the proportion of PCV13-types among pneumococcal meningitis decreased from 95.5% (42/44) to 76.9% (50/65) (p=0.01), whereas the proportion of serotype 1 was stable (75.0% (33/44) vs. 69.2% (45/65); p=0.51).

Conclusion

The high incidence of pneumococcal meningitis in adults with a large proportion of serotype 1 disease raises concerns about a lack of herd protection from PCV13 infant immunization.
PLENARY 3: EPIDEMICS, OUTBREAKS AND EMERGENCY SETTINGS

ISPPD-0262
WHOLE GENOME PHYLOGENETIC ANALYSIS OF STREPTOCOCCUS PNEUMONIAE CAUSING AN OUTBREAK OF SEROTYPE 4 INVASIVE PNEUMOCOCCAL DISEASE OUTBREAK IN ALBERTA, CANADA

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Background and Aims:

Since 2014, there has been a sharp increase in serotype 4 (ST4) invasive pneumococcal disease (IPD) cases in adults in the province of Alberta, particularly in homeless persons. In the city of Calgary, ST4 has caused 14% of all IPD in adults from 2014-16.

Methods:

All ST4 IPD isolates from Calgary and Edmonton from 2010-16 were analyzed by whole genome sequencing (WGS).

Results:

Isolates from 140 cases that occurred primarily in males (76%), with a median age of 48 and, when recorded, 55% were homeless. Two major multi-locus sequence types (MLST) were found consisting of ST-205 (n = 19) and ST-244 (n = 115). WGS using core single nucleotide variant (SNV) phylogenetic cluster analysis identified the two clades (n=15) of ST-205 isolates from Calgary, which grouped distantly from clades of ST-244 isolates (n=115). The ST-244 strains clustered phylogenetically into 8 clades (n=53) with regional and temporal clustering evident. Two clades had a large proportion of isolates from homeless people and other homeless isolates were distributed among the miscellaneous isolates not grouped into clades. Temporal clustering was observed in clades C and K with strains collected from 2010–2013, whereas clades D, E, F, G, H and J were more recently collected during 2014–2016.

Conclusion

The increase of ST4 IPD isolates in Alberta can be attributed predominantly to a cluster of ST-205 isolates in Calgary and a larger increase of ST-244 isolates in Calgary and Edmonton. WGS defined sub-clades of the ST-244 isolates associated with homelessness, with temporal and regional clustering.
PLENARY 4: INDIGENOUS POPULATIONS WORLD-WIDE

ISPPD-0181
RISING DISPARITY: AN INCREASING BURDEN OF INVASIVE PNEUMOCOCCAL DISEASE IN AUSTRALIAN ABORIGINALS (2002-2014)
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Background and Aims:

Given the increased incidence of invasive pneumococcal disease (IPD) in Aboriginal Australians, an addition childhood dose of 13-valent conjugate vaccine is recommended. Routine use of 23-valent polysaccharide vaccine (23vPPV) from 50 years and for those with select medical and behavioural risk-factors is also recommended. Ongoing assessment of the relative burden of IPD over time is necessary to inform future vaccination recommendations.

Methods:

Data from National Notifiable Disease Surveillance System were used to examine IPD notification rates in Aboriginal and non-Aboriginal Australians (2002-2014).

Results:

23,238 cases of IPD were notified with 2427 (10.4%) episodes in Aboriginal Australians. Compared with non-Aboriginal Australians, higher rates of IPD were noted in all ages and time periods. In contrast to non-Aboriginal Australians, the incidence of IPD has risen in all age groups >5 years of age. The overall incidence of IPD in Aboriginal Australians (2011-2014) remains seven times greater than in non-Aboriginal Australians (IRR: 7.0 [95%CI 6.5-7.6], 2011-2014), up from 4.2 [95% CI 3.8-4.6] in 2002-2006. The rising disparity is attributable to i) greater persistence of IPD secondary to 7-valent serotypes in Aboriginal populations and ii) a more dramatic increase in IPD due to 13v-non-7v serotypes and 23v-non-13v serotypes in Aboriginal populations.

Conclusion

The use of targeted pneumococcal vaccination has had no discernible overall impact on IPD in Aboriginal populations >5 years of age. The disparity between Aboriginal and non-Aboriginal Australians continues to climb with many episodes of IPD secondary to serotypes contained within 13vPCV and 23vPPV. An urgent review of the current vaccine program is required.
Background and Aims:

American Indians living on reservations experience high rates of invasive pneumococcal disease (IPD). Introduction of 7-valent PCV in 2000 for children aged <5 years led to a dramatic reduction in vaccine-type (VT) IPD among American Indians and worldwide. In 2010, a 13-valent PCV, targeting 6 additional serotypes, replaced PCV7 in the US.

Methods:

We conducted active, laboratory-based surveillance for IPD in American Indians living on or around the Navajo Nation from 1995-2016. Pneumococcal isolates were serotyped by the Quellung reaction. Age-stratified IPD rates were calculated and compared before and after PCV13 introduction using Poisson regression.

Results:

The rate of PCV13-VT IPD decreased in children <5 years (65 vs 6/100,000; IRR 0.10 [95%CI: 0.04, 0.20), and adults ≥18 years (24 vs 12/100,000; IRR 0.48 [95%CI: 0.36, 0.60), including adults ≥65 years (57 vs 26/100,000; IRR 0.46 [95%CI: 0.30, 0.68]), comparing 2001-2009 to 2011-2016. The rate of non PCV13-VT IPD remained unchanged in children and adults. Comparing pre-PCV period (1995-1997) to 2011-2016, the rate of all serotype IPD declined 82% in children <5 years (222 vs 40/100,000; IRR 0.18 [95%CI: 0.13, 0.25]) and 22% in adults (60 vs 47/100,000; IRR 0.78 [95%CI: 0.67, 0.91]).

Conclusion

Use of PCVs has resulted in a significant and sustained reduction in the rate of IPD among American Indian children and adults. The remaining burden of IPD on the Navajo Nation is substantially higher than the general U.S. population and other strategies (e.g., broader serotype coverage vaccines, risk factor reduction) are necessary to address this persistent disparity.
CROSS-TALK OF ALVEOLAR MACROPHAGES AND T-CELLS BOOSTS THE LUNG IMMUNITY POST NASOPHARYNGEAL PNEUMOCOCCAL COLONISATION

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Background and Aims:

Whereas pneumococcal colonisation of the nasopharynx is considered a precursor for pneumonia, it is an important step in the development of pneumococcal immunity. Lung mucosal immune-responses to pneumococcus (Spn) are poorly described in humans. We previously demonstrated that experimental human pneumococcal carriage (EHPC) increases the frequency of pneumococcal-specific CD4+ Th17 cells in the lung. We now investigate the cross-talk between alveolar macrophages (AM) and components of cell-mediated adaptive immunity of lung mucosa post nasopharyngeal colonisation.

Methods:

Bronchoalveolar lavage (BAL) samples were obtained from 42 healthy volunteers following intranasal challenge with live Spn6B. AM and CD4+ T cells were isolated by FACs sorting. AM were used in opsonophagocytic killing assay in presence or absence of autologous CD4+ T cells. Moreover, BAL lymphocytes were stimulated with heat-killed SPN6B overnight, following staining for surface markers, transcription factors and cytokines production.

Results:

Uptake of Spn by AM was enhanced in carriers than non-carriers and correlated with nasal pneumococcal density (p=0.038). Co-incubation with autologous CD4+ T cells augmented Spn uptake by AM, this increase was not different between the two groups. Carriers had increased expression of pro-inflammatory cytokines, IFN-g, TNF-a and IL-17, by lymphocytes. The main contributor of IL-17 secretion was TCR-γδ T cells.

Conclusion

Micro-aspiration during colonisation can introduce Spn to the pulmonary mucosa, triggering the local immune-responses. The increased levels of IFN-g and TNF-a in the lung of carriers may lead to brisker AM-mediated responses. Our findings suggest that a mucosal delivered attenuated pneumococcal vaccination could be a good strategy to for increased protection against pneumonia.
Background and Aims:

The management of pneumonia in many low- and middle-income countries is based on World Health Organization (WHO) guidelines that classify children based on clinical signs that define thresholds of risk. We aimed to determine if some children categorized as eligible for outpatient treatment might have levels of risk warranting hospitalization.

Methods:

We undertook a retrospective cohort study of children aged 2–59 months admitted with pneumonia before the adoption of revised WHO pneumonia guidelines in Kenya. Associations with inpatient mortality were modelled using logistic regression. Absolute risks of mortality were calculated for presenting clinical features amongst children that would, according to revised WHO guidelines, be eligible for outpatient treatment (non-severe pneumonia).

Results:

We studied 16162 children admitted between March 2014 and February 2016. Overall 832/16031 (5·2%) children died. Amongst groups defined according to new WHO guidelines mortality was 321/11788 (2·7%) for non-severe and 488/3434 (14·2%) for severe pneumonia. Three characteristics were strongly associated with death of children retrospectively classified as having non-severe pneumonia; severe pallor (adjusted risk ratio (aRR) 5·9; 95% confidence interval (CI) 5·1–6·8), mild/moderate pallor (aRR 3·4; 95% CI 3·0–3·8), and weight-for-age Z (WAZ) score <-3SD (aRR 3·8; 95% CI 3·4–4·3).

Conclusion

Our findings suggest that admission should not be denied to children with non-severe pneumonia and WAZ <-3SD, or any degree of pallor. We urge clinicians to consider these risk factors in addition to WHO criteria in decision-making.
PLENARY 5: THE LUNG

ISPPD-0264
PNEUMOCOCCAL COMMUNITY-ACQUIRED PNEUMONIA DETECTED BY SEROTYPE-SPECIFIC URINARY ANTIGEN DETECTION ASSAYS

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Background and Aims:

Streptococcus pneumoniae is considered the leading bacterial cause of pneumonia in adults. Yet, it was not commonly detected by traditional culture-based and conventional urinary testing in a recent multicenter etiology study of adults hospitalized with community-acquired pneumonia (CAP). We used novel serotype-specific urinary antigen detection assays to determine whether pneumococcal cases were missed by traditional testing.

Methods:

We studied adult patients hospitalized with CAP at five hospitals in Chicago and Nashville (2010-2012), and enrolled in the Etiology of Pneumonia in the Community (EPIC) study. Traditional diagnostic testing included blood and sputum cultures and conventional urine antigen detection (i.e. BinaxNOW). We applied serotype-specific urinary antigen detection (SSUAD) assays that target serotypes included in the 13-valent pneumococcal conjugate vaccine (PCV13) to stored residual urine specimens.

Results:

Among 1736 patients with SSUAD and >1 traditional pneumococcal test performed, we identified 169 (9.7%) cases of pneumococcal CAP. Traditional tests identified 93 (5.4%) and SSUAD identified 76 (4.4%) additional cases. Among 14 PCV13-serotype cases identified by culture, SSUAD correctly identified the same serotype in all of them. Cases identified by SSUAD vs. traditional tests were similar in most demographic and clinical characteristics, although disease severity and procalcitonin concentration were highest among those with positive blood cultures. The proportion of PCV13 serotype cases identified was not significantly different between the first and second July-June study periods (6.4% vs 4.0%).

Conclusion

Although restricted to the detection of only 13 serotypes, SSUAD testing substantially increased the detection of pneumococcal pneumonia among adults hospitalized with CAP.
Background and Aims:

Seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in South Africa in 2009, using a novel schedule (2+1 infant doses at 6, 14 and 40 weeks), and in 2011 was replaced by PCV13. We assessed PCV impact on invasive pneumococcal disease (IPD) in adults.

Methods:

We conducted national, active, laboratory-based surveillance for IPD. We calculated the percentage change in rates (per 100,000 population), comparing post-vaccine (2016) and pre-vaccine years (2005-2008), among adults aged ≥25 years.

Results:

From 2005 through 2016, surveillance identified 45,853 IPD cases, 26,144/43,708 (60%) in adults aged ≥25 years. Among adults aged ≥25 years, IPD rates declined 45% (95%CI: -48%,-43%; rates: 10.8 to 5.9). PCV13-serotype IPD rates declined 74% (95%CI: -77%,-72%; rates 7.3 to 1.9) with a marked decline in serotype 1 IPD (-93%; 95%CI: -96%,-89%; rates:
Vaccine serotypes causing disease in 2016 were serotypes 3, 4, 19A and 19F: reductions were 19% (95%CI:-35%,+2%; rates: 0.4 to 0.3), 61% (95%CI:-71%,-49%; rates: 0.5 to 0.2), 55% (95%CI:-64%,-44%; rates: 0.7 to 0.3) and 61% (95%CI:-73%,-45%; rates: 0.3 to 0.1), respectively. Non-vaccine serotypes increased 15% (95%CI:+7%,+23%; rates: 3.5 to 4.0). Increases were significant for non-vaccine serotypes 8, 15A, 22F and 35B: 34% (95%CI:+9%,+63%; rates: 0.4 to 0.5), 76% (95%CI:+13%,+169%; rates: 0.07 to 0.1), 66% (95%CI:+15%,+137%; rates: 0.1 to 0.2) and 98% (95%CI:+20%,+221%; rates: 0.05 to 0.1), respectively.

**Conclusion**

Seven years after infant PCV introduction, herd effects continue to be important for IPD prevention in adults, despite some replacement disease. Benefits for serotype 3 were less notable than for other vaccine types.
Background and Aims:

We conducted a post-hoc analysis of a double blind, randomized controlled trial (RCT) of 13-valent pneumococcal conjugate vaccine (PCV13) among adults aged ≥65 years to assess public health impact.

Methods:

We included all randomized subjects, using a modified-intention-to-treat (mITT) approach to determine vaccine efficacy (VE), incidence rate reductions (IRR), and numbers needed to vaccinate (NNV) (based on five-year duration of protection).

Results:

Results are reported for, in order, clinical, adjudicated (clinical plus radiologic infiltrate determined by committee), pneumococcal, and vaccine-type pneumococcal (VT-Sp) community-acquired pneumonia; invasive pneumococcal disease (IPD) and VT-IPD. VEs (95%CI) for all hospital episodes were 8.1% (-0.6-16.1), 6.7% (-4.1-16.3), 22.2% (2.0-38.3), 37.5% (14.3-54.5), 49.3% (23.2-66.5), and 75.8% (47.6-88.8). IRRs per 100,000 person-years of observation (PYOs) were 72, 37, 25, 25, 20, and 15 with NNVs of 277, 535, 816, 798, 1016, and 1342. IRRs (95%CI) for all hospitalization days per 100,000 PYOs were 909 (-115,2013), 443 (-374,1357), 355 (42,700), 356 (134,602), 293 (61,546), and 213 (72,371) with NNVs of 22, 45, 56, 56, 68, and 94. When comparing at-risk persons (defined by self-report of diabetes, chronic lung disease, or other underlying conditions) to not at-risk persons, VEs were similar or lower, but because baseline incidences were higher the IRRs were approximately 2-10 times higher and NNVs 50-90% lower.

Conclusion

A public health analysis of pneumonia and IPD outcomes in a RCT found substantial burden reduction following adult PCV13 immunization implemented in a setting with an ongoing infant PCV7-PCV10 program. IRRs were higher among at-risk adults.
Joint Sequencing of Host and Pathogen Genomes Reveals the Genetics Underlying Susceptibility to and Severity of Pneumococcal Meningitis

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Background and Aims:

Genetic variation of both host and pathogen is known to play a role in susceptibility to pneumococcal meningitis, yet the overall importance in clinical cases of disease is unknown. To answer this question, we performed a large genome-wide association study (GWAS) on both the host and the pathogen.

Methods:

We have collected a well-characterised cohort of Dutch adults with bacterial meningitis, from which we have whole genome sequenced over 1800 pneumococci. We extensively catalogued variation in the bacteria, including specific tests of antigen alleles and R-M systems. Additionally, we have genotyped around 1200 hosts and matched controls.

Results:

Bacterial variation did not contribute to severity, but explained a large amount of invasive potential. We calculated that serotype explained half of the variation in invasiveness, and we developed new bacterial GWAS methods to identify other genes involved in meningitis: discovering competence, bacteroicins and metabolic pathways.

Host variation explained 42% of the variation in susceptibility to meningitis, and 35% of the variation in severity. To validate our hits, we collected replication cohorts from Denmark and the UK biobank. After meta-analysis, we found variants in CCDC33 to be associated with susceptibility. Finally, using 500 patients with both host and pathogen sequence we performed the first human-bacteria interaction analysis, finding associations to STK32C.

Conclusion

Using a hypothesis-free approach, we defined the overall role of genetic variation in host and pathogen in clinical cases of meningitis. We confirmed the role of known virulence genes in natural cases of infection, and discovered many new associations.
Background and Aims:

The pneumococcal capsule is considered its primary virulence factor. Invasiveness can be estimated using odds ratios (ORs) for a serotype or genetic lineage. We compared lineage ORs, controlling for serotype, in the Global Pneumococcal Sequencing (GPS) genome collection to further assess lineage contribution to invasiveness.

Methods:

As host age, temporal and geographical sampling of carriage to disease could affect ORs we limited our analysis to one country: South Africa, with temporally matched sampling (2009-2013) of carriage (n=1280; Agincourt, Soweto) and disease (n=1061; nationwide) from children <=5 years. 2,341 genomes had previously been assigned to Global Pneumococcal Sequence Clusters (GPSCs). ORs were calculated per lineage, stratified by serotype.

Results:

Twenty of the 56 serotypes in this collection were represented by >=5 isolates in more than one of the 125 GPSCs, which allowed comparisons of ORs. ORs that differed between GPSCs despite sharing a serotype were observed for three serotypes where 95% confidence intervals were not overlapping (6A,14,19F, Table 1.). For 6A lineages GPSC4 and GPSC25 the OR were both significant.
Conclusion

This analysis suggests lineage contributes to invasiveness beyond the expressed capsule. As carriage was restricted geographically and sampled intermittently, it may not represent nationwide circulation. Stratifying lineages by serotype reduces sample size and power, evident from the non-significant OR p-values. These findings need to be replicated in other large collections and confirmed with virulence assays.
Background and Aims:

*S. pneumoniae* serotype 1 continues to cause invasive disease and fatal outbreaks in the West African sub-region in spite of PCV-13 use. In The Gambia, a clonal replacement of dominant clones, i.e. ST3081 replacing ST618 was observed. This study aims to describe the genomic characteristics of the different STs of serotype 1 to aid understanding of the evolution of *S. pneumoniae* in The West African Sub-region.

Methods:

Serotype 1 isolates (n=251) collected from 1996-2016 across all age groups were randomly selected. Of these, 188 were invasive and 63 carriage isolates from Gambia, Senegal, Togo and Niger. Whole genome sequencing was performed and used for phylogenetic, recombination and pan genome analysis.

Results:

Isolates belonging to the same ST clustered into three unique clades. Clade 1 consisted mostly of ST3081 isolates (57%, 142/251), clade 2 of ST303 and ST217 isolates while clade 3 consisted mostly of ST618 isolates (26%, 64/251). Unique patterns of recombination blocks were observed in each of the four clades. Regions under recombination included genes within the capsular loci, antibiotics resistance genes and colonization genes such as neuraminidases. Pan genome analysis revealed clade specific clustering with differences occurring among virulence genes and antibiotic resistance genes. It also revealed different clusters of carriage isolates and invasive isolates, e.g. genes implicated in toxin-antitoxin systems were present in carriage isolates but absent in invasive isolates.

Conclusion

This study highlights the possible roles of recombination, antibiotic resistance, virulence and
colonization factors as possible key factors involved in the evolution of pneumococcal serotype 1 in West Africa.
PLENARY 7: GENOMICS AND TRANSMISSION

ISPPD-0700
THE IMPACT OF SEROTYPE-SPECIFIC VACCINATION ON PHYLODYNAMIC PARAMETERS OF STREPTOCOCCUS PNEUMONIAE AND THE PNEUMOCOCCAL PANGENOME
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Background and Aims:

In the United States, the introduction of the heptavalent pneumococcal conjugate vaccine (PCV) largely eliminated vaccine serotypes (VT); non-vaccine serotypes (NVT) subsequently increased in carriage and disease. Yet little is known about how vaccine disrupts the composition of the pneumococcal pangenome, which includes polymorphic non-capsular protein antigens important for virulence, transmission, and pneumococcal ecology.

Methods:

To investigate the evolutionary impact of vaccination, we assessed recombination, evolution, and pathogen demographic history of 937 pneumococci collected from 1998-2012 among Navajo and White Mountain Apache communities. We analyzed pre- to post-PCV changes in the pneumococcal pangenome, focusing on 13 polymorphic protein antigens.

Results:

We found the impact of PCV on the pneumococcal population could be observed in reduced diversity, a smaller pangenome, and changing frequencies of accessory genes. Post-PCV7, diversity rebounded through clonal expansion of NVT lineages and inferred in-migration of two previously unobserved lineages. Accessory gene frequencies trended toward pre-PCV7 values with increasing time since vaccine introduction. Additionally, frequencies of protein antigen variants prior to the introduction of PCV (1998-2000) were highly predictive of contemporary frequencies (2010-2012), suggesting balancing selection may have acted in maintaining variant frequencies in this population.

Conclusion

We present the largest genomic analysis of pneumococcal carriage in the United States to date, which includes a snapshot of a true vaccine-naïve community prior to the introduction of PCV7. These data improve our understanding of pneumococcal evolution and emphasize the need to consider pangenome composition when inferring the impact of vaccination and developing future protein-based pneumococcal vaccines.
PLENARY 8: NEW VACCINES AND NEW TRIALS

ISPPD-0139
A DOSE RANGING STUDY OF 15-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV-15) IN HEALTHY INFANTS

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Background and Aims:

A phase I/II study was conducted in adults and infants to assess optimal concentrations of pneumococcal polysaccharide (PnPs) and Merck Aluminum Phosphate Adjuvant (MAPA) in Formulation A of PCV-15 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F*, 23F, 33F*).

Methods:

Lot-1 of PCV-15 containing PnPs at 2µg/dose per serotype (except 6B at 4µg/dose) and formulated with 125µg of MAPA, Lot-2 (1x PnPs but 2x MAPA), Lot-3 (2x PnPs and 2x MAPA), Lot-4 (0.5x PnPs and 2x MAPA), and PCV-13 were compared. Adults (n=20/arm) received single dose and infants (50/arm) received 4 doses at 2, 4, 6, and 12-15 months of age. Adverse events (AEs) were collected after each dose. Serotype-specific IgG geometric mean concentrations (GMCs) and opsonophagocytic activity (OPA) subset were measured at postdose (PD) 3, pre-dose4 (ECL only), and PD4 in infants. NCT02531373

Results:

Safety profiles were comparable across vaccination groups. At PD3, serotype-specific IgG GMCs were generally lower for PCV-15 than PCV-13, except for serotype 3. PCV-15 induced higher antibodies to serotypes 22F and 33F than PCV-13. For most serotypes, higher MAPA concentration was not associated with increase in IgG levels. Except for 6A and 6B, no differences in IgG levels were observed for most serotypes between different lots of PCV-15. Overall, serotype-specific antibody levels decreased at pre-dose4 and significantly increased at PD4.

Conclusion

PCV-15 is safe and induces IgG and OPA responses to all 15 serotypes in the vaccine. No significant differences were observed with increase in PnPs and/or MAPA.

*Non-shared serotypes with PCV-13
PLENARY 8: NEW VACCINES AND NEW TRIALS

ISPPD-0153
IMMUNOGENICITY OF PCV24, A NEXT GENERATION PNEUMOCOCCAL CONJUGATE VACCINE, IN MACAQUES

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Background and Aims:

The epidemiology of pneumococcal serotypes causing disease continues to evolve based on pneumococcal vaccine use. Both the pneumococcal conjugate vaccine (PCV) and the pneumococcal polysaccharide vaccine (PPV) have been recommended for adults. Current recommendations for pneumococcal vaccination in adults ≥65 years vary between countries and range from single immunization with either PPV23 or PCV13 to a sequential administration of PCV13 followed by PPV23. Immunogenicity responses between PCV and PPV vaccinated individuals differ based on serotype, prior vaccination or exposure to S. pneumoniae.

Methods:

As life cycle management for PPV23, we have developed a 24-valent pneumococcal conjugate vaccine (PCV24) which includes polysaccharides from serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F. All polysaccharides are conjugated to CRM197 and formulated with aluminum adjuvant. Adult Rhesus macaques were intramuscularly immunized with PCV vaccines (n=5/group) and sera were collected prior to and 30 days post immunization. A multiarray electrochemiluminescence (ECL) assay measured serotype-specific IgG antibodies and opsonophagocytic killing assay (OPA) measured functional antibody responses.

Results:

Study results show that PCV24 is immunogenic and induces functional antibody. For the majority of common serotypes, there was no significant difference in IgG responses when comparing recipients of PCV24 to recipients of either PCV13 or PCV15, with the exception of serotype 23F which was more immunogenic in both PCV13 and PCV15 and serotype 7F which was more immunogenic in PCV13. OPA functional antibody responses showed no statistical differences between the three PCVs evaluated.
PLENARY 8: NEW VACCINES AND NEW TRIALS

ISPPD-0525
SAFETY AND IMMUNOGENICITY OF A 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY PCV-NAÏVE INDIAN TODDLERS – A PHASE 2 DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL
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Background and Aims:

There is an unmet need in the developing world for sustainable supply of lower cost pneumococcal conjugate vaccines (PCVs). To address this, Serum Institute of India has developed a 10-valent PCV candidate (PNEUMOSIL®) which includes serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F representing the serotypes with highest invasive pneumococcal disease (IPD) burden in India, Asia and Africa. PNEUMOSIL® safety was first established in healthy Indian adults. This phase 2 trial presents safety and immunogenicity data in PCV-naïve toddlers.

Methods:

114 healthy PCV-naïve toddlers (aged 12-15 months) were randomized in a 1:1 ratio to receive PNEUMOSIL® or Prevenar 13® (catch-up schedule of two 0.5 mL intramuscular doses given eight weeks apart). Toddlers were monitored for safety after each dose and immune responses (IgG and OPA) were assessed at screening and 28 days post final vaccination.

Results:

PNEUMOSIL® was safe and well tolerated; no safety signals were identified. PNEUMOSIL® was immunogenic for all 10 serotypes, with seroresponse (IgG ≥ 0.35 μg/mL) rates >90% for all serotypes except 9V (89.09 %). IgG GMCs were > 1 μg/mL for all 10 common serotypes in both treatment groups. Functional (OPA) responses were elicited, with seroresponse (titer ≥ BLQ) rates ≥ 92% in both groups. PNEUMOSIL® elicited comparable OPA GMTs to Prevenar 13® for all 10 common serotypes.

Conclusion

PNEUMOSIL® was shown to be safe and immunogenic in PCV-naïve toddlers for the 10 vaccine serotypes, supporting advancement into pivotal phase 3 non-inferiority trials in infants for licensure.
PLENARY 8: NEW VACCINES AND NEW TRIALS

ISPPD-0644
A LIPIDATED PROTEIN-BASED MUCOSAL PNEUMOCOCCAL VACCINE IS SELF-ADJUVANTED AND PROVIDES BROAD PROTECTION IN MICE
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Background and Aims:

Current licensed pneumococcal vaccines are effective but provide protection against restricted serotypes. The aim of this study was to develop a new pneumococcal vaccine, based on surface proteins that contribute to bacterial virulence and are common to all serotypes, to improve the vaccine coverage against emerging serotypes and reduce vaccine cost.

Methods:

Using a novel protein lipidation platform, we generated a recombinant lipidated PsaA fusion protein (referred as “rlipo-PsaA”) in E. coli using the native PsaA lipid signal peptide. Mice were immunized intranasally with the vaccine with or without mucosal adjuvant and the immunogenicity and protection efficacy against clinical isolates of different serotypes assessed.

Results:

Intranasal immunization of mice with the rlipo-PsaA vaccine induced potent antigen-specific immune responses including mucosal IgA and the production of Th1 and Th17 cytokines by the splenocytes. Moreover, the vaccine is self-adjuvanted and induced mucosal immunity against co-administered non-lipidated pneumococcal protein antigens which are otherwise non-immunogenic by themselves. More significantly, the vaccine protected mice against intranasal challenge with multiple clinical isolates including serotypes that are not covered by current vaccines in mouse models of invasive pneumococcal disease and nasopharyngeal colonization. The protection is associated with the induction of antigen specific IgG2a and mucosal IgA responses and enhanced serum opsonophagocytic function.

Conclusion

Lipidation of surface pneumococcal protein antigens is a promising approach for the development of safe and effective mucosal universal vaccine for S. pneumoniae infection.
PARALLEL 1: VACCINE IMPACT AND SEROTYPE REPLACEMENT

ISPPD-0221
CORRELATING PCV IMPACT ON CARRIAGE WITH IMPACT ON DISEASE: A SYSTEMATIC REVIEW
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Background and Aims:

We conducted a systematic review of published literature to compare the impact of pneumococcal conjugate vaccines (PCVs) on nasopharyngeal carriage (NPC) with the impact on invasive pneumococcal disease (IPD) in children to determine if these two outcomes were correlated.

Methods:

We searched PubMed as outlined in Figure 1.

Figure 1. Search strategy and outcome

Search strategy

Search conducted August 15, 2017
*Inclusion criteria:
• IPD and carriage data in the same (or similar) populations of children <5 years of age
• Data comparing pre-PCV periods to post-PCV7, PHiD-CV or PCV13 introduction
*Exclusion criteria:
• Studies confined to adults
• Studies reporting ONLY IPD or carriage reductions

Of 160 identified publications, 12 are included in the analysis. No studies evaluating PHiD-CV were found. When serotypes are grouped (e.g. vaccine type [VT], overall IPD) there appears to be a limited correlation between PCV impact on NPC and impact on IPD (Figure 2). Non-VTs also appear to be correlated, but independently of IPD or NPC. For individual
serotypes substantial variability between impacts on NPC and IPD was observed.

**Conclusion**

The conventional dogma suggests that PCV impact on IPD is likely proportional to the impact on NPC and the current analysis generally supports this conclusion for grouped VTs, although impact appears more variable for non-VTs. However, at an individual serotype level, a very poor correlation suggests that variations in carriage may not translate to equivalent variations in disease. Heterogeneity in serotype colonization dynamics, invasiveness and cross-protection afforded by PCVs may contribute to these variations.

**Funding:** GlaxoSmithKline Biologicals SA.
PARALLEL 1: VACCINE IMPACT AND SEROTYPE REPLACEMENT

ISPPD-0336
TRENDS IN INVASIVE PNEUMOCOCCAL DISEASE AMONG CHILDREN AGED LESS THAN 5 YEARS, SOUTH AFRICA, 2005-2016
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Background and Aims:
South Africa introduced seven-valent pneumococcal conjugate vaccine (PCV7) in 2009 using a novel 2+1 infant-dose schedule (6, 14 and 40 weeks) and transitioned to 13-valent PCV in 2011. We assessed PCV impact on invasive pneumococcal disease (IPD).

Methods:
We conducted national, active, laboratory-based surveillance for IPD. We calculated the percentage change in rates (per 100,000 population), comparing post-vaccine (2016) and pre-vaccine years (2005-2008), among children aged <5 years.

Results:
During 2005-2016, surveillance identified 45,853 IPD cases of which 11,119/43,708 (25%) were among children aged <5 years. Pre-vaccine IPD rates compared with 2016 declined 76% (95% CI: -79% to -73%; rates: 29.2 to 7.0); whereas PCV13-serotype IPD rates declined 94% (95%CI: -96% to -93%; rates: 24.8 to 1.4); with a marked decline in serotype 1 IPD (-98%; 95%CI: -100% to -91%; rates: 1 to 0.02). Vaccine serotypes causing disease in 2016 were
serotypes 19F, 19A and 3: reductions of 89% (95%CI:-94%,-81%; rates: 2.1 to 0.2); 86% (95%CI:-92%,-75%; rates: 1.7 to 0.2) and 54% (95%CI:-84%,+8.5%; rates: 0.2 to 0.1), respectively. Non-vaccine serotypes rate increased 29% (95%CI:+9%,+54%; rate: 4.3 to 5.6). Non-vaccine serotypes 8 and 35B were the most common causes of IPD in 2016, with increases of 98% (95%CI:+32%,+194%; rates: 0.4 to 0.7) and 348% (95%CI:+125%,+805%; rates: 0.08 to 0.4), respectively.

Conclusion

PCV-serotype disease, including serotype 1, continued to decrease in children, with smaller reductions for serotype 3 than other vaccine serotypes. Changes likely reflect vaccine effects, HIV prevention and treatment, and secular trends. Increases in non-vaccine serotypes were seen, most notably in serotypes 8 and 35B.
PARALLEL 1: VACCINE IMPACT AND SEROTYPE REPLACEMENT

ISPPD-0349
IMPACT OF HIGHER-VALENCY PNEUMOCOCCAL CONJUGATE VACCINES ON INVASIVE PNEUMOCOCCAL DISEASE IN CHILDREN UNDER 5 YEARS (2011-2016): SPIDNET – A EUROPEAN MULTICENTRE STUDY
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Background and Aims:

SpIDnet is a network aimed at enhancing surveillance of invasive pneumococcal disease (IPD) in 10 European countries. We measured the impact of higher-valency pneumococcal conjugate vaccines (PCV10/13) on IPD in children <5 years.

Methods:

We compared annual IPD incidence after PCV10/13 introduction (2011-2016) by serotype categories (all-types, PCV7, PCV10nonPCV7, PCV13nonPCV10, nonPCV13) to the average incidence of prePCV7 and PCV7 periods. We used random effects meta-analysis to compute pooled incidence rate ratios (IRR), 95% confidence intervals (CI) and heterogeneity (I² test). The impact was calculated as (1-IRR)*100.

Results:

After six years, all-type IPD incidence decreased by 61% (IRR=0.39, 95%CI: 0.31-0.49, I²=81%) versus prePCV7 and 45% (IRR=0.55, 95%CI: 0.46-0.65, I²=70%) versus PCV7 period. PCV7 serotype IPD incidence decreased by 98% (IRR=0.02, 95%CI: 0.01-0.04, I²=26%) and by 90% (IRR=0.10, 95%CI: 0.04-0.23, I²=80%) versus prePCV7 and PCV7 periods, respectively. IPD incidence caused by PCV10nonPCV7 serotypes decreased by 89% (IRR 0.11, 95%CI: 0.06-0.20, I²=0%) versus prePCV7 and 95% (IRR 0.05, 95%CI: 0.03-0.10, I²=24%), versus PCV7 period. IPD incidence caused by PCV13nonPCV10 serotypes decreased by 51% (IRR 0.49, 95%CI: 0.39-0.63, I²=0%) and 57% (IRR 0.43, 95%CI: 0.29-0.66, I²=65%) respectively. NonPCV13 IPD incidence increased 172% (IRR=2.72, 95%CI: 1.22-4.07, I²=70%) versus prePCV7 and 84% (IRR=1.84, 95%CI: 1.42-2.38, I²=62%) versus PCV7 period.

Conclusion

SpIDnet results suggest a decrease in all-type IPD incidence post-PCV10/13 introduction, higher for PCV10nonPCV7 than for PCV13nonPCV10 serotypes. NonPCV13 IPD incidence increased as compared to both reference periods. Heterogeneity may be related to different reference period and vaccination uptake by site. Continuous surveillance is crucial to monitor IPD trends.
PARALLEL 1: VACCINE IMPACT AND SEROTYPE REPLACEMENT

ISPPD-0387
IMPACT OF INTRODUCTION OF INFANT VACCINATION WITH 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV13) ON PNEUMONIA AND INVASIVE PNEUMOCOCCAL DISEASE (IPD) HOSPITALIZATIONS IN THE UNITED STATES, 2005-2014

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Background and Aims:

Pediatric 7-valent pneumococcal conjugate vaccine (PCV7) decreased U.S. pneumonia and IPD hospitalizations in vaccinated children and non-vaccinated individuals. We evaluated long-term benefits of switching from PCV7 to PCV13 in 2010 on pneumonia and IPD hospitalizations.

Methods:

We used 2005-2014 inpatient data from 23 US states to calculate monthly rates of all-cause pneumonia (ACP), lobar pneumonia without IPD (LP), and IPD hospitalizations per 100,000 population. Cases were defined using published algorithms based on discharge codes. We grouped discharge codes not included in our case definitions into clinically meaningful categories using AHRQ’s clinical classification software (CCS). We performed time-series analyses for each outcome using as a control a composite measure of CCS category hospitalization rates (“synthetic control” method). We defined pre-PCV13 as January 2005-June 2009 and post-PCV13 as July 2010-December 2014.

Results:

We included 83.4 and 78.8 million hospitalizations pre- and post-PCV13. ACP, LP, and IPD represented 3.74%, 0.11% and 0.05%, and 3.89%, 0.08%, 0.05% of all hospitalizations for pre- and post-PCV13, respectively. Declines in ACP for the entire post-PCV13 period were only observed for children aged <2 (28,453 ACP cases averted [Credible Interval (CI): 1,368–46,584]) and 2-4 (14,816 cases averted [775–65,056]) years. LP decreased in all age groups with a total of 23,674 [12,637–38,484] hospitalizations averted after PCV13 introduction. IPD hospitalizations decreased by 1,574 [907–3,907], 846 [280–3,639], and 1,251 [494–6,539] among those <18, 18-39, and 65-74 years.

Conclusion

After switching to PCV13, all-cause pneumonia hospitalizations declined among young US children. Direct and indirect PCV13 effects were observed for LP and IPD.
PARALLEL 1: VACCINE IMPACT AND SEROTYPE REPLACEMENT

ISPPD-0446
EVOLUTION OF PNEUMOCOCCI CAUSING INVASIVE DISEASE IN THE GAMBIA BEFORE AND AFTER THE INTRODUCTION OF PNEUMOCOCCAL CONJUGATE VACCINES

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Background and Aims:

Routine surveillance of invasive pneumococcal disease (IPD) has been on-going within the Basse demographic surveillance system in The Gambia since 2007. Five years after the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13), genomics offers novel insights into the evolutionary mechanisms driving IPD in rural Gambia.

Methods:

Whole genome sequencing was performed on 354 pneumococci causing IPD including pneumonia, meningitis, sepsis and other infections (n=255, 53, 37 and 8) aged 7 days to 62 years between 2008 and 2016. Phylogenetic and pan genome analyses were performed and visualised using Microreact. For major serotypes a recombination analysis was performed using Gubbins.

Results:

The predominant serotypes causing IPD were serotypes 1 (82, 23.2%), 5 (54, 15.3%) and 12F (48, 13.6%). Serotype 1 was dominant in the post-PCV13 era and the phylogeography suggests on-going transmission. Within serotype 5, the sequence type (ST) ST289, which has unique accessory genes conferring increased competitiveness, was dominant in the post-PCV13 era. The non-vaccine serotypes/sequence types, 12F, ST989 and 35B/D, ST3329, which emerged post-PCV13, have low within-clade core genome diversity suggesting ongoing clonal expansion. Serotype 12F showed a distinct clustering of accessory genes that encompassed unique variants of virulence-associated genes including fliY, pezA, wcaJ and ecsA. Within serotype 9V, there was temporal clustering by syndrome with differences in accessory genome content.

Conclusion

Persistence of vaccine serotypes and emergence of non-vaccine serotypes in the post-PCV13 era may be linked to altered accessory genome content and evolution through recombination.
PARALLEL 1: VACCINE IMPACT AND SEROTYPE REPLACEMENT

ISPPD-0539
RAPID INCREASE IN NON-VACCINE SEROTYPES CAUSING INVASIVE PNEUMOCOCCAL DISEASE IN ENGLAND AND WALES: A PROSPECTIVE NATIONAL OBSERVATIONAL COHORT STUDY, 2000-2017
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Background and Aims:
Pneumococcal conjugate vaccines (PCVs) have significantly reduced the incidence of invasive pneumococcal disease (IPD) caused by vaccine serotypes. Replacement disease with non-PCV serotypes, however, remains a concern. We describe the population impact of the 7-valent (PCV7) and 13-valent (PCV13) pneumococcal conjugate vaccines on IPD in England and Wales.

Methods:
Using national IPD surveillance data for 2016/17, we compared incidence rate ratios (IRRs) against pre-PCV13 (2008/09-2009/10) and pre-PCV7 (2000/1-2005/06) baselines. We also estimated the number of IPD cases prevented since PCV introduction.

Results:
In 2016/17, IPD incidence (9.87/100,000) was 37% (IRR, 0.63; 95%CI, 0.60-0.65) lower compared to the pre-PCV7 period (14.79/100,000) and 7% lower (IRR, 0.93; 95%CI, 0.89-0.97) than pre-PCV13 incidence (10.13/100,000). By 2016/17, PCV7-type IPD incidence had fallen by 97% (0.24/100,000; IRR, 0.03; 95%CI, 0.02-0.04) compared to the pre-PCV7 period, while additional PCV13-type IPD declined by 64% (1.66/100,000; IRR, 0.36; 95%CI, 0.32-0.40) since PCV13 introduction. IPD incidence due to non-PCV13 serotypes doubled (7.97/100,000; IRR, 1.97; 95%CI, 1.86-2.09) since PCV7 introduction, and accelerated since 2013/14, especially serotypes 8, 12F and 9N, which were responsible for >40% of IPD cases by 2016/17. IPD incidence in <5 year-olds remained stable since 2013/14, with nearly all replacement disease occurring in adults. We estimated 38,366 IPD cases have been prevented since PCV7 introduction.

Conclusion
Both PCV7 and PCV13 have had a major impact in reducing the burden of IPD in England and Wales; recent rapid increases in some non-PCV13 serotypes, however, are compromising the benefits of the programme.
PARALLEL 1: VACCINE IMPACT AND SEROTYPE REPLACEMENT

ISPPD-0643

CHANGES IN INVASIVE PNEUMOCOCCAL DISEASE (IPD) AMONG CHILDREN FOLLOWING 6 YEARS OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV13) USE IN THE UNITED STATES

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Background and Aims:

In February 2010, PCV13 was introduced for routine use among children <5 years, replacing PCV7. We evaluated the effects on invasive pneumococcal disease (IPD) in children 6 years post-PCV13 introduction.

Methods:

IPD cases (pneumococcus isolated from sterile sites) were identified among residents of Active Bacterial Core surveillance (ABCs) areas during 2007–2016. Isolates were serotyped by Quellung or sequencing and classified as PCV13 (plus 6C) and non-PCV13 serotypes. We estimated percent changes in incidence as one minus the rate ratio of pre-PCV13 (2007–2008) and post-PCV13 (2016) periods.

Results:

ABCs identified 3113 IPD cases among children <5 years. Overall IPD and PCV13-type rates declined significantly (Table), with reductions driven by serotypes 19A and 7F. In 2016, 21% of IPD was due to PCV13 serotypes. Among 51 patients in 2015-2016 with PCV13-type IPD and known vaccine history, 40 (80%) received >1 PCV13 doses (breakthrough infections), with 18 (35%) receiving 4 doses. Serotypes 19A and 3 accounted for 63% of breakthrough cases. Non-PCV13-type IPD did not increase significantly. Serotypes 15A/B/C(18%), 23B(9%), 22F(8%), 33F(8%), 19A(7%), 19F(7%), 3(6%) were the most common IPD causes in 2015–2016.
Conclusion

PCV13 use reduced IPD incidence among children, but serotypes 3 and 19A continue to circulate and caused the majority of breakthrough infections in 2015–2016.

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<tbody>
<tr>
<td>Overall</td>
<td>21.9</td>
<td>8.6</td>
<td>61 (54, 67)</td>
</tr>
<tr>
<td>PCV13-type+6C</td>
<td>14.1</td>
<td>1.9</td>
<td>87 (82, 91)</td>
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<tr>
<td>19A</td>
<td>8.9</td>
<td>0.5</td>
<td>95 (90, 97)</td>
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<tr>
<td>7F</td>
<td>3.1</td>
<td>0</td>
<td>100 (ND)</td>
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<tr>
<td>3</td>
<td>0.8</td>
<td>0.6</td>
<td>25 (73, 63)</td>
</tr>
<tr>
<td>6C</td>
<td>0.5</td>
<td>0</td>
<td>100 (ND)</td>
</tr>
<tr>
<td>Non-PCV13-type</td>
<td>7.8</td>
<td>6.7</td>
<td>14 (-7, 31)</td>
</tr>
<tr>
<td>38</td>
<td>0.6</td>
<td>0.3</td>
<td>48 (-29, 79)</td>
</tr>
<tr>
<td>15B</td>
<td>0.3</td>
<td>0.5</td>
<td>-49 (-290, 43)</td>
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PARALLEL 2: DIAGNOSIS AND TREATMENT

ISPPD-0074
DETECTION AND SEROTYPING OF PNEUMOCOCCI IN ADULT PNEUMONIA PATIENTS: COMPARISON OF HIGH-THROUGHPUT REAL-TIME PCR ASSAY USING SPUTUM SPECIMENS AND MULTIPLEX URINARY ANTIGEN DETECTION ASSAY
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Background and Aims:
A high-throughput nanofluidic real-time PCR assay using sputum specimens (Sp-PCR) and a multiplex serotype-specific urinary antigen detection assay (UAD) are used for serotyping of pneumococci in adult pneumonia studies. However, the diagnostic performance of these assays for vaccine-type pneumococcal pneumonia have not been fully demonstrated.

Methods:
Sputum and urine specimens were collected from pneumonia patients (≥ 15 years old) at a community-based hospital from 2012 to 2014. Pneumococcus were isolated by sputum culture and serotyped by the capsular quellung reaction assay (conventional assay). Sputum specimens were also tested by a PCR assay to identify lytA gene, and positive samples were examined for 50 serotypes by the Sp-PCR assay. Urine specimens were tested by the UAD assay. The performance of three assays for identifying 13 vaccine-covered serotypes were assessed by Bayesian latent class models.

Results:
A total of 244 patients were enrolled in the study. The sensitivity and specificity of Sp-PCR (the cut-off value=10^4 DNA copies/ml), UAD, and conventional assays were 90.2% (95% CI, 71.2-99.7) and 96.9% (93.4-99.7), 75.6% (55.4-92.4) and 97.9% (95.1-99.9), and 45.8% (27.5-65.8) and 95.5% (98.2-100), respectively. The performance of Sp-PCR was almost constant across the different cut-off values (10^2 to 10^7 DNA copies/ml). The pneumococcal DNA loads were higher in the UAD positive patients than in the UAD negative patients (median; 1.4 x 10^6 DNA copies/ml vs. 1.5 x 10^5 DNA copies/ml, p<0.001).

Conclusion
The Sp-PCR and UAD assays efficiently identify pneumococcal serotypes in adult pneumonia patients.
Background and Aims:

Concerns that treating acute otitis media (AOM) with antimicrobial drugs may select for resistant bacterial lineages have led to conflicting guidelines for clinical management of AOM.

Methods:

We measured effects of amoxicillin-clavulanate on carriage of penicillin-susceptible Streptococcus pneumoniae (PSSP) strains and on carriage of strains with reduced penicillin susceptibility (RSSP) at end-of-treatment and 15d, 30d, and 60d after treatment in a randomized, double-blind, placebo-controlled trial in Finland. The trial enrolled 322 children 6 to 35 months of age with stringently-defined AOM. Children who did not show clinical improvement received open-label rescue treatment with antimicrobial drugs. The intention-to-treat populations of the trial arms thus received care resembling immediate antimicrobial therapy and watchful waiting.

Results:

We analyzed data from 1358 nasopharyngeal specimens. Immediate amoxicillin-clavulanate reduced PSSP carriage prevalence by 88% (95%CI: 76-96%) at end-of-treatment and by 27%(-4-49%) after 60d, but did not measurably impact RSSP carriage prevalence. By end-of-treatment, 7% of children who carried PSSP at enrollment remained colonized in the amoxicillin-clavulanate arm, compared to 61% of PSSP carriers who received placebo; efficacy persisted 60d after treatment among children who carried PSSP at enrollment. In contrast, no treatment effect was detected among children who carried RSSP at enrollment. At follow-up visits up to 60d after treatment, the proportion of carried pneumococcal strains with reduced sensitivity to penicillin was higher among children assigned amoxicillin-clavulanate than among children assigned placebo.
Conclusion

In Finland, amoxicillin-clavulanate therapy for AOM exerted selective pressure on colonizing *S. pneumoniae* but did not increase children’s absolute risk of carrying RSSP.
PARALLEL 2: DIAGNOSIS AND TREATMENT

ISPPD-0303
EFFICACY OF TRANSTYMPCAN GEMIFLOXACIN AND CIPROFLOXACIN GEL FORMULATION AGAINST EXPERIMENTAL OTITIS MEDIA IN A CHINCHILLA MODEL DUE TO STREPTOCOCCUS PNEUMONIAE
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Background and Aims:

BACKGROUND: Prolonged and subsequent systemic exposure to antibiotics as treatment of acute otitis media (OM) is partially responsible for emergence of drug-resistant strains of pathogenic bacteria. Transtympanic drug delivery of antibiotics directly to the middle ear (ME) has the potential to provide local bioavailability sufficient to achieve sterilization while minimizing systemic exposure.

AIMS: To evaluate pharmacokinetics (PK), middle ear fluid (MEF)/ nasopharyngeal (NP) concentrations, and efficacy of ciprofloxacin and gemifloxacin transtympanic gel formulation against S.pn in chinchilla model of experimental otitis media (EOM).

Methods:

S.pn with selected antimicrobial susceptibility pattern, was inoculated initially into the NP and 3 days later into the chinchilla ME. Plasma, NP and MEF were collected for transtympanic gemifloxacin/ ciprofloxacin PK studies, NP and MEF cultures were performed subsequently to determine efficacy.

Results:

In chinchilla model of EOM, one application of gemifloxacin-containing gel (1mg/ml) abutting intact tympanic membrane sterilized MEF in >92% (n=13/14) of animals challenged with S.pn with MIC ≤ 0.02µg/ml compared to untreated ears in which only 25%(n=1/5) cleared infection (p-value < .005). There was no evidence of systemic absorption of either gemifloxacin or ciprofloxacin in the chinchilla plasma at 24 hours after application. There was no effect on NP colonization, no damage to inner hair cells based upon the preliminary results compared to control animals not treated.

Conclusion

Transtympanic drug delivery is highly promising alternative to oral antibiotics for treatment of OM. Localized antibiotic delivery directly to ME enhances local bioavailability while minimizing systemic antibiotic exposure thus potentially reducing the selective pressures for antibiotic resistance.
PARALLEL 2: DIAGNOSIS AND TREATMENT

ISPPD-0322
COMPARISON OF WHO PNEUMONIA CASE DEFINITION AND RADIOLOGY FOR THE DIAGNOSIS OF PNEUMONIA IN CHILDREN AT PATAN HOSPITAL, NEPAL

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Background and Aims:

The diagnosis of pneumonia in children in developing countries is challenging. There is no gold standard that is easily applied in clinical settings. We compared WHO pneumonia case definition (i.e., cough or difficulty breathing with tachypnea) and WHO radiographic research criteria in the context of a broader pneumococcal disease surveillance program.

Methods:

Children 2-59 months admitted to Patan Hospital in Kathmandu, Nepal from March 2014 to December 2016 with pneumonia diagnosed/suspected by a clinician were enrolled. Chest radiographs (CXR) were reviewed using standard WHO methodology. The relationship between the WHO pneumonia case definition and WHO radiographic criteria was retrospectively examined.

Results:

Of fully interpretable chest radiographs, 370/806 (46%) were abnormal: 254/806 (32%) showed endpoint consolidation (EPC) and 116/806 (14%) showed other infiltrates (OI) only. Of children with an abnormal CXR, 99/370 (27%) did not meet the WHO pneumonia case definition. The WHO pneumonia case definition was fulfilled by 543/806 (67%) children, of whom 272/543 (50%) had a normal CXR. The difference between children who were identified as pneumonia by the WHO case definition and those with an abnormal CXR was 21% (p<0.001). Of children with EPC, 76/254 (30%) did not meet the WHO pneumonia case definition largely due to lack of tachypnea on admission.

Conclusion

Using WHO radiographic findings as the comparator, a substantial proportion of children 2-59 months with radiographic EPC would have been missed by the WHO pneumonia case definition alone. Chest radiography is helpful to guide treatment protocols and in epidemiological studies.
PARALLEL 2: DIAGNOSIS AND TREATMENT

ISPPD-0452
MICROARRAY DETECTION OF PNEUMOCOCCAL SEROTYPES IN MIDDLE EAR FLUID IN CHILDREN WITH ESTABLISHED EAR DISEASE

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2Starship Children’s Health, Department of Paediatric Infectious Diseases, Auckland, New Zealand
3Starship Children’s Health, Department of Otorhinolaryngology- Head and Neck Surgery, Auckland, New Zealand
4University of London, Institute for Infection and Immunity- St George’s, London, United Kingdom
5London Bioscience Innovation Centre, BUGS Bioscience, London, United Kingdom
6Canterbury District Health Board, Canterbury Health Laboratories, Christchurch, New Zealand
7The University of Otago- Christchurch, Dean-University of Otago- Christchurch, Christchurch, New Zealand
8The University of Otago- Christchurch, Department of Paediatrics, Christchurch, New Zealand
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Background and Aims:

Molecular techniques such as microarray are better able to detect multiple pneumococcal serotypes when compared to conventional techniques. We investigated presence of multiple serotypes in middle ear fluid (MEF) from children with established ear disease.

Methods:

Samples were obtained from PCV7 vaccinated children aged <3 years having ventilation tubes. Paired MEF and nasopharyngeal (NP) samples, culture or lytA PCR positive for S.pneumoniae were tested using microarray-based detection of serotypes.

Results:

Thirty six of 76 children had no detectable S.pneumoniae in 105 MEF by microarray. A single pneumococcal serotype was identified in all but one MEF. This child had 2 distinct serotypes simultaneously in MEF with serotypes 15B and 35F detected at relative abundances of 56% and 44% respectively. The matched NP for this child had only serotype 35F detected by microarray. No non-typeable (NT) pneumococci or non-pneumococcal Streptococcal species were detected in MEF.

Of 76 NP samples, 69 had pneumococcus detected with 39 having a single serotype only detected (56%) and a further 3 having a single NT pneumococci detected. The remaining 27 NP samples (40%) had a combination of 2-4 serotyped, NT and non-pneumococcal species detected. In contrast to MEF samples, 20% contained NT pneumococci and 16% contained related Streptococcal species.

Conclusion

Microarray detected a wider range of serotypes in MEF than conventional culture and Quelling. Multiple serotype carriage, non-typeable and related Streptococcal species were
shown in NP samples. Detection of multiple serotypes in MEF was very uncommon and only encapsulated pneumococci were present in MEF despite frequent detection of NT in nasopharynx.
PARALLEL 2: DIAGNOSIS AND TREATMENT

ISPPD-0581
Computer Aided Diagnosis for WHO Standardized Chest X-Ray Interpretation in Children, Phase 2

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Background and Aims:

Pneumonia is the leading infectious cause of morbidity in children under 5 years globally, and the chest X-ray (CXR) remains important. Standardization of CXR interpretation in children has been proposed by the WHO as measure of pneumococcal conjugate vaccine (PCV) efficacy. To determine the sensitivity and specificity of Computer Aided Diagnosis (CAD) for WHO-defined chest X-ray primary end-point pneumonia (CXR-PEP) vs non CXR-PEP in a multi-centre study, compared to a consensus human interpretation used as the reference standard.

Methods:

This study was nested within hospitalized South African children with pneumonia in the PERCH study and the PCV-13 study. The PERCH South African database with a total of 858 CXRS, 333 with CXR-PEP was used as the training set and the test set was the PCV-13 CXRS from Redcross and Ngwelezane hospitals. The areas of CXR-PEP were manually drawn to train CAD using deep learning based texture analysis; pixels in outlined regions were used as positive examples.

Results:

From 1286 interpretable test set CXRs, 414 with CXR-PEP and 872 with no CXR-PEP, CAD had a sensitivity of 70%, specificity of 72% and area under the ROC curve of 0.732 (95% CI 0.700-0.762) for CXR-PEP. This is lower compared to the results of CAD phase 1, where the PERCH South African database of 858 CXRS was used for training and testing, using a 10-fold cross-validation, the sensitivity was 80%, specificity 78% with an area under the ROC curve 0.850 (95% CI 0.823-0.876).

Conclusion

The results of CAD phase 2 in a multicentre study are promising.
Background and Aims:

Indigenous Fijians (iTaukei) have greater pneumococcal nasopharyngeal (NP) carriage and density burdens than Fijians of Indian Descent (FID). We report the association between ethnicity, social contact and vaccine-type / non-vaccine-type (VT / NVT) pneumococcal carriage and density post 10-valent pneumococcal conjugate vaccine (PCV10) introduction.

Methods:

Infants (5–8 weeks), toddlers (12–23 months), children (2–6 years) and caregivers participated in a cross-sectional NP pneumococcal carriage survey (n=2,020). Risk factors and contacts were recorded by questionnaire. NP swabs were collected. Carriage was determined by lytA qPCR, with molecular serotyping by microarray. Factors associated with carriage and density were examined using generalised estimating equations.

Results:

Carriage prevalence, contacts, and household size were greater in iTaukei vs. FID. iTaukei ethnicity (aOR 1.69, 95%CI 1.04–2.73; p = 0.033), physical contact with 7-14 year olds (aOR/additional contact 1.26, 95%CI 1.07-1.48; p = 0.005), and coryza (aOR 1.51, 95%CI 1.00–2.28; p=0.052) were associated with VT carriage. Increased odds of NVT carriage were associated with iTaukei ethnicity (aOR5.96, 95%CI 4.47–7.94; p <0.001), coryza (aOR1.86 95%CI 1.46–2.37; p<0.001) and physical contact with toddlers (aOR/additional contact 1.26, 95%CI 1.03–1.54; p = 0.026). Increases in density (log10GE/ml) of 0.85 (95%CI 0.62-1.08; p<0.001), 0.64 (95%CI 0.26-1.02; p = 0.001), and 0.32 (95%CI 0.15-0.49; p <0.001), were associated with being caregivers, aged 2-6 years, and coryza, respectively.

Conclusion

Post-PCV10, ethnicity remains associated with pneumococcal carriage, but not density. Physical contact with toddlers increases NVT carriage odds. Odds of VT carriage is increased by physical contact with older children, who may be a VT reservoir post-PCV10 introduction.
PARALLEL 3: HOST AND ENVIRONMENT

ISPPD-0288

COMPARISON OF NASOPHARYNGEAL CARRIAGE PREVALENCE OF STREPTOCOCCUS PNEUMONIAE IN UNDERNOURISHED CHILDREN HOSPITALIZED WITH SUSPECTED PNEUMONIA

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Background and Aims:

Malnutrition is a contributing factor in many infectious diseases. We evaluated whether nutrition status impacted the carriage prevalence of Streptococcus pneumoniae (pneumococcus) among children hospitalized with pneumonia at Patan Hospital in Kathmandu, Nepal.

Methods:

From 2014-2016, all children aged 2 to <60 months admitted with a clinical diagnosis or suspicion of pneumonia whose parents consented for a nasopharyngeal (NP) swab were enrolled. Antibiotic use prior to NP swabbing was recorded. Z-scores were determined for weight/age (W/A) and height/age (H/A). Those with < -2 standard deviations were considered undernourished (low W/A or low H/A). NP swabs were transported in STGG for culture and serotyping.

Results:

Of 829 children enrolled, pneumococcal carriage in those with low W/A was 34% (46/134) and with normal W/A was 32% (220/695) (p=0.650). Carriage prevalence in those with low H/A (40/129) and normal H/A (218/700) were both 31% (p=0.976). In the 188 children with no antibiotics prior to NP swab collection, the low W/A carriage rate was 83% (25/30) compared with the normal W/A which was 67% (106/158) (p=0.081). Similarly, low H/A children with no antibiotics had a carriage prevalence of 76% (29/38) compared to normal H/A children’s rate of 68% (103/150) (p=0.338).

Conclusion

Pneumococcal carriage prevalence in children with pneumonia in those who are undernourished (low W/A and low H/A) compared with well-nourished children was not statistically different.
Background and Aims:

Nasopharyngeal (NP) pneumococcal carriage is a prerequisite for pneumococcal disease. However, the association between pneumococcal carriage and pneumonia is unclear. This study in Lao People’s Democratic Republic describes risk factors for pneumococcal carriage in hospitalised children with acute respiratory infections (ARIs), and investigates whether pneumococcal detection and density are associated with severe pneumonia.

Methods:

A prospective observational study was conducted in children less than five years old admitted with ARI at Mahosot Hospital. Demographic, socioeconomic and clinical data were recorded. Collected NP swab samples were analysed using quantitative PCR to detect pneumococci and molecular serotyping conducted by microarray. Associations between pneumococcal detection and density with various \textit{a priori} exposure factors were analysed using multivariate linear and logistic regression, respectively.

Results:

There were 924 participants from 2014 to 2016. Cooking with wood \([\text{aOR}=0.69(0.49-0.96), p=0.028]\) and antibiotic use \([\text{aOR}=0.71(0.52-0.96), p=0.027]\) were moderately protective against any pneumococcal detection compared to other fuels and non-antibiotic use respectively. PCV13 was a strong protective factor for vaccine-type carriage, especially in children 12-23 months old \([\text{aOR}=0.32(0.16-0.64), p=0.001]\). For non-vaccine type carriage, antibiotic use \([\text{aOR}=0.52(0.36-0.76), p=0.001]\) and kindergarten/day-care attendance \([\text{aOR}=1.75(1.16-2.66), p=0.008]\) were strongly protective and moderate risk factors, respectively. No exposures were associated with pneumococcal density. Pneumococcal detection carriage or density was not a risk factor for severe pneumonia.
Conclusion

In this study, pneumococcal detection or density was not associated with pneumonia severity in <5 years old children hospitalised with ARI. Other unmeasured factors such as viruses may be associated with pneumococcal density.
Background and Aims:

In England and Wales, replacement of the childhood 7-valent pneumococcal conjugate vaccine (PCV7) with a 13-valent vaccine (PCV13) in 2010 was associated with a significant reduction in PCV13-serotype invasive pneumococcal disease (IPD), with a small increase in IPD due to non-vaccine serotypes. Here, we describe the clinical presentation, comorbidity prevalence, serotype distribution and outcomes of childhood IPD during the first six years after PCV13 introduction.

Methods:

Public Health England conducts enhanced IPD surveillance in England and Wales, with detailed information requested from general practitioners for all cases in children aged <5 years. Invasive isolates are routinely serotyped at the PHE reference laboratory.

Results:

From April 2010 to March 2016, 1,282 IPD episodes were confirmed in 1,255 children aged 3-59 months; 84.3% (1059/1255) isolates were serotyped. Clinical presentation with meningitis was most prevalent in 3-11-month-olds (45.8%, 209/456) and LRTI in 24-59-month-olds (46.7%, 133/285). Overall, 20.6% (259/1255) of children had 292 comorbidities, particularly immunosuppression (31.6%, 92.292). Twenty-one children (1.8%) had recurrent IPD. The case fatality rate was 5.1% (64/1,255; 95%CI 3.9-6.5%) and independently associated with meningitis (aOR 3.53; 95%CI 1.62-7.70) and comorbidity (aOR, 2.41; 95%CI 1.25-4.64). In 2015/16, PCV13 serotypes were responsible for 10.8% (25/232) of serotyped cases; the most prevalent non-PCV13 serotypes were 12F (18%), 10A (12%), 23B (10%), 33F (10%), 15B/C (10%) and 8 (8%).

Conclusion

Most childhood IPD cases are now due to non-PCV13 serotypes. A higher proportion of children with IPD have underlying comorbidity but, reassuringly, the risk of recurrent IPD or death remains low.
PARALLEL 3: HOST AND ENVIRONMENT

ISPPD-0585
PREVALENCE OF ACUTE RESPIRATORY INFECTIONS AND ITS RISK FACTORS IN AFGHANISTAN: A MULTILEVEL ANALYSIS
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Background and Aims:

According to the WHO, in Afghanistan, about 25% of all under-five years child deaths in 2010 were due to pneumonia. This study aims to examine the risk factors associated with acute respiratory infections (ARI) among Afghan children aged under-five years for making some recommendations to evolve the health system.

Methods:

Data has been drawn from the first Afghanistan Demographic and Health Survey (AfDHS) 2015. A sum of 30,304 surviving children aged under-five years living in 955 communities has been analysed. Two-level multilevel logistic regressions have been employed to model the relationship between water and sanitation, demographic, and socioeconomic factors and ARI.

Results:

About 13% children aged under-five years suffer from ARI illness. The multilevel logistic regressions revealed that the odds of having ARI have decreased and increased with the increase in child age and birth order, respectively. Odds of having ARI sharply reduced with the increase in mother’s education level. Further, polluting cooking fuel (OR=1.21;p<0.001) and unimproved toilet (OR=1.16;p<0.010) has higher odds of having ARI than clean fuel and improved toilet, respectively. Odds of having ARI is highest for manual women worker (OR=1.81; p<0.001) than not working women and western region (OR=2.39;p<0.001) than other regions. Besides, wealth status, ethnicity is also significant risk factor for ARI. The between-community variance in the log-odds of having ARI is estimated as 1.19 (SE 0.043).

Conclusion

Program-oriented strategies that are designed at reducing ARI illness should accept policies that cover available basic housing standards, providing non-polluting cooking fuel, increasing awareness and enhancing healthy behaviours.
Background and Aims:

Iron, a cofactor for many enzymes, regulates gene expression in many pathogens including *Streptococcus pneumoniae*. *S. pneumoniae*, a gram-positive bacteria normally found in the upper respiratory tract can invade the blood. Here, we studied the effect of iron status on pneumococcal carriage population and Pneumococcal serotype distribution in five year olds in the Gambia.

Methods:

Nasopharyngeal swabs (NPS) and blood samples were collected at four and one sampling points respectively, from 78 subjects aged 5-6 years within the Kombo North district in The Gambia. Identification of *S. pneumoniae* was done by both optochin susceptibility test and Quantitative Polymerase Chain Reaction (qPCR). *Staphylococcus aureus* was detected by coagulase test and qPCR targeting *nuc*, *meca* and *mecC* genes. Hepcidin and iron markers were measured using the Hepcidin-25 (human) EIA Kit (Bachem) and Cobas Integra 400 plus respectively. Inflammation was measured using C-reactive protein (CRP) and Alpha1-acid Glycoprotein (AGP).

Results:

Carriage of *S. pneumoniae* among children who were iron deficient and non-iron deficient were 57.1% (4/7) and 57.7% (41/71) respectively using ferritin cut-off. Prevalence of *S. pneumoniae* was more in inflamed children compared to the non-inflamed, 77.8% (7/9) and 55.1% (38/69) respectively. Pneumococcal carriage was more than *S. aureus* carriage in both high and low iron markers. Inflammation rate was higher using AGP compared to CRP, 83.3% (65/78) and 11.5% (9/78) respectively. The most prevalent Pneumococcal serotypes were 19A, 13 and 23.

Conclusion

Non-iron deficient and inflamed children are more susceptible to *S. pneumoniae* and *S. aureus* carriage compared to the iron deficient and the non-inflamed.
PARALLEL 3: HOST AND ENVIRONMENT

ISPPD-0649

PERIOD PREVALENCE AND RISK FACTORS OF CHILDHOOD PNEUMONIA IN TWO DISTRICTS OF MAHARASHTRA, INDIA: A COMMUNITY BASED CROSS SECTIONAL STUDY

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Background and Aims:

Childhood Pneumonia is a public health problem in India, although robust epidemiological data is not available on its incidence. Identifying the children at greater risk and targeting them with interventions of proven efficacy may reduce the burden of the pneumonia. The aim of the study was to measure the burden of pneumonia among under five children, to determine the risk factors of pneumonia by assessing the indoor housing environment and by determining the nutritional and immunization status of children and to assess the knowledge and practices of mother related to pneumonia.

Methods:

Descriptive cross sectional study done on 16 randomly selected clusters i.e urban slums and villages in Pune and Sangli district of Maharashtra state, India. A validated pre structured questionnaire was used to assess information from mother of under five children.

Results:

The average family size of household was 4.48 (SD=1.9). Unclean fuel is used by 15.1% of households. Majority of households i.e.43% were inadequately ventilated and overcrowded. The mean birth weight of children was 2.6 kg(SD=0.61).The percentage of fully immunized children was found to be 95%. Seventeen percent children were severely malnourished. Only 2% of mothers could correctly tell the symptoms of pneumonia. The practice of exclusive breast feeding till 6 months was found to be poor. Majority of women do not practice hand wash after specific occasions.

Conclusion

Among the risk factors studied, immunization status of children and mother’s awareness was found to be associated with Pneumonia.
Background and Aims:

Pneumococcus colonizes the nasopharynx alongside other bacteria species. We predict that AmiA, AliA and AliB, substrate-binding proteins of a pneumococcal ABC transporter, play a role in interspecies communication. We have previously shown that peptides matching other bacterial species are recognized by homologues of AliB (AliB-like ORF1 and ORF2) in nonencapsulated S. pneumoniae. AmiA, AliA and AliB, unlike AliB-like ORFs, are universally present in virulent, encapsulated pneumococci. Here we aimed to determine: (i) whether AmiA, AliA and AliB also bind foreign peptides of other bacterial species and (ii) the effect of binding on pneumococcal phenotype.

Methods:

We expressed recombinant AmiA, AliA and AliB proteins and incubated them with human nasopharyngeal swabs to capture specifically bound ligands. Manual de novo peptide sequencing was performed to confirm the sequences of the peptides from their MS/MS spectra. Tryptophan fluorescence binding assay confirmed binding of the proteins to their ligands. Growth assays were performed in defined peptide-free medium (CDM).

Results:

We found a total of 11 possible ligands. Among these, we confirmed binding for one peptide for each protein: AmiA, AliA and AliB bind three different peptides matching ribosomal proteins of Gammaproteobacteria, including common colonizers of the nostrils and nasopharynx. Phenotypic assays showed binding of the peptides results in altered pneumococcal growth.

Conclusion

We propose a novel route of interspecies bacterial communication in the nasopharyngeal microbiota via ribosomal protein-derived peptides which bind AmiA, AliA and AliB proteins, resulting in changes to pneumococcal phenotype. Such interspecies communication is a potential target for intervention.
Background and Aims:

Mixed-species otitis media caused by *Streptococcus pneumoniae* (Spn) and nontypeable *Haemophilus influenzae* (NTHi) is associated with complex manifestations that are less common in pneumococcal infections without NTHi. We analyzed the microbiological composition of middle ear fluid (MEF) cultures and nasopharyngeal samples obtained before PCV7/13 rollout to better understand bacterial factors influencing disease progression in single-species and mixed-species infections.

Methods:

Data included OM episodes submitted for MEF cultures during a 10-year prospective study in southern Israel prior to PCV7 introduction and nasopharyngeal samples from unvaccinated, asymptomatic children. We compared pneumococcal serotype diversity across carriage and disease isolates with and without NTHi co-isolation, and measured the similarity of serotype distributions via Kullback-Leibler divergence. We also measured associations between pneumococcal phenotype and rate of progression from colonization to OM in the presence and absence of NTHi.

Results:

Whereas pneumococcal serotype diversity in single-species OM is lower than in single-species colonization, serotype diversity does not differ significantly between colonization and OM in mixed-species episodes. Moreover, the pneumococcal serotype distribution of mixed-species OM corresponds more closely to that of mixed-species carriage than to the distribution of pneumococcal serotypes colonizing without NTHi. Pneumococcal phenotypes predicting prolonged carriage duration—such as efficient metabolic properties and strong negative surface charge—are associated with higher rate of progression to single-species OM. These factors are weaker predictors of the progression of mixed-species episodes.
Conclusion

Immune-evasive pneumococcal serotypes able to persist in the nasopharynx have elevated rates of progression to OM. However, these serotype differences in progression rate are attenuated in the presence of NTHi.
Background and Aims:

Streptococcus pneumoniae (SP) and Respiratory syncytial virus (RSV) are major respiratory pathogens. There is increasing evidence that SP and RSV interact and increase respiratory disease severity but the interaction in tropical countries remains unclear. We characterized SP positive hospitalized children and determined the interaction between SP and RSV in Vietnam.

Methods:

Clinical information and nasopharyngeal swab samples were collected from children <15 years old at their acute respiratory illness (ARI) hospitalization in Nha Trang, Vietnam, from 2012 to 2016. SP and 13 respiratory viruses were detected using culture and multiplex PCRs, respectively. Demographic and clinical characteristics and co-detection with the viruses were compared between children with and without SP≥1x10^5/ml. Among children with SP, clinical severity and bacterial load were compared between those with RSV and without any of the viruses.

Results:

5,365 were enrolled and the median age was 16.7 months (interquartile, 19.8). SP was detected in 1,674 (31.2%). Children with no clinical pneumonia (p=0.006), going to nursery (p<0.001), and co-detection with any viruses (p<0.001), RSV (p=0.011), human-metapneumovirus (p=0.038), rhinovirus (p<0.001), and adenovirus (p=0.015) were more likely to have SP. Among children with SP, those with RSV (n=351, 43.4%) had more clinical pneumonia (27.1% VS 16.8%, p<0.001), longer duration of hospitalization (mean, 5.1 VS 4.5 days, p=0.001), and more SP bacterial load (10^7.53 VS 10^7.14/ml, p<0.001) compared with those without the 13 viruses (n=458).

Conclusion

SP was likely to be detected with major respiratory viruses. RSV was associated with higher severity and more pneumococcus bacterial load among SP positive hospitalized children.
PARALLEL 4: INTERACTION WITH VIRUSES AND OTHER BACTERIA

ISPPD-0136
PNEUMOCOCCAL SEROTYPE-SPECIFIC INTERACTION WITH NONTYPEABLE HAEMOPHILUS INFLUENZAE (NTHI) IS CONSISTENT IN ACUTE BACTERIAL CONJUNCTIVITIS AND OTITIS MEDIA

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Background and Aims:

*Streptococcus pneumoniae* and NTHi are the leading causes of bacterial conjunctivitis (ABC) and otitis media (OM) in children. While interactions between the species have been reported, their influence on carriage and disease patterns is not well understood.

Methods:

We compared pneumococcal serotypes isolated in the presence and absence of NTHi from 4496 conjunctival cultures, 11,811 middle ear fluid cultures, and 1588 nasopharyngeal cultures obtained from PCV7/13-unvaccinated children ages 0-18m prior to routine vaccination in Israel.

Results:

Pneumococcal serotypes isolated from mixed-species carriage more closely resembled those isolated from mixed-species ABC (m-ABC) and mixed-species OM (m-OM) than single-species ABC (s-ABC) or single-species OM (s-OM). Pneumococcal serotypes isolated from m-ABC and m-OM were more diverse than those isolated from s-ABC and s-OM, respectively. Whereas pneumococcal phenotype tended to predict whether a serotype was isolated from carriage or disease, fewer phenotype factors predicted isolation from ABC versus OM.
Conclusion

Beyond the factors traditionally recognized to trigger upper respiratory diseases, such as viral infections, a combination of serotype-specific factors, including interactions with NTHi in carriage, influence the capacity of pneumococci to cause single-species or mixed-species disease in the upper respiratory tract.
Background and Aims:

Phage-inducible chromosomal islands (PICIs) are a recently discovered type of satellite virus that do not have the ability to replicate on their own and have a life cycle dependent on a helper virus. These elements can exploit bacteriophages integrated within a bacterial chromosome as helpers, by manipulating the bacteriophage life cycle to enable their own replication and promiscuous spread. Originally identified in *Staphylococcus aureus*, they were shown to be vectors for the spreading of toxin genes and other virulence factors. The prevalence, diversity and genetic stability of PICIs in pneumococcus are virtually unknown. We aimed to identify and categorise pneumococcal PICIs and investigate their molecular epidemiology in the context of the pneumococcal population structure.

Methods:

We analysed the genomes of 482 diverse pneumococci recovered since 1916 from ill and healthy persons in 36 different countries for evidence of PICIs. PICI sequences were defined as those having a genomic organisation similar to the previously reported staphylococcal PICIs.

Results:

We identified 45 unique pneumococcal PICIs. The genomic organisation of the PICIs indicated conserved modular structures, with genes clustered according to function. Multiple sequence alignment analyses suggested that pneumococcal PICIs can be categorised into four major groups. 34.4% (166/482) of the pneumococcal genomes harboured at least one PICI and 5.6% (n = 27) contained two. Some PICIs were detected in multiple clonal complexes (CC), while others were found exclusively in a single CC. Several PICIs persisted for decades.

Conclusion

PICIs are widespread among the pneumococci and demonstrate a structured population.
Background and Aims:

Nasopharyngeal colonization by *Streptococcus pneumoniae* (pneumococcus) and chronic gastrointestinal infection with soil-transmitted helminths (STH) are common childhood events in many areas of the developing world. It is likely, therefore, that a large proportion of children worldwide are co-infected with pneumococcus and one or more helminths.

Helminths modulate systemic host immunity in such a way that ensures chronic infection, with polarization away or towards a Th1 or T regulatory response often playing a crucial role. Given the importance of balance between these pathways in maintaining long-term asymptomatic pneumococcal carriage, STH-driven immune perturbation may have a significant impact on carriage and susceptibility to invasive pneumococcal disease (IPD).

Methods:

Using a murine pneumococcal-*Trichuris muris* (whipworm) co-infection model, we investigated the dynamics of pneumococcal carriage and assessed immune responses during simultaneous STH infection. Pneumococcal-specific antibody levels and functionality were measured using whole cell pneumococcal ELISAs and opsonophagocytosis killing assays.

Results:

*T. muris* infection led to increased nasopharyngeal bacterial loads and enhanced dissemination of pneumococci into the lungs. Serum and alveolar macrophages from co-infected mice showed reduced killing capacity compared to that of control mice, suggesting that *T. muris*-driven host immune modulation plays a role during co-infection. Preliminary studies show that anthelmintic treatment of co-infected mice "normalizes" carriage levels and reduces dissemination of pneumococci to the lungs.

Conclusion

These data address a previously unrealised developing world health issue and data from this study could eventually inform treatment options to combat IPD as well as enhance our understanding of pneumococcal disease dynamics in the developing world.
PARALLEL 4: INTERACTION WITH VIRUSES AND OTHER BACTERIA

ISPPD-0672
EFFECT OF RESPIRATORY SYNCYTIAL VIRUS INFECTION ON PNEUMOCOCCAL COLONISATION AND INVASIVE DISEASE
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Background and Aims:

*Streptococcus pneumoniae* (Pneumococci) and Respiratory Syncytial Virus (RSV) are two major respiratory pathogens responsible for a significant healthcare burden. Epidemiological data suggest a mixed aetiology and possible interaction between these two pathogens as evidenced by co-detection in respiratory secretions.

In this study we aimed to investigate whether RSV exerts a boosting effect on the colonisation or invasive properties of pneumococci and shed light on the underlying mechanism.

Methods:

We examined the co-infection dynamics of RSV and pneumococci using both *in vitro* respiratory epithelial cell and *in vivo* mouse co-infection models.

Results:

Our results showed a significant increase in bacterial load in the nasopharynx and lungs of mice co-infected with pneumococci and RSV. These mice also presented heightened weight loss and disease symptoms as well as delayed recovery compared to mono-infected animals. While investigating the host immune response we found significant differences in pro-inflammatory cytokine levels consistent with the respective infection profile.

Using an *in vitro* transepithelial electrical resistance (TEER) model, we demonstrated that RSV did not have any effect on respiratory epithelial integrity. However we made the interesting observation that *Streptococcus pneumoniae* growth was enhanced by two-fold in the presence of RSV. We also gathered evidence that there were no direct interaction between the two pathogens, in contradiction with current literature.

Conclusion

Our results suggest that RSV promotes pneumococcal colonisation and exacerbates disease severity inclined by altered host immune response. These findings help towards elucidating the pathogenesis of pneumococcal disease and understanding the significance of viral-bacterial co-infection in clinical settings.
PARALLEL 5: GLOBAL PNEUMONIA CONTROL AND VULNERABLE POPULATIONS

ISPPD-0122
SAFETY AND IMMUNOGENICITY OF 15-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV-15) COMPARED TO PCV-13 IN HEALTHY OLDER ADULTS


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Background and Aims:

Safety and immunogenicity of two new formulations (Formulations A and B) of PCV-15 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F*, 23F, 33F*) were compared to PCV13 in healthy, pneumococcal-vaccine naïve adults ≥50 years of age.

Methods:

Subjects (230/arm) received a single dose of either PCV-15 Formulation A, PCV-15 Formulation B, or PCV-13 and were followed for safety for 14 days postvaccination. Randomization was stratified by age (50-64, 65-74, ≥75 years). Serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) and Immunoglobulin G (IgG) geometric mean concentrations (GMCs) were measured immediately prior and 30 days postvaccination.

NCT02547679

Results:

Both PCV-15 formulations had generally comparable safety profiles to PCV-13. Baseline IgG GMCs were comparable across vaccination groups. At 30 days postvaccination, both PCV-15 formulations induced serotype specific antibodies to all 15 serotypes in the vaccine. IgG GMCs in recipients of either PCV-15 formulation were non-inferior to those measured in recipients of PCV-13 for shared serotypes and superior for serotypes unique to PCV-15 (22F and 33F). Formulation B generally induced higher IgG responses than Formulation A. Additional analyses based on OPA responses as well as impact of age on both IgG and OPA responses will be presented.

Conclusion

In healthy adults ≥50 years of age, both new formulations of PCV-15 displayed acceptable safety profiles and induced serotype-specific immune responses comparable to licensed PCV-13.

[*Non-shared serotypes with PCV-13]
Background and Aims:

Pneumonia is a leading cause of hospitalization in individuals with sickle cell disease, described as a high-risk group for pneumococcal infection. Data on hospitalization and outcomes in such patients are lacking in the Brazilian population. Therefore, we’ll describe the effect of the routine PCV10 immunization (introduced in 2010) in hospitalization due to pneumonia in children with sickle cell disease.

Methods:

We’ve conducted a hospital-based retrospective observational study of children under 17 yrs. with sickle-cell disease and hospitalized due to pneumonia from 2005 through 2015. Hospitalization information in such group was extracted from medical records and analyzed according to the pre-vaccination period (2005-2009) and post-vaccination period (2010-2015).

Results:

A total of 416 hospitalizations were identified in this population – 204 before (average 40.8/year) and 212 after PCV10 introduction (average 42.4/year). An infectious cause was responsible for 89 (43.6%) and 101 (47.6%) of them when comparing periods, of which 58 (28.4%) and 59 hospitalizations (27.8%) were due to pneumonia, respectively. When analyzing pneumonia-related hospitalization before and after the vaccine use, there were no changes in the average annual rates (11.6 vs 11.8), median hospitalization duration (7 days vs 8 days). The median age increased from 119 months to 135 months in the post-vaccination era, as well as female distribution (39.7% vs 61%), respectively. Only one pneumonia-related death occurred during the study period.

Conclusion

Preliminary data suggest that there was no reduction in hospitalization and hospitalization length due to all-cause pneumonia in children with sickle cell disease after PCV10 vaccination.
PARALLEL 5: GLOBAL PNEUMONIA CONTROL AND VULNERABLE POPULATIONS

**ISPPD-0258**

**TRENDS IN INCIDENCE AND MEDICAL EXPENDITURES FOR OTITIS MEDIA POST-INTRODUCTION OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINATION (PCV13) IN CHILDREN IN THE UNITED STATES**

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**Background and Aims:**

Routine infant PCV13 use in infants began in February 2010 by replacing PCV7 (implemented in 2000). We analyzed incidence and medical expenditures for otitis media (OM) post-PCV13.

**Methods:**

Data sources included: for OM cases, The National Disease & Therapeutic Index (NDTITM) projections by IMS; for medical expenditures, The Medical Expenditure Panel Survey; for population estimates, the US Census. NDTITM is a continental U.S. level medical audit of ~4,000 physicians randomly selected, who self-report on all office-based patient visits. Because physicians reported two randomly selected workdays per quarter, we assumed that otitis media visits (based on “unspecified” OM (ICD-9 code: 3829) --over 90% of all OM diagnoses) belonged to different episodes. We used 2014 medical expenditure estimate per OM episode ($520) as proxy for all years. Analysis focused on children age ≤9 years between 2011 and 2016.

**Results:**

IRs of OM in 2011 were 476, 204, and 284 per 1000 children age 0-2, 3-9, and 0-9 years, respectively. All subsequent years had lower IRs and by 2016, IRs were ~25% lower (Figure 1). Compared to 2011, from 2012-2016 nationwide there were ~10.8 million fewer cumulatively OM episodes associated with ~$5.6 Billion lower medical expenditures.

**Conclusion**

Routine infant PCV13 use may have contributed to observed 25% decrease in OM incidence rates in 2016 compared to 2011 and large cumulative reductions in OM episodes and medical expenditures.
Figure 1. Annual Incidence Rates for Otitis Media in Children by Age Group from 2011 through 2016 in the United States based on The National Disease & Therapeutic Index (NDTI™) Projections of Otitis Media Visits

- 0-2 Years
- 3-9 Years
- 0-9 Years

Incidence Rate (OM episodes per 1000 Children)

PARALLEL 5: GLOBAL PNEUMONIA CONTROL AND VULNERABLE POPULATIONS

ISPPD-0413
LONG TERM FOLLOW-UP STUDY TO EXAMINE THE IMMUNOGENICITY OF 7-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV7) COMPARED TO 23-VALENT POLYSACCHARIDE VACCINE (23vPPV) IN FRAIL, HOSPITALIZED ELDERLY

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Background and Aims:

We conducted a clinical trial among hospitalized older adults admitted to various wards at a tertiary hospital to compare the immunogenicity of 23vPPV and PCV7. Some 312 patients were recruited to receive 23vPPV (n=153) or PCV7-23vPPV (n=159). At 12 months, there were no significant differences between the two vaccines. Single dose of PCV7 was more immunogenic for serotypes 9V and 23F, and 23vPPV was more immunogenic for serotype 19F. Here we present the results of 60-months follow-up study.

Methods:

We conducted a long term follow up for patients who were enrolled in our RCT. Of the 312 original participants, 136 (43.6%) were followed up at 60-months.

Results:

The GMT was higher for both 23vPPV and PCV7-23vPPV groups at 60-months compared to the baseline by ELISA. OPA results were available for serotypes 14, 18C, 19A, 19F and 23F and all titres were higher at 60 months compared to the baseline, except 23F in 23vPPV group and 19F and 23F in PCV7-23vPPV group. GMT of serotype 4 (ELISA) and 19F (OPA) in the 23vPPV group was significantly higher at 60-months, compared to PCV7-23vPPV group at baseline.

Conclusion

We demonstrated sustained residual immunity at 60 months post-vaccination with both 23vPPV alone or PCV7 followed by 23vPPV vaccines, except for serotypes 23F and 19F. We found substantial waning between 12 to 60 months post-vaccination for all serotypes using OPA, but not by ELISA. Whilst OPA is more reflective of functional immunity, the clinical implication of waning in terms of protection is unknown.
PARALLEL 5: GLOBAL PNEUMONIA CONTROL AND VULNERABLE POPULATIONS

ISPPD-0470
HUMAN CENTERED DESIGN USABILITY TESTING OF A REUSABLE UNIVERSAL PEDIATRIC PULSE OXIMETER PROBE DEVELOPED FOR CHILDREN <5 YEARS OLD IN LOW-RESOURCE SETTINGS (LRS)


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Background and Aims:

Hypoxemia is strongly associated with pneumonia mortality among children in LRS. Although pulse oximeters identify hypoxemia, current high quality pediatric oximetry probes are prohibitively expensive for LRS, while inexpensive devices produce low quality measurements. To address these issues we employed a human centered design process to develop a reusable, low-cost, universal pediatric oximeter probe for LRS. Here we report on probe usability testing.

Methods:

Six experienced physicians (‘experts’) and 51 healthcare workers (HCWs) in Malawi, Bangladesh, and the United Kingdom tested a novel pulse oximetry probe on children <5 years old. We defined a quality oxygen saturation (SpO2) measurement as having a consistent, high-amplitude plethysmographic waveform and biologically plausible value. We analysed the proportion of quality SpO2 measurements in <1, <2, and <5 minutes and used multivariable regression to predict <1 minute quality measurements.

Results:

We conducted four testing rounds and 1,307 SpO2 readings by experts and HCWs. Overall, 67% (876) of readings were <1 minute, 81% (1,059) <2 minutes, and 90% (1,181) <5 minutes. We found, compared to neonates, that increasing age (infant adjusted odds ratio (aOR) 1.87, 95%CI, 1.16, 3.02; toddler aOR 4.33, 95%CI, 2.36, 7.97; child aOR 3.90, 95%CI, 1.73, 8.81) and being asleep, versus being awake and calm (aOR 3.53, 95%CI, 1.89, 6.58), were associated with <1 minute quality readings.

Conclusion

We designed a novel, re-usable, universal pediatric oximetry probe that was effectively used by HCWs and experts on children. When combined with training this probe may be suitable for wide-scale LRS implementation.
PARALLEL 5: GLOBAL PNEUMONIA CONTROL AND VULNERABLE POPULATIONS

ISPPD-0491
ANTIBODY TITRES AGAINST PNEUMOCOCCAL PROTEIN VACCINE ANTIGENS IN PAPUA NEW GUINEAN CHILDREN AT HIGH RISK OF PNEUMOCOCCAL DISEASE
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Background and Aims:
Current pneumococcal vaccines have limited coverage against pneumococcal carriage and disease in high risk areas due to large number of circulating non-vaccine serotypes. Pneumococcal protein antigens may afford serotype-independent protection. Measuring natural immunity to these protein antigens in different populations informs vaccine development, and can be used to understand association between humoral immunity and protection from pneumococcal colonisation and disease.

Methods:
Serum was collected from Papua New Guinean children at 1, 4, 9, 10, 23 and 24 months of age as part of a pneumococcal conjugate vaccine trial (CTN NCT01619462, where no pneumococcal proteins were administered). Serum IgG against pneumococcal protein vaccine candidates PspA1, PspA2, CbpA and Ply were measured by multiplexed bead-based immunoassay.

Results:
715 serum samples from 133 children were assessed. Antibody titres against all 4 pneumococcal proteins were high in the first month of life then declined between 1 and 4 months of age (p<0.001 for all proteins). IgG titres then increased between 9 or 10 and 24 months of age (p<0.001 for all proteins). PspA1&2 24 month titres were still lower than the 1 month titres (p<0.0001 and p=0.05, respectively), whereas CbpA and Ply titres were higher by 24 months (p<0.001 for both proteins).

Conclusion
High level of antibody against pneumococcal proteins at 1 month of age likely reflects the presence of maternal antibody, which wanes within 4 months of life. Longitudinal pneumococcal carriage (including density) will be correlated with antibody titres to advance understanding of colonisation and natural antibody development in this high-risk population.
Background and Aims:

Pneumonia accounts for the largest percentage of global child deaths and about six million pneumonia episodes occur annually in Bangladesh. Hypoxemia, or low arterial oxyhemoglobin saturation (SpO2), is common in childhood pneumonia and can be measured non-invasively using a portable pulse oximeter. Our aim was to evaluate the diagnostic performance of community health workers (CHWs) in identifying pneumonia using a clinical algorithm and pulse oximetry in low resource setting.

Methods:

A total of 31 study CHWs received 14 days training on Integrated Management of Childhood Illness (IMCI) and pulse oximetry use. CHWs clinically assessed and measured a SpO2 using a Masimo Rad5™ pulse oximeter in children aged <3 years weekly from January 2016 to September 2017. Trained study physicians assessed a sample of those children clinically and by SpO2 within 12 hours from the CHW evaluation. The IMCI algorithm or a SpO2 <90% defined pneumonia. The physician’s assessment was considered as gold standard.

Results:

Out of 5,189 evaluations, CHWs correctly identified pneumonia by IMCI with a sensitivity of 50.0% (95%CI: 39.0%, 60.9%), specificity of 99.3% (95%CI: 99.0%, 99.5%) and a kappa of 0.57 and adjusted kappa of 0.97 (p<0.001). Using pulse oximetry, the sensitivity and specificity among 1,086 SpO2 measurements were 60.0% (95%CI: 14.6%, 94.7%) and 98.9% (95%CI: 98.2%, 98.5%) respectively with a kappa of 0.31 and adjusted kappa of 0.80 (p<0.001).

Conclusion

Trained CHWs can diagnose childhood pneumonia using IMCI clinical algorithm and pulse oximetry with moderate validity.
Background and Aims:
Conjugate-pneumococcal vaccines need to be administered 3 to 4 times during the first 15 months of life in order to elicit adult-like protective antibody responses. Limited T follicular helper (Tfh) cell-development is implicated in the slow development of immune response to conjugate-pneumococcal vaccines in newborns.

Methods:
We used gene array analysis and flow cytometry to investigate the underlying mechanisms for the impaired Tfh formation in immunized newborn-mice.

Results:
We found higher ratio of inhibitory CD4+CXCR5+PD-1+Foxp3+ T follicular regulatory (Tfr) cells to CD4+CXCR5+PD-1+Foxp3- (Tfh) cells in immunized newborn mice than in adult mice. The Tfh promoting cytokine, IL-6 preferentially induced TFR-cell differentiation instead of TFH cells in immunized newborn mice (Fig. 1). The beneficial effect of IL-6 on newborn TFR-cell expansion was a result of higher IL-6R expression on TFR cells than TFH cells. Indeed, co-injection of IL-6 and a pneumococcal type 14 polysaccharide tetanus toxoid (PPS14-TT) conjugate vaccine suppressed antibody development in newborn mice. Moreover, compared to PPS14-TT vaccine, the IL-6 containing vaccine elicited higher TFR:TFH ratio in newborn mice. In contrast, inclusion of IL-21 or CpG to PPS14-TT vaccine not only boosted the anti PPS14 IgG responses but also decreased TFR:TFH ratio and increased GC B cell development.

Conclusion
These findings reveal a mechanism for the ablated Tfh development in immunized newborn mice and provide insights into adjuvant mediated immune response-improvements in newborn age group (Fig. 1).
Background and Aims:

Maternal pertussis vaccination has been shown to effectively reduce pertussis in the infants first few weeks of life. However, it has also been shown that presence of maternal antibodies not only reduces the infant's immune response to pertussis, tetanus and diphtheria but also to pneumococcal vaccine serotypes conjugated to CRM197 carrier protein of pneumococcal-13-valent-conjugate-vaccine (PCV13). Our aim is to test the hypothesis that maternal tetanus, diphtheria and acellular pertussis (Tdap) vaccination does not reduce the infant's response to pneumococcal vaccine serotypes conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein of pneumococcal-10-valent-conjugate-vaccine (PCV10).

Methods:

In a randomized controlled trial infant geometric mean antibody concentrations against 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) measured by Multiplex-ImmunoAssay (MIA) pre- and post-PCV10 vaccination were compared in infants of mothers that had received a Tdap vaccination during pregnancy or not (control group).

Results:

IgG antibodies against pneumococcal vaccine polysaccharides conjugated to protein D were not significantly different between infants in the maternal vaccination group and control group. Whereas antibodies against serotype 19F, which is conjugated to diphtheria toxoid, were significantly lower, post primary series and post booster, in infants from mothers that had received a Tdap vaccination during pregnancy compared to infants from the control group.

Conclusion

After Tdap vaccination during pregnancy infants should preferably be vaccinated with protein D conjugated polysaccharide vaccines since they do not show the blunted pneumococcal serotype specific serum antibody responses that have been shown after infant vaccination with CRM197-conjugated polysaccharide vaccines.
PARALLEL 6: INFANT DISEASE AND PROTECTION

ISPPD-0276
A NON-INFERIORITY TRIAL, COMPARING TWO-DOSE PRIMING WITH THE 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE AT 6 AND 10 WEEKS WITH 6 AND 14 WEEKS IN NEPALI CHILDREN.
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Background and Aims:
Nepal introduced PCV10 in 2015 using a unique 3-dose schedule (4-week interval between 2-priming doses; 6 weeks/10 weeks/9 months). A previous Nepali study demonstrated better and longer-lasting immunity after the third dose of the standard 2p+1 schedule (8-week interval between priming doses; 6w/14w/9m) than after the 3p+0 schedule (6w/10w/14 w) used in most GAVI countries; both schedules are WHO recommended.

A single centre open-label, parallel-group, randomised, controlled trial was undertaken to determine whether the 6w/10w schedule is non-inferior to the 6w/14w priming schedule, each followed by a booster dose at 9 months of age (9m).

Methods:
From August 2015 to April 2016, 304 healthy Nepali children were randomised to 2 groups of 152 participants each. Blood was collected one month after the PCV10 second priming dose, and pre-post boost at 9 and 10 months of age; serotype-specific antibody concentrations were determined by ELISA using 22F adsorption at a WHO pneumococcal serology reference laboratory.

Results:
GMCs at 9m differed only for serotypes 18C and 19F (higher in 6w/14w group). At 10m, there was no significant difference in GMCs for any serotype. At 9m, based on the proportion of children with IgG ≥0.35μg/mL, the 6w/10w schedule was non-inferior to the 6w/14w schedule for serotypes 5, 9V, 14, and 19F, but not for serotypes 1, 4, 6B, 7F, 18C, and 23F.

Conclusion
The 6w/10w/9m and 6w/14w/9m schedules are comparably immunogenic following the booster. At 9m the 6w/14w priming schedule is more immunogenic for some serotypes than the 6w/10w schedule, and preferred where delivery logistics allow.
Background and Aims:

Historically, Nigeria has experienced large bacterial meningitis outbreaks causing high mortality in children. *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* are the predominant causes of this invasive disease which is preventable by immunization. In collaboration with the World Health Organization, we conducted a longitudinal surveillance study across sentinel hospitals within Nigeria to establish the burden of bacterial meningitis.

Methods:

From 2010 to 2016, Cerebrospinal fluid (CSF) was collected from children <5 years, admitted to five sentinel Hospitals across Nigeria. Microbiological and latex agglutination techniques were performed to detect the presence of *S.pneumoniae*, *N.meningitidis* and *H.influenzae*. Species-specific polymerase chain reaction and serotyping and serogrouping, were conducted to determine specific causative agents.
Results:

A total of 5134 children with suspected meningitis were enrolled at the participating hospitals. Infection was observed in more children with turbid CSF samples (10.5%) compared to those with clear CSF (2.2%). The dominant pathogen was pneumococcus (46.4%), followed by meningococcus (34.6%) and *H. influenzae* (18.9%). The mortality rate was 15%. The number of cases varied seasonally and annually, with peaks in April and 2013. Most pneumococcal meningitis cases (53.6%) were caused by serotypes covered by PCV vaccines. The most prevalent meningococcal and *H. influenzae* strains were serogroup W and Hib respectively.

Conclusion

Due to Nigeria’s large population vaccine programs for preventing meningitis have been introduced in phases. Continued surveillance within Nigeria is required to estimate vaccine impact as vaccination coverage improves and also to determine the distribution of serogroups and serotypes of target meningeal pathogens across the country, post-vaccine introduction.
PARALLEL 6: INFANT DISEASE AND PROTECTION

ISPPD-0402
EARLY-LIFE INFECTION EXACERBATES SUSCEPTIBILITY TO OTITIS MEDIA
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Background and Aims:

Otitis media (OM) is the leading cause of pediatric healthcare visits and antimicrobial prescribing. Because much of this burden occurs among highly-susceptible otitis-prone children, causes of the “otitis-prone condition” have been of longstanding interest. Whereas otitis-prone children tend to experience early-life OM more frequently than other children, the contributions of tissue damage sustained during early-life episodes to future susceptibility have been difficult to distinguish from the confounding role of innate host factors. Changes in the epidemiology of OM after pneumococcal conjugate vaccine (PCV7/13) rollout provided a natural experiment to distinguish the impact of early-life infections on future susceptibility.

Methods:

Using data from surveillance for carriage and complex OM incidence in southern Israel, we measured changes in the susceptibility of children ages 0-35m to OM progression following PCV7/13 rollout. We used a mathematical model to estimate the strength of PCV7/13 protection against OM progression, distinguishing the independent, age-dependent contribution of OM episodes to disease risk.

Results:

Vaccine rollout was associated with reduced progression rates for PCV7/13-targeted and non-vaccine serotypes. We estimated that PCVs reduce vaccine-serotype progression rates from carriage to OM by 46.8% (95%CI: 30.7-61.5%). We identify an independent contribution of early-life OM episodes to otitis proneness, estimating that this effect declines 78.6% (48.0-91.8%) by the third year of life.
Conclusion

Early-life infections exacerbate susceptibility of children to OM progression. Preventing such episodes—historically associated with PCV7/13 serotypes—has contributed to reductions in susceptibility of children to all-cause OM.
PARALLEL 6: INFANT DISEASE AND PROTECTION

ISPPD-0444
DIRECT AND INDIRECT IMPACT OF 13v- PNEUMOCOCCAL CONJUGATE VACCINE ON INVASIVE PNEUMOCOCCAL DISEASE IN BLANTYRE, MALAWI

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Background and Aims:

In high income settings PCV protects unvaccinated age-groups through indirect effects. In Malawi, a 3+0 EPI schedule and persistent nasopharyngeal carriage among older unvaccinated persons may mitigate indirect effects. We sought to determine PCV13 impact on invasive disease in vaccine-eligible and older groups.

Methods:

IPD surveillance has been ongoing in Blantyre (population 1.3 million) at Queen Elizabeth Central Hospital (~13,000 blood cultures and ~5,000 CSFs performed annually) since 2000. We serotyped all available viable blood or CSF pneumococcal isolates from 1 January 2007 to 31 December 2015, using triplex PCR during 2009-2014 or latex agglutination otherwise. Case numbers were divided by age-specific census population, and VT and NVT incidence were Poisson regressed against year and PCV13 age-eligible-population coverage.

Results:

1,110 VT and 752 NVT cases occurred from 6,818,248 person-years observed. Adjusting for temporal trend, infant IPD reduced by 1% with every 1% increase in vaccine coverage. Similar vaccine-associated reduction in incidence of VT-disease was seen in children 1-14 years, but not in adults. Among infants a significant reduction in NVT-disease was noted, though absent in other age groups.

Conclusion

Long term sentinel surveillance reveals complex interactions between temporal trends in IPD and vaccine effectiveness in Malawi, likely reflecting additional impact of other socioeconomic, nutritional and disease control improvements, particularly in infants. PCV13 had demonstrable direct effects among vaccine-eligible age groups and indirect effects among older children, but no effect on adults. It remains crucial to fully ascertain the long-term total population benefits of vaccine introduction in the context of broader health policy.
ISPPD-0521
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Background and Aims:
Acute lower respiratory infections (ALRI) are a leading cause of hospitalisation and mortality for Northern Territory (NT) Indigenous children. We compared rates of childhood ALRI hospitalisation during three eras of pneumococcal conjugate vaccination: PCV7 (2006-2009); PCV10 (2009-2011); PCV13 (2011-2015).

Methods:
Design: Historical cohort study. Population: All NT Indigenous children born between 2006-2015 (inclusive). Exposure: ≥3 primary series (scheduled 2-4-6 months) doses of PCV7, 10, or 13 by age 7 months; source NT immunisation register. Outcome: ALRI hospitalisation episodes <12 months (ICD-10-AM: J09-J22; subgroups bacterial pneumonia: J13-J18.9; RSV-ALRI: J12.1, J20.5, J21.0); source NT Department of Health. <14 days of birth or between episodes were excluded.

Results:
Overall 22% (n=2420) of the 10964 cohort children were hospitalised with ≥1 ALRI before age 12 months (3807 episodes; median 1/child, range 1-8). ALRI rates did not vary significantly by year. Approximately 50% of children received 3 timely doses of PCV7 (n=2382), 10 (n=1032) or 13 (n=1743). Rates of any ALRI and RSV-ALRI were similar across the vaccine groups. Rates of bacterial pneumonia were lowest and time to first bacterial pneumonia was highest among PCV13 vaccinees (Table).

Conclusion
The proportion of NT Indigenous children hospitalised with an ALRI before age 12 months has remained above 20% for over a decade. Differences in ALRI hazard will be assessed in more detail using Cox modelling.
Background and Aims:

Our understanding of the bacterial genetic determinants of pneumococcal transmission, acquisition rates and carriage duration is limited. This study examines lineage- and locus-specific genetic variation amongst pneumococci colonizing the nasopharynx and interactions with environmental factors amongst African children enrolled in an intensively sampled birth cohort.

Methods:

Pneumococcal isolates were obtained from nasopharyngeal (NP) swabs collected 2-weekly from 800 infants enrolled from birth through their first year of life in a birth cohort in Cape Town, South Africa. Confirmatory lytA real-time qPCR was performed on all presumptive pneumococci before whole genome re-sequencing (WGS). Detailed metadata were longitudinally collected on selected environmental, infectious, nutritional, genetic, immunological, psychosocial and maternal health determinants.

Results:

A total of 19 289 NP swabs were collected from infants. Culture has been completed on 15 906 swabs. Pneumococci were isolated from 53% (8 422 /15 906); yielding a point prevalence of 0.5% at birth and reaching a maximum prevalence of 71% at 38 weeks. Of the planned 12,000 pneumococcal isolates to be sequenced, data for 96 isolates are available, with an additional 1330 genomes currently in the sequencing pipeline. Complete results will be presented at ISPPD. 314 pneumonia cases occurred amongst enrolled children (incidence 0·27 episodes per child-year, 95% CI 0·24–0·31; median age 5 months [IQR 3–9]) in 967 children during 1145 child-years of follow-up. PCV13 coverage was high (90%, 90% and 81% for 6, 14 weeks and 9-month vaccines respectively).

Conclusion

This study will report, lineage and locus-specific variation associated with pneumococcal carriage dynamics in an intensively sampled, PCV-13-vaccinated population.
PARALLEL 7: MICROBIOLOGY

ISPPD-0224

PNEUMOCOCCAL SEROTYPING OF MALAWI CARRIAGE SAMPLES BY LATEX AGGLUTINATION, WHOLE GENOME SEQUENCING (PNEUMOCAT) AND DNA MICROARRAY IS HIGHLY CONCORDANT: WHICH SHOULD YOU CHOOSE?

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Background and Aims:

The polysaccharide capsule is the target of current pneumococcal vaccines making accurate serotyping essential for surveillance, evaluating vaccine efficacy and informing vaccine policy. Serotyping of pneumococcal nasopharyngeal carriage by latex agglutination, whole genome sequencing (WGS) and microarray was compared.

Methods:

Nasopharyngeal swabs (NPS) from community-based surveillance (2015-2017) were collected following WHO recommendations. Phenotypic serotyping used a 13-valent latex kit (SSI, Denmark); genomic serotyping applied PneumoCaT analysis on WGS libraries (from isolates identical to those used for phenotyping) and molecular serotyping by microarray, using DNA from NPS cultures. Latex serotyping did not differentiate individual non-vaccine serotypes (NVT).

Results:

Amongst 502 carriage samples serotyped by the three methods, 81% (405/502) were concordant by serotype and 13% (70/502) concordant by serogroup only (including 10 samples that were NVT by genotype but VT by phenotype (e.g. 23A/23F). An additional 3% (14/502) were concordant by latex and WGS but the serogroup was not detected by microarray. Only 3% (13/502) of latex results were discordant with PneumoCaT and microarray, although these were concordant.

Conclusion
High concordance was observed between the three serotyping methods in identifying dominant serotypes. Though more limited in output, latex was less costly and required limited expertise for field-site implementation and analysis, with results more rapidly available. WGS outputs include NVT resolution and molecular data for epidemiological analysis. Microarray detects multiple serotype carriage with NVT resolution and relative serotype abundances, outputs likely critical for understanding vaccine efficacy. Therefore, selection of serotyping tools should be carefully considered and guided by the particular research question and applied context.
PARALLEL 7: MICROBIOLOGY

ISPPD-0381
STREPTOCCCUS MITIS EXPRESSING PNEUMOCOCCAL SEROTYPE 1 CAPSULE
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Background and Aims:

Serotype1 pneumococci are rarely found in healthy persons and are a rare cause of disease in the US population, but common worldwide. We screened nasopharyngeal (NP) and oropharyngeal (OP) specimens from US adults for cps1-positive non-pneumococcal streptococci and assessed cross-reactivity of these strains with serotype1 pneumococcal antisera.

Methods:

NP and OP specimens from US adults ≥65 years recruited from the community underwent culture and real-time PCR targeting lytA. A subset of lytA-positive and -negative specimens were screened using cps1-specific PCR. Five specimens that were culture-negative for pneumococci with the lowest cps1 cycle thresholds were cultured for cps1-positive non-pneumococcal streptococci. Capsule expression and cps1 homologs were compared between the non-pneumococcal streptococci and a pneumococcal serotype1 reference strain.

Results:

Of 1,299 adults enrolled, 1,283 (98.8%) were culture-negative for pneumococcus. Of those, 75 (5.8%) had lytA-positive specimens (71 from OP, 1 from NP and 3 from both). Fifty-three lytA-positive and 395 lytA-negative specimens yielded 8 (15.1%) and 41 (10.4%) cps1-positive specimens, respectively. Five cps1-positive Streptococcus mitis strains were isolated from two lytA-positive and three lytA-negative OP specimens. Whole genome sequence analysis of these five S. mitis isolates revealed three distinct cps1 operons, each highly similar to the S. pneumoniae serotype1 reference operon (e.g. 96.4-96.5% wzy similarity), and three distinct clones. Quellung and immunodiffusion verified serotype1 capsule expression from isolates.

Conclusion

Although pneumococcal carriage was uncommon, S. mitis expressing pneumococcal capsular serotype1 was recovered from some US adults. It is possible that these commensal organisms might induce immunity contributing to low US rates of serotype1 pneumococcal disease.
Identification of Streptococcus pneumoniae by a real-time PCR assay targeting SP2020

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Background and Aims:

A real-time PCR assay, targeting the major autolysin gene—lytA, is currently used as the gold-standard culture-independent assay for Streptococcus pneumoniae identification. A second real-time PCR assay, targeting the permease gene of the pia ABC transporter—piaB, is used in parallel to increase the specificity of identification. Although piaB has been described as pneumococcus-specific, it is not ubiquitous, since it is absent from some non-encapsulated pneumococci. Also, there is evidence that lytA homologues can be present in closely related species of Streptococcus. Still, to the best of our knowledge, this has not been sufficiently tested. In this study we evaluated the performance of a new real-time PCR assay—targeting SP2020, a putative transcriptional regulator gene—and compared its performance with the assays previously described.

Methods:

A collection of 150 pneumococci (50 capsular types plus non-encapsulated pneumococcus) and 427 non-pneumococci (over 20 Streptococcus species) was tested.

Results:

SP2020 and the lytA-CDC assays showed the best performance (100% sensitivity for both assays; 99.3% and 98.7% positive predictive value (PPV), respectively, p=0.564). For piaB the sensitivity was 93.3% and the PPV 98.6%. Misidentification occurred among strains of S. pseudopneumoniae (for lytA and piaB), and S. pneumoniae (for piaB; serotype 6B and non-encapsulated). One strain of S. pseudopneumoniae/S. mitis group was misidentified by SP2020. No misidentifications occurred when the results of lytA-CDC and SP2020 were combined.

Conclusion

This study suggests that detection of lytA-CDC in combination with SP2020 is a powerful strategy for the identification of pneumococcus particularly in the study of polymicrobial samples by culture-independent methods.
Background and Aims:

Pneumococcal carriage is considered a prerequisite to pneumococcal disease and is the source of pneumococcal transmission. The aims of this study were to investigate pneumococcal carriage prevalence, acquisition, and duration of carriage during the first year of life.

Methods:

200 infants were enrolled at 8 - 12 weeks of age in one urban and one semi-rural site in Bandung, Indonesia. Nasopharyngeal swabs were collected monthly for 7 months with a final swab at 12 months of age. Pneumococci were detected by qPCR and molecular serotyping performed by microarray, with a representative isolate typed by latex agglutination/Quellung.

Results:

Carriage prevalence was 22% at enrolment and increased to 68% at 12 months of age. The number of pneumococcal acquisitions during the study period ranged from 0 to 5. The median duration of carriage was 84 days (IQR 59, 164) for the first carriage episode and 63 days (IQR 56, 77) days for subsequent episodes; p <0.0001, Mann Whitney test. No significant differences in carriage duration were observed among serotypes, although 23F, 15B/C, and 11A tended to be carried for longer. Infants in the semi-rural site acquired pneumococci earlier than infants from the urban site (median age at acquisition 117 days vs. 140 days, p = 0.047, Mann-Whitney test).

Conclusion

Infants living in rural areas acquired pneumococci earlier compared to infants from urban areas. Results will be helpful for consideration of pneumococcal vaccine strategies in Indonesia, and increase our understanding of pneumococcal carriage dynamics.
PARALLEL 7: MICROBIOLOGY

ISPPD-0626
SHOTGUN SEQUENCING TO ELUCIDATE PNEUMOCOCCAL STRAIN LEVEL NASOPHARYNGEAL COLONIZATION PATTERNS AND ANTIMICROBIAL RESISTANCE IN A SOUTH AFRICAN BIRTH COHORT
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Background and Aims:
In a proof of concept study, we used shotgun sequencing of nasopharyngeal (NP) samples from children participating in a South African birth cohort study to explore strain-level pneumococcal colonization and associated antibiotic-resistance determinants.

Methods:
NP swabs were obtained fortnightly from 23 infants during the first year of life; samples were selected from infants on the basis of changes in pneumococcal serotype or antimicrobial-resistance over the study period. NP swabs underwent short-term enrichment for pneumococci, and total nucleic acid was extracted for shotgun sequencing. In silico pneumococcal capsular and multilocus sequence typing was performed. Pneumococcal penicillin-binding protein (PBP) 1a, 2x, and 2b genes were analysed for mutations associated with beta-lactam-resistance.

Results:
196 samples were included, from which pneumococci were cultured in 174 samples. We were able to derive pneumococcal serotype, sequence type (ST) and antimicrobial-resistance profile directly from shotgun sequence data from 87% (152/174) of samples. Co-colonization with different serotypes was detected in 13% (23/174) of samples. We identified 24 different STs (2 novel STs) including 11 STs which have only been described in South Africa. These 11 STs were detected in samples containing erythromycin- and cotrimoxazole-resistant pneumococci, which also had an H394L PBP2x-mutation, known to confer β-lactam-resistance. ST7052 and ST361 were detected, for the first time in South Africa, in samples containing pneumococci with resistance to cotrimoxazole and penicillin, due to S351A, I358T, and P432T mutations in the PBP1a gene.

Conclusion
Direct shotgun sequencing from NP samples is a valuable technique for detailed evaluation of the pneumococcal component of the NP microbiome.
ISPPD-0632
EXPANSION AND VALIDATION OF A MALDI-TOF MS-BASED PNEUMOCOCCAL CAPSULAR TYPING PROPOSAL: PREDICTING SEROTYPES 6, 9, 14, 19 AND 23
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Background and Aims:

*Streptococcus pneumoniae* isolates are classified in more than 90 capsular types, as determined by Quellung reaction or PCR. Such methods are expensive, laborious or unable to accurately discriminate among certain serotypes; thus, development of novel typing methods is required. Recently, we proposed an approach based on MALDI-TOF MS for predicting serotypes 6A, 6B, 6C, 9N, 9V and 14. Here we tried to validate and extend this proposal.

Methods:

The previous proposal was extended to comprise serotypes 19A, 19F (including type 19F wzy variant common in Brazil), 23A, 23B and 23F by analyzing 311 pneumococcal isolates belonging to these serotypes; and submitted to validation by testing 180 additional isolates. The isolates had their capsular types previously determined by Quellung reaction and/or multiplex PCR. For MALDI-TOF MS analysis, an extraction protocol using formic acid and acetonitrile and CHCA matrix were used. Measurements were performed with a Microflex LT mass spectrometer using the default parameters and generating spectra in the range of 2,000-20,000 m/z. Spectra were analyzed with BioNumerics software v7.6 to determine serotype-specific biomarkers.

Results:

Seven biomarkers (in the range of 4,000-10,000 m/z) out of the fourteen previously determined were validated for the prediction of serotypes 6A, 6B, 6C, 9N, 9V and 14. Two of these biomarkers were also useful to discriminate between serotypes 19A and 19F, while serotypes 23A, 23B and 23F were differentiated by the presence/absence of three other biomarkers.

Conclusion

MALDI-TOF MS is a promising alternative for typing pneumococcal strains, highlighting its usefulness for rapid and cost-effectiveness routine application in clinical laboratories.
PARALLEL 8: IMMUNOLOGY

ISPPD-0052
IMMUNE RESPONSE TO PNEUMOCOCCAL CONJUGATE VACCINE (PCV13) SEROTYPES IN TANZANIAN CHILDREN WITH HIV/AIDS.
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Background and Aims:

Up to one million children die every year due to pneumococcal disease, particularly in children infected with Human Immunodeficiency Virus (HIV), who appear to have higher rates of pneumococcal carriage and invasive disease. With an estimated 110,000 Tanzanian children living with HIV infection, S. pneumoniae is a significant cause of morbidity and mortality. Successful immunity is dependent on mounting a sufficient immune response to the vaccine, we therefore aimed to determine the serum antibody response (>4-fold and geometric mean concentration) to pneumococcal vaccine (PCV13) serotypes at 3 months after a second (additional) vaccine dose.

Methods:

We conducted a double blinded crossover randomised controlled trial in 226 HIV infected children aged 1-14 years using Haemophilus influenzae-type b (Hib) vaccine as the control. Serum samples were collected at baseline and 4-6 months later, antibodies to pneumococcal serotypes were ELISA quantified to obtain antibody geometric mean concentration (GMC).

Results:

There was no statistically significant difference in antibody GMC for all vaccine serotypes at baseline. Statistically significant better responses were found for 11 of the 13 vaccine serotypes (1, 3, 4, 5, 14, 18C, 23F, 6A, 6B, 7F, 9V) among pneumococcal vaccine participants with above putative protective antibody concentration (0.35ug/mL) 2-4 months post second vaccine dose. However, only 6 of the 13 vaccine serotypes (1, 4, 14, 18C, 19F, 7F) had statistically significant 4 fold rise in antibody GMC.

Conclusion

There is likely to be value in an extra booster dose in immune compromised individuals.
Background and Aims:

*Streptococcus pneumoniae* (*Spn*) remains a leading cause of mortality in children, despite the existence of polysaccharide-based vaccines. Protein-based vaccines could offer an advantage by conferring protection against all pneumococcal serotypes. Carriage is a prerequisite for disease and a reservoir for transmission. Murine models have revealed that protection against colonization is mediated by IL-17A-secreting CD4+ T cells. Therefore, the use of IL-17A as a readout could be a good strategy for screening novel vaccine candidates to control carriage and transmission. We aim to investigate whether protein-specific IL-17A levels correlate with protection against Experimental Human Pneumococcal Carriage (EHPC) and bacterial density.

Methods:

Baseline PBMCs from healthy volunteers inoculated in previous EHPC studies (of which 46% were susceptible and acquired *Spn*, and 54% were naturally protected) were used to stimulate a library of 70-pneumococcal proteins. These proteins are predicted to be on the surface of pneumococcus and have been purified from *E. coli*. Proteins were used at a concentration of 7μg/ml to stimulate 1x10^6 PBMCs/ml for 7 days.

Results:

Optimization assays were performed to establish the optimal protein concentration and the stimulation duration to induce IL-17A secretion. Preliminary data showed that all proteins tested after a 7-day incubation induced protein-specific IL-17A secretion with a mean of 160.9 pg/ml (23.9-460.8 pg/ml).

Conclusion

This work will combine the largest existing pneumococcal protein library with an experimental human challenge platform to identify protein antigens to be further developed as vaccine candidates.

Acknowledgements: Medical Research Council; Bill & Melinda Gates Foundation; Robert Austrian Award 2016
Background and Aims:

Understanding antibody responses to pneumococcal colonisation early in life can lead to targeted interventions and next generation pneumococcal vaccines. This study profiled IgG responses in a birth cohort residing in the Maela refugee camp near the Thailand-Myanmar border.

Methods:

The immunoglobulin G (IgG) antibody responses to 2,188 proteins were measured by probing a panproteome microarray with longitudinally-sampled sera from 63 infants.

Results:

Seroreactivity was identified for 410 functionally diverse cell surface-associated proteins, including maternally-derived antibodies. The IgG kinetic profile of most proteins followed a trend of sharp decline and seroreversion during the first 6 months, followed by a gradual increase during the following 18 months. Paradoxically, the highest rate of seroconversion also occurred during the first 6 months, suggesting that as maternally-derived antibodies decline, colonisation promotes a distinct antibody repertoire in newborn infants. Frequent nasopharyngeal swabs and diverse protein variants on the microarray allowed us to map exposures to specific protein variants with antibody responses following or prior to colonisation. We observed a trend for higher IgG levels following exposure to specific protein variants of PspA, PspC, ZmpA and ZmpB, but there was no evidence that IgG to these proteins reduced the odds of future colonisation with pneumococci expressing the same variants. IgG to a limited set of conserved proteins including neuraminidase C (NacN), the backbone protein of type 2 pili and zinc metalloprotease D (ZmpD) were higher following single exposures.

Conclusion

Early life antibody profiles may lead to discovery of specific biomarkers of exposure and correlates of broad protective immunity to pneumococci.
Background and Aims:

Current pneumococcal vaccines have important limitations, including restricted serotype coverage facilitating replacement by non-vaccine serotypes and high manufacturing costs. Therefore, serotype-independent and protein-based next-generation vaccines are favored to combat pneumococcal infections. In this study, we investigated the potential of selected pneumococcal lipoproteins to elicit protective immune responses against pneumococcal colonization.

Methods:

The cell-surface abundance of selected lipoproteins was examined by flow cytometry using protein specific polyclonal IgGs generated in mice. Their immunogenicity was determined by analyzing the antibody titers in sera of immunized mice or in convalescent patient sera using a multiplex bead-based immunoproteomics approach. Highly abundant and immunogenic lipoproteins were selected to decipher the efficacy of the elicited immune response to protect against pneumococcal colonization. We determined IL-17A levels in the nasal tissue and performed IgG subtyping analysis using ELISA.

Results:

We identified DacB, MetQ and PnrA as highly abundant lipoproteins on the pneumococcal surface. The immunoproteomics approach revealed high antibody titers post immunization of mice or in convalescent patient sera. Mice, intranasally immunized with CTB as adjuvant and challenged with D39 had lower bacterial loads in the nasal cavity 3 days post-infection. Protectivity correlated with increased production of nasal IL-17A. In contrast, protection was only partially accompanied by high antigen-specific IgG titers.

Conclusion

Lipoproteins are interesting targets for future vaccine strategies as they are highly conserved, abundant and immunogenic. We identified PnrA, DacB and MetQ as potential vaccine antigens to induce protection against pneumococcal colonization which in turn will lead to a decline in transmission.
PARALLEL 8: IMMUNOLOGY

ISPPD-0377
PRODUCTION OF IGG2 ANTIBODIES TO PNEUMOCOCCAL POLYSACCHARIDES REQUIRES ICOS+ CIRCULATING MEMORY FOLLICULAR HELPER T-CELLS AND IS IMPAIRED BY HIV-1 INFECTION
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Background and Aims:

Follicular helper T-cells (TFH) are critical for immunoglobulin isotype switching by B-cells and their dysfunction may contribute to impaired isotype switching. We examined the relationship between production of IgG1+ and IgG2+ antibody secreting cells (ASCs) and ICOS+ and ICOS- circulating memory (cm)TFH cells after pneumococcal polysaccharide vaccine (23PPV) in HIV patients and controls.

Methods:

HIV patients receiving antiretroviral therapy (ART) (n=28), ART-naive HIV patients (n=11) and controls (n=20) were vaccinated with 23PPV and PBMCs cryopreserved at days (D) 0, 7 and 28 post-vaccination. ASCs producing IgG1+ or IgG2+ antibodies to serotypes 4, 6B, 9V and 14 were enumerated by ELISpot. ICOS+ and ICOS- cmTFH (CXCR5+CD27+CD45RA-CD4+PD-1+) cells were assessed by flow cytometry.

Results:

ICOS+ cmTFH cells alone correlated with IgG1+ and IgG2+ ASC (R>0.63, p<0.004 and R>0.51, p<0.0007 respectively) to all serotypes after vaccination in controls only. All HIV patients had fewer serotype-specific IgG1+ and IgG2+ ASCs D7 post-vaccination compared with controls (p<0.05) but this was not associated with ICOS+ cmTFH cells. Serum IgG2 titres at D28 also correlated with ICOS+ cmTFH cells in controls but not in HIV patients (R≥0.46, p≤0.04).

Conclusion

We have shown that a dysfunctional TFH cell response impacts upon antibody responses to pneumococcal vaccination. Harnessing the helper capabilities of TFH cells may enhance vaccine-induced protection from pneumococcal disease in susceptible populations.
Background and Aims:

Whole cell vaccines (WCVs) potentially represent an inexpensive approach to eliciting immunity protective against all pneumococci. This study aimed to identify the strongest antibody responses to a WCV based on strain RM200.

Methods:

A panproteome array was used to measure serum immunoglobulin G (IgG) responses at multiple timepoints during a placebo-controlled phase I trial in 35 healthy volunteers.

Results:

Pre-vaccination sera revealed consistently strong IgG responses to at least 100 antigens. These included adhesins, surface-associated degradative enzymes, transporter solute binding proteins and cell wall synthesis machinery, as well as multiple variants of the diverse PspA, PspC, ZmpA and ZmpB proteins. In post-vaccination samples, trial participants exhibited similarly consistent responses to the WCV, which elicited increased IgG binding to 137 probes from 73 distinct proteins. Nevertheless, individuals’ overall immune ‘fingerprint’ was detectable throughout. Vaccine antigens were functionally similar to those targeted by natural immunity, but were enriched for solute-binding proteins and cell wall synthesis machinery likely to be unusually highly exposed on the unencapsulated WCV. There were also complex IgG responses to different variants of diverse proteins in vaccinated individuals. While many increases in IgG appaered anamnestic, other WCV antigens were not associated with high levels of pre-vaccination immunity, and the increase in IgG binding after multiple doses likely mirrors the development of novel humoral responses.

Conclusion

The overall responses to WCV reproducibly increased IgG responses to a limited, but functionally diverse, set of conserved proteins, as well as multiple variants of diverse proteins, with the potential to afford broad protection against pneumococcal disease.
PARALLEL 8: IMMUNOLOGY

ISPPD-0642

INFLAMMATION INDUCED BY LIVE ATTENUATED INFLUENZA VIRUS IMPAIRS INNATE CONTROL OF HUMAN PNEUMOCOCCAL COLONIZATION

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Background and Aims:

The immunological mechanisms that control pneumococcal carriage in humans remain unclear. Loss of this control following influenza infection is associated with secondary bacterial pneumonia during seasonal and pandemic flu outbreaks. Here, we used a controlled human co-infection model, coupled with minimally-invasive nasal sampling to elucidate the underlying immunological mechanisms.

Methods:

We performed a double-blinded, placebo-controlled, randomized clinical trial, in which volunteers received either LAIV (n=62) or tetravalent inactivated flu vaccine (TIV) as a control (n=55), followed by pneumococcal inoculation three days later. We collected nasal microbiopsies and nasal lining fluid in a serial manner before and after vaccination and Spn inoculation to assess immune responses.

Results:

Pneumococcal carriage in the control group led to a recruitment of monocytes to the nose. In contrast, nasal neutrophils in those protected from carriage displayed upregulated CD66b at day+2. Overnight re-stimulation of nasal cells in vitro with heat-killed pneumococcus demonstrated increased responses in carriage-positive volunteers, which correlated with pneumococcal clearance. Importantly, prior administration of LAIV impaired these innate responses. Nasal transcriptomic data revealed markedly different responses to pneumococcus in the setting of LAIV co-infection. LAIV vaccination was associated with inflammatory cytokine production and IP-10 levels at time of inoculation associated with pneumococcal density.

Conclusion

Activation of nasal-resident neutrophils and recruitment of monocytes associated with control of pneumococcal carriage. Prior infection with attenuated influenza virus altered nasal responses to carriage and disrupted this innate control. Levels of the cytokine IP-10 at the time of pneumococcal encounter predicted bacterial density.

Acknowledgments: BMGF;MRC;NIHR-CRN
Background and Aims:

Innate lymphoid cells including ILC3 are increasingly appreciated as being critical in local immune homeostasis and inflammation. Similar to Th17 cells, ILC3 express IL17A and/or IL22. Recent data from animal models suggest there is a reciprocal interaction between ILC3 and T cell responses. It is not known what is the relationship between ILC3 and Th17 cells in human nasopharynx and whether ILC3 contributes to the regulation of pneumococcal carriage in humans.

Methods:

We have studied the ILC3 and Th17 populations in the nasopharynx-associated lymphoid tissue (NALT) from children and adults following stimulation by PMA or a Staphylococcal extract, and analysed their association with pneumococcal carriage. ILC3 and Th17 frequencies and responses following stimulation were examined by flow-cytometry following staining for lineage markers, CD127, NKP44, c-kit, IL17A and IL-22.

Results:

We showed the ILC3 frequency in NALT was higher in children than in adults, which was in contrast to the markedly higher Th17 frequency in adults than in children. Further analysis revealed that there was an inverse relationship between the IL22-expressing ILC3 and IL17A- producing Th17 cells, and a higher ratio of ILC3/Th17 responses was associated with pneumococcal carriage in children. Staphylococcal stimulation reduced ILC3 frequency but markedly increased Th17 response.

Conclusion

Our results suggest there is significant interactions between homeostatic ILC3 and pathogen-induced Th17 response, and through that mediate pneumococcal carriage in children. Further studies are ongoing to interrogate the cellular interactions between ILC3 and Th17 in the context of nasopharyngeal carriage.
PARALLEL 9: EPIDEMIOLOGY AND MATHEMATICAL MODELLING

ISPPD-0040
MODELLING THE IMPACT OF CHANGING FROM A 2+1 TO 1+1 PCV13 SCHEDULE IN ENGLAND AND WALES
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Background and Aims:

In countries with mature pneumococcal conjugate vaccine (PCV) programmes changing to 1+1 schedule, if it sustained herd immunity, could improve programmatic simplicity while reducing costs.

Methods:

We used a dynamic transmission model to explore the effect of this change in England and Wales but the rapid increase in non-PCV serotype (NVT) invasive pneumococcal disease (IPD) observed from 2014/15 was larger than the worst scenario predicted by the model. The model was adjusted to explore the potential effect of introducing live attenuated influenza vaccine (LAIV) for children in 2014/15, or an increase in invasiveness or transmissibility of the NVT group.

Results:

Fitting results were inconsistent with an LAIV effect but suggested that a small increase (1%) in transmissibility and/or a 15% increase in invasiveness of the NVT group overall could produce a substantial increase in NVT IPD. These NVT changes were consistent with those observed in a pneumococcal carriage study conducted in 2015/16. The model results indicated that despite reduced protection against carriage in infants by removing a priming dose, if the booster in a 1+1 schedule generated the same carriage protection as a 2+1 schedule, vaccine-type IPD would only increase marginally.

Table. Additional IPD cases by changing to 1+1 schedule from 2018

<table>
<thead>
<tr>
<th>Age Group</th>
<th>&lt;2</th>
<th>2-4</th>
<th>5-14</th>
<th>15-44</th>
<th>45-64</th>
<th>65+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2030/31</td>
<td>4(3,6)</td>
<td>1(1,2)</td>
<td>1(1,2)</td>
<td>9(5,12)</td>
<td>15(9,21)</td>
<td>32(19,45)</td>
<td>62(38,88)</td>
</tr>
<tr>
<td>Over 13 years</td>
<td>20(13,27)</td>
<td>5(3,7)</td>
<td>6(4,8)</td>
<td>44(30,58)</td>
<td>73(48,97)</td>
<td>136(85,189)</td>
<td>283(182,385)</td>
</tr>
</tbody>
</table>

Conclusion

In countries with good PCV-induced herd immunity change to a 1+1 schedule could be considered.
PARALLEL 9: EPIDEMIOLOGY AND MATHEMATICAL MODELLING

ISPPD-0210
TWENTY-SIX YEARS OF INVASIVE PNEUMOCOCCAL DISEASE IN CANADIAN CHILDREN, 1991-2016, THE CANADIAN IMMUNIZATION MONITORING PROGRAM, ACTIVE


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Background and Aims:

Before implementation of the first Canadian pneumococcal conjugate vaccine (PCV) program in 2002, invasive pneumococcal disease (IPD) accounted for most severe, invasive bacterial infections in children. PCV programs were implemented with the expectation that the IPD disease burden would decrease. This study examines 26 years of surveillance data to describe the epidemiology of Canadian IPD.

Methods:

The Canadian Immunization Monitoring Program, Active (IMPACT) captures all lab-confirmed IPD cases presenting at 12 tertiary care pediatric hospitals across Canada. Nurses complete a standardized report form. Isolates are serotyped at a central reference laboratory.

Results:

The pre-vaccine era (1991-2004) averaged 279 IMPACT cases each year (range 245-332) with a hospitalization rate of 5.3 - 7.7/10,000 inpatient admissions. The PCV7 era (2005-2010) averaged 141 cases annually (range 142-197) with a hospitalization rate of 3.1 – 5.3/10,000 inpatient admissions. The PCV13 era (2011-2016) averaged 159 cases annually (range 153-181) with a hospitalization rate of 3.6 – 4.3/10,000 inpatient admissions. Any penicillin nonsusceptibility was 12.4% in the pre-vaccine era, 18.6% in the PCV7 era and 11.8% in the PCV13 era. Over 90% of cases in the pre-vaccine era were vaccine preventable (i.e. contained a serotype in the 13-valent vaccine) compared with 10% of cases in 2016. Serotype 19A significantly decreased in the PCV13 era (32% of cases in 2010 to 0 in 2016). The proportion of cases in children 5-9 years of age increased significantly over time, from 11% to 24%.

Conclusion

The epidemiology of pediatric IPD has changed significantly with since the implementation of PCVs.
Background and Aims:

In November 2011, Malawi introduced PCV13 vaccination (3+0) for all infants. A prospective cross-sectional study (2015-2017), in the context of high vaccine uptake, showed a slow reduction in vaccine-type (VT) carriage in vaccinated 3-6y (22-17%), a faster reduction in unvaccinated 5-10y (27-15%) and no change in unvaccinated 18-40y (HIV- infected on ART). We developed a model to investigate the dynamics and derive insights into the factors that determine the outcome of vaccine introduction in this population.

Methods:

We used Bayesian Markov-chain Monte Carlo to fit an age-structured model to these data, estimating (i) vaccine-induced reduction in individual risk of colonization, (ii) age-specific duration of carriage, (iii) age-specific risk of infection, and projecting vaccine impact 10 years into the future.

Results:

Direct vaccine-induced protection against colonization was estimated to be 88% (CI 95% 85-90). Decrease in duration of carriage with age (for which there is empirical support) was required to fit the data. The reduction in carriage among unvaccinated children (in contrast with adults) could be attributed to indirect immunity and suggests higher mixing between younger age classes.

Conclusion

This exercise indicates that PCV13 offers high levels of direct protection against colonization and some degree of indirect protection across younger ages. However, 10y projections suggest that VT carriage will remain high compared to other settings where the vaccine has been deployed. Our results underline the need to understand age-specific contact patterns and transmission routes of *S. pneumoniae* if robust herd protection in high transmission settings is to be achieved.
Background and Aims:

Kenya introduced the ten-valent pneumococcal conjugate vaccine (PCV10) in 2011 with financial support from Gavi, the Vaccine Alliance. Kenya will transition from Gavi support starting 2022 and need to either discontinue PCV use or gradually take over the full costs by 2027. We assessed the cost-effectiveness of these policy options.

Methods:

We fitted a dynamic transmission model to annual carriage prevalence surveys and invasive pneumococcal disease (IPD) incidence in Kilifi obtained two years pre- and six years post-vaccine introduction and extrapolated this to the whole of Kenya. Based on these predictions we calculated the cost-effectiveness of PCV continuation using a societal costing model.

Results:

We predict that continuing rather than discontinuing vaccination would prevent 15,355 (10,196–21,125) deaths and 112,050 (79,620–130,981) IPD and non-bacteraemic pneumonia cases between 2022 and 2032. The incremental cost per disability-adjusted-life-year averted for PCV continuation was predicted to decrease to $142 (85 - 252) in 2032, however continuation will cost US$15.6 million annually; approximately three times Kenya’s current annual immunization expenditure.

Conclusion

Continuing PCV use is essential to sustain its health gains. Based on the Kenyan GDP per capita of US$1445, and in comparison to other vaccines, continued PCV use is cost-effective. This supports an expansion of the vaccine budget, however, affordability may be a concern.
Background and Aims:

Fiji introduced 10-valent pneumococcal conjugate vaccine (PCV10) in 2012. We report risk factors of vaccine-type (VT) carriage pre- and three years post-PCV10.

Methods:

Infants (5-8 weeks), toddlers (12-23 months), children (2-6 years), and caregivers participated in nasopharyngeal (NP) carriage surveys annually pre- (2012) and post-PCV10 (2013-2015). Risk factors were documented and NP swabs were collected. Pneumococci were detected via lytA quantitative-PCR and serotyping by molecular microarray. Carriage risk factors were calculated by logistic regression.

Results:

There were 8,109 participants. VT carriage prevalence declined from 14.0% (pre) to 10.7% (2013), 5.1% (2014) and 5.7% (2015). VT carriage prevalence was 2.15- and 6.63-fold higher in children compared with infants and caregivers, and similar compared with toddlers.

VT carriage was positively associated with Indigenous ethnicity (aOR 2.7; 95%CI 2.20–3.32; p<0.001) despite similar PCV10 coverage rates; coryzal symptoms (aOR 1.41; 95%CI 1.17–1.69; p<0.001); urban residence (aOR 1.32; 95%CI 1.11-1.57; p=0.001); living with >2 children <5 years (aOR 1.22; 95%CI 1.02–1.46; p=0.026); poverty (aOR 1.29; 95%CI 1.07–1.55, p=0.008); and exposure to household cigarette smoke (aOR 1.19; 95%CI 1.00–1.42; p=0.047)

Protective factors for VT carriage were being aged 5-8 weeks (aOR 0.49; 95%CI 0.37–0.64, p<0.001) and each additional year post-PCV10, (2013 aOR 0.79; 95%CI 0.63-0.98, p=0.034, 2014 aOR 0.33, 95%CI 0.26-0.43, p<0.001, 2015 aOR 0.36; 95%CI 0.28-0.45; p<0.001).

Conclusion

Ethnicity is the strongest predictor of VT carriage and may partially explain why Indigenous Fijians have greater pneumococcal disease burden than Fijians of Indian Descent. Toddlers and older children may be VT transmission reservoirs.
OPTIMISING VACCINE FORMULATIONS TO MINIMISE DISEASE AND ANTIBIOTIC TREATMENT FAILURES

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Background and Aims:

The effectiveness of polysaccharide conjugate vaccines is limited by serotype replacement disease. Optimisation of future partial-coverage vaccines requires identifying those antigens that will result in a final population composed of the most benign strains. However, this is complicated by the ecology of the pneumococcus, which makes it difficult to predict which strains will increase in prevalence following vaccine introduction. Using a genomics-based model of post-vaccine population dynamics, this study aimed to identify vaccine formulations that minimised the burden of pneumococcal disease.

Methods:

We ran simulations using population genomic datasets, incorporating evolution under negative frequency-dependent selection (Corander et al 2017 Nat. Ecol. Evol.). Isolates’ propensity to cause invasive disease in infants and adults was inferred from their serotypes. This was calculated from a systematic meta-analysis of studies comparing serotype prevalences in carriage and disease. Different metrics were used to define disease burden scores, which were minimised through vaccine optimisation using a genetic algorithm.

Results:

Disease burdens were calculated based on expected cases in infants, across all ages, or minimising only antibiotic resistant disease. Formulations predicted to outperform the current 10 and 13-valent vaccines could be identified, while containing the same number of serotypes. However, the ideal formulation depended on the score used to optimise the design. Optimal protein-based formulations were also investigated, based on antigens identified using a panproteome array, assuming such antibodies have some inhibitory effect on bacterial transmission.

Conclusion

Modelling can aid rational vaccine design, but defining an optimal vaccine depends on the relative importance attached to different modes of pneumococcal disease.
PARALLEL 9: EPIDEMIOLOGY AND MATHEMATICAL MODELLING

ISPPD-0663
IMPROVING CREDIBILITY OF PCV IMPACT ESTIMATES USING POOLED ANALYSIS
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Background and Aims:

There is often a need to estimate the impact of pneumococcal conjugate vaccines against pneumonia using noisy data. Due to variations in pneumonia trends unrelated to vaccine (e.g., caused by respiratory virus epidemics), it can be difficult to estimate true effects. We aim to explore the use of statistical methods that pool findings between multiple studies to obtain more precise vaccine effect estimates for each individual study and to obtain average effects across all studies. These methods will be used in PAHO's analysis of the impact of PCV against mortality.

Methods:

We obtained national-level hospital administrative data on all-cause pneumonia from select countries in the PAHO region. We also simulated time series data where the vaccine effect was known. Initial estimates of PCV impact (rate ratio) were calculated for each dataset using synthetic controls. Bayesian hierarchical meta-analysis was performed to combine information and to obtain “improved” estimates for each location. Information on uptake, schedule, and other factors were considered in the model.

Results:

We will present initial estimates for each post-vaccine time point and estimates from the newly developed model. We expect the meta-analysis approach will increase the probability of detecting a true effect and will decrease bias compared with the initial estimates obtained from individual time series. Number of cases averted and relative decline will be presented for each location and time point.

Conclusion

This modeling approach will allow for the generation of credible estimates of vaccine impact, even in locations with sparse or noisy data.
BI-DIRECTIONAL ADJUVANT ACTIVITY OF CO-ADMINISTERED PNEUMOCOCCAL AND INFLUENZA A VACCINES

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Background and Aims:

Current Streptococcus pneumoniae vaccines offer limited serotype coverage, and their widespread use has ultimately led to serotype replacement. To circumvent these issues, we have developed a whole-cell inactivated S. pneumoniae vaccine. The vaccine preparation is inactivated using gamma-irradiation (generating γ-PN), which abolishes cell viability whilst antigenic proteins remain intact and functional. The vaccine strain also lacks a capsule, exposing key surface antigens that confer serotype-independent protection. Importantly, protection was induced against both vaccine and non-vaccine serotypes following non-adjuvanted intranasal vaccination with γ-PN.

Methods:

γ-PN was co-administered with an irradiated whole-influenza A vaccine (γ-Flu). Intranasal challenge models of pneumococcal and influenza infections were utilised to demonstrate vaccine efficacy.

Results:

Intranasal co-administration enhanced pneumococcal-specific IgG and IgA titres in serum. Additionally, Th17, Th1, and tissue-resident memory cell populations were heightened by co-administration, as was protection against lethal pneumococcal challenge. Importantly, recent data demonstrates bi-directional adjuvant activity. Specifically, co-administration of γ-PN and γ-Flu resulted in superior protection against lethal influenza challenges compared to vaccination with γ-Flu alone. This enhancement is related to the ability of γ-PN to modulate innate responses, particularly the cytokine milieu in the lung microenvironment to enhance influenza-specific immunity. In addition to protection against single pathogens, the bi-directional adjuvant activity associated with this novel co-vaccination approach enhanced protection against superinfection with both virulent pneumococci and influenza virus.

Conclusion

This synergistic effect between inactivated pneumococcal and influenza A vaccines could drastically reduce mortality due to influenza infections (seasonal and pandemic), and the associated enhanced susceptibility to secondary pneumococcal infection.
E-POSTER SPOTLIGHT SESSION 1

ISPPD-0170
SPREAD OF CEFTRIAXONE NONSUSCEPTIBLE PNEUMOCOCCI: NURSING FACILITIES AS A POTENTIAL RESERVOIR
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Background and Aims:
Despite pneumococcal national Immunization program, which provides free PPSV23 vaccination for older adults aged ≥65 years in South Korea, pneumococcal pneumonia still remained as one of the common respiratory infections with increasing antimicrobial resistance.

Methods:
From 2015 January to 2016 January, all pneumococcal isolates were collected at Korea University Guro Hospital. All isolates were analyzed for serotype, genotype and antimicrobial susceptibility. Demographic, clinical and microbiological data were compared between ceftriaxone susceptible and nonsusceptible cases.

Results:
Among 92 microbiologically identified Streptococcus pneumoniae, ceftriaxone nonsusceptible pneumococci were 32 cases (34.8%). Some of them also showed levofloxacin resistance (25%, 8 of 32 isolates) and multidrug resistance (96.6%, 31 of 32 isolates). Compared to ceftriaxone susceptible cases, nursing home residents were more common (15.6% versus 3.3%, p=0.047), and solid cancer was less common (9.4% versus 33.3%, p=0.011) in ceftriaxone nonsusceptible cases, although both did not reach statistical significance in multivariate analysis. Overall, pneumococcal vaccination rate was 35.7% (PPSV23, 30%; PCV13, 8.3%; both 5.0%), which was similar in both ceftriaxone susceptible and nonsusceptible cases. As for the genotypes, ST320 (10 cases), ST166 (7 cases) and ST8279 (3 cases) were dominant in ceftriaxone nonsusceptible cases, and ST8279 was all detected from prior nursing home residents. According to serotype distribution, ceftriaxone nonsusceptible pneumococci account for 53.1% of PCV13 serotype and 78.1% of PPV23 serotype.

Conclusion
Most ceftriaxone nonsusceptible pneumococci showed multi-drug resistance, and one fourth of them were even resistant to levofloxacin. Clonal expansion and spread of ceftriaxone nonsusceptible pneumococcal strains should be monitored among residents in long-term care facilities.
E-POSTER SPOTLIGHT SESSION 1

ISPPD-0191
NON-CAPSULAR ANTIBODIES REDUCE PNEUMOCOCCAL COLONISATION DENSITY FOLLOWING THERAPEUTIC ADMINISTRATION OF PNEUMOCOCCAL WHOLE CELL VACCINE
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Background and Aims:

The pneumococcal whole cell vaccine (WCV) induces immunity against non-capsular antigens, and protects mice against nasopharyngeal colonisation via antibody-independent, Th17 mechanisms when administered before infectious challenge. In high disease-burden settings infants are exposed to pneumococci soon after birth. Therefore, we investigated the effect of WCV on colonisation when administered after established colonisation (“therapeutic” vaccination).

Methods:

Infant mice were colonised with pneumococcal strain EF3030 (19F) before subcutaneous immunisation with WCV or adjuvant-only control.

Results:

Therapeutic WCV significantly reduced the density of pneumococcal colonisation in a dose dependent manner by 4.3-fold (one dose, p<0.0001) and 8.6-fold (two doses, p=0.014) compared to therapeutic adjuvant (Mann-Whitney). This reduction was dependent on non-capsular antibodies: therapeutic WCV did not affect colonisation in antibody-deficient μMT-/- mice compared to therapeutic adjuvant, and levels of plasma IgG specific for the WCV antigen (p=0.003), PspA (p=0.004), CbpA (p=0.022) and PiaA (p=0.028) were inversely correlated with colonisation density in wild type mice (Spearman's correlation). No associations between systemic, local or splenic IL-17A responses and colonisation density were observed. In addition, shedding of pneumococci from the upper respiratory tract of mice was reduced after each WCV dose (p<0.0001, Mann-Whitney).

Conclusion

Therapeutic WCV immunisation effectively reduced pneumococcal colonisation. We identified a novel role for non-capsular antibodies in controlling colonisation density. Given that WCV reduces colonisation density and shedding, it is likely that WCV could reduce pneumococcal transmission and contribute to herd protection. These data support further
investigation of WCV in high disease-burden settings where children are more likely to carry pneumococci at the time of vaccination.
E-POSTER SPOTLIGHT SESSION 1

ISPPD-0255
PREDICTING COMPLICATED PARAPNEUMONIC EFFUCTION IN CHILDREN WITH COMMUNITY ACQUIRED PNEUMONIA: A HOSPITAL BASED CASE CONTROL STUDY IN LUCKNOW, NORTH INDIA
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Background and Aims:
Complicated parapneumonic effusions (CPE) occur in about 5-10% cases with severe community acquired pneumonia (CAP) and common bacterial isolates are Streptococcus pneumoniae and Staphylococcus aureus. CPE necessitate special medical care. Aim of this study was to identify predictors of CPE using clinical and simple laboratory variables like haemoglobin (Hb), C-reactive protein (CRP) and serum albumin levels and total leukocyte counts (TLC).

Methods:
Prospective case control study after institutional ethical approval including subjects between ages of 2 -59 months with written informed parental consent. Cases has CAP with CPE diagnosed by pleural centesis. Controls had CAP without CPE on chest X-ray (CXR). Excluded were congenital and chronic diseases/infections and possible immune deficiency.

Results:
From 2016-17, included were 30 cases (66.6% males, 38.7+14.9 months) and 118 controls (78% males, 17.8+16.9 months) with CXR normal in 19 (16%), endpoint consolidation 50(42.4%), non-end-point infiltrates49(41.6%). Almost all subjects had taken prehospitalization medications, possibly antibiotics. In forward stepwise logistic regression, predictors of CPE were ibuprofen intake (adj OR 6.8,95%CI:1.07-43.6), infective focus elsewhere (adj OR 28.2;95%CI: 1.4-563.1), hypoalbuminemia <3 g/dL (adj OR 6.9;95%CI:1.22-39.3), CRP >20 mg/dL (adj OR 59;95% CI:1.86-1874.7) Hb <10g/dL (adj OR 21.1;95%CI:2.8-158.1) and TLC >10000 (adj OR 37:95%CI:5.7-239.8).

Conclusion
Using simple clinical and laboratory parameters it is possible to identify CAP with CPE and refer them to higher centre for care. Use of ibuprofen is to be avoided in CAP as it can lead to CPE.
THE MAL-IFNGR AXIS AND TIRAP-S180L POLYMORPHISM AS DETERMINANTS OF SUSCEPTIBILITY TO PNEUMOCOCCAL DISEASE AND PNEUMOCOCCAL VACCINE EFFICACY.


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Background and Aims:

TIRAP encodes the MyD88-adaptor like protein (Mal) which bridges Toll Like Receptors (TLR)2 or 4 and MyD88 signalling. Homozygous carriage of the TIRAP-S180L polymorphism associates with tuberculosis, Haemophilus influenzae (Hib) and pneumococcal infection, Hib-vaccine failure and low pneumococcal capsular antibodies. During tuberculosis Mal mediates interferon (IFN)-γ receptor (IFNGR) signalling. TIRAP-S180L attenuates Mal-IFNGR signalling in macrophages impairing mycobacterial killing. Here we investigated the role of Mal and the Mal-IFNGR axis in antipneumococcal defences and vaccine-induced antibodies.

Methods:

To establish the role of Mal in antipneumococcal defences we assessed susceptibility of Tirap⁻/⁻ and wild-type mice to invasive pneumococcal pneumonia. Bacterial killing and cytokine responses were assessed in vitro in Tirap⁻/⁻, Tlr2/4⁻/⁻, Tirap²⁰⁰L/L (murine equivalent of TIRAP¹⁸⁰L/L) or wild-type macrophages infected with pneumococci +/- IFN-γ. Finally humoral responses were compared in Tirap⁻/⁻ and wild-type mice vaccinated intramuscularly with ovalbumin formulated in polystyrene particles that act as a potent IFN-γ-inducing adjuvant in absence of TLR ligands.

Results:

Tirap⁻/⁻ mice showed increased susceptibility to pneumococcal pneumonia compared to wild-types (mean survival time 58h vs 120h). Tirap⁻/⁻ and Tlr2/4⁻/⁻ macrophages expressed lower Tnfa transcripts than Tirap²⁰⁰L/L or wild-types. However, pneumococcal killing was mainly impaired in Tirap²⁰⁰L/L and Tirap⁻/⁻ macrophages.

After vaccination Tirap⁻/⁻ mice had reduced anti-OVA IgG2c/IgG2b titres suggesting that Mal is required for class-switching.

Conclusion

Our results highlight the requirement of Mal for protection against pneumococcal pneumonia. While Mal-TLR signalling seems to be required for cytokine production, the Mal-IFNGR axis contributes to pneumococcal killing. Finally a TLR-independent role of Mal could be required for T-dependent vaccine-induced IgG class-switching.
Background and Aims:

Pneumococcal pneumonia remains a major cause of childhood mortality. New adjunctive therapies that directly modulate pulmonary immunity could offer additional protection to infants and children. Mice lacking a protein controlling cell motility, L-plastin (LPL), exhibit profound susceptibility to pneumococcal pneumonia due to impaired alveolar macrophage maturation. Alveolar macrophages form during a neonatal, time-limited developmental window. We tested if a clinically-relevant intervention, intra-nasal administration of the growth-factor GM-CSF, could rescue alveolar macrophage maturation and protect animals from subsequent pneumococcal lung infection.

Methods:

GM-CSF was administered to wild-type (WT) and LPL<sup>-/-</sup> neonatal pups on post-natal days 1, 2 and 3. Control animals received PBS. After maturing to adulthood (8 weeks of age), mice were challenged with intra-tracheal pneumococci and followed for bacterial dissemination and survival. We also analyzed alveolar macrophage numbers in mice.

Results:

GM-CSF administration restored alveolar macrophages and protected LPL<sup>-/-</sup> mice from infection. WT and LPL<sup>-/-</sup> mice receiving GM-CSF as pups had equivalent bacterial dissemination and survival as control WT animals. Control LPL<sup>-/-</sup> mice exhibited increased susceptibility, increased bacterial dissemination, and reduced alveolar macrophage numbers compared to WT mice.

Conclusion

Administration of GM-CSF to neonatal mice, during the normal time period of alveolar macrophage development, induced sustained amplification of alveolar macrophages and protected otherwise susceptible animals from pneumococcal infection. Our results show that manipulating normal developmental signals can successfully enhance anti-pneumococcal pulmonary immunity, offering a novel paradigm for developing new therapies for young children.

Acknowledgements: Funding for this project was provided by NIH R01AI104732.
E-POSTER SPOTLIGHT SESSION 1

ISPPD-0726
RAPID PNEUMOCOCCAL CLEARANCE FOLLOWING CELLULAR AND HUMORAL IMMUNE RESPONSES INDUCED IN THE BRONCHOALVEOLAR FLUIDS BY RECOMBINANT BCG PSPA-PDT PRIME / PROTEIN BOOST
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Background and Aims:

An effective immunological response in the lungs during a pneumococcal infection is a key factor to the bacterial clearance and prevention of sepsis. In order to develop broad-range pneumococcal vaccines several pneumococcal proteins and strong adjuvants have been investigated. In this context, we constructed a recombinant BCG (rBCG) strain expressing a fragment of PspA (Pneumococcal surface protein A) in fusion with PdT (detoxified form of pneumolysin). Here, we investigated the immunological response induced in the bronchoalveolar fluids (BALF) of immunized mice after pneumococcal challenge.

Methods:

Mice immunized with rBCG PspA-PdT and a single dose of recombinant PspA-PdT fusion protein were challenged intrapulmonary with the virulent WU2 pneumococcal strain. BALF samples were collected at several time points and used for evaluation of differential cell count, antibody and cytokine production. Pneumococcal loads were determined in the BALF and blood.

Results:

Immunization with rBCG PspA-PdT/rPspA-PdT promoted a rapid clearance of the pneumococci, reduced the cellular influx and inflammatory cytokine levels in the BALF. In addition, rBCG PspA-PdT/rPspA-PdT induced higher lymphocyte recruitment to the lungs at 48 h, showing an increased percentage of CD4+ T cells. Furthermore, BALF samples from mice immunized with rBCG PspA-PdT/PspA-PdT showed high binding of IgG2c and enhanced complement deposition on the pneumococcal surface.

Conclusion:

These results suggest that immunization with rBCG PspA-PdT/rPspA-PdT induces humoral and cellular immune responses in the lungs, promoting an early clearance of pneumococci, which protects against the systemic dissemination of the pneumococci and consequently increases mouse survival.

Financial support: Fundação Butantan.
E-POSTER SPOTLIGHT SESSION 1

ISPPD-0747
SYSTEMIC ANTIBIOTICS PRESCRIPTION RATES AND PATTERNS IN INDIA: EVIDENCE FROM PRIVATE SECTOR MEDICAL AUDIT DATA
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Background and Aims:
Evidence suggest that high per-capita antibiotic consumption is correlated with higher rates of antibiotic resistance. Given that India was one of the top consumers of antibiotics in 2010, the aim of the present study was to describe systemic antibiotic (J01) prescription rate and pattern in India by analysing private sector’s antibiotic prescribing data.

Methods:
We analysed IMS medical audit data to estimate systemic antibiotics consumption in the Indian private sector for the year 2014. We reported antibiotic use as annual prescription rate per 1,000 persons. Antibiotic utilization was plotted and reported by age group, antibiotic class and disease condition. We used statistical software STATA 14.0 to perform the analytics.

Results:
In India, approximately 519 million antibiotic prescriptions were dispensed in the private sector, which translates into 412 prescriptions per 1,000 persons. The top five disease conditions that contribute approximately 50% of the prescriptions were acute upper respiratory infections (J06) (20.4%), unspecified acute lower respiratory infection (J22) (12.8%), other disorders of urinary system (N39) (6.0%), cough (R05) (4.7%) and acute nasopharyngitis (J00) (4.6%). The antibiotic prescription rates were highest in the age group 0-4 years (636 prescriptions per 1,000 persons) and lowest in the age group 10-19 years (280 prescriptions per 1,000 persons). The most commonly prescribed antibiotic class was cephalosporins (J01D) (38.2%) followed by penicillins (J01C) (22.8%), quinolones (J01M) (16.3%) and macrolides (J01F) (14.0%).

Conclusion
Our study has provided first ever national level estimates on antibiotic prescription pattern in terms of usage by age, antibiotic class, and disease conditions.
REGULATORY T CELLS RECRUIT IN RESPONSE TO INTRADERMAL STREPTOCOCCUS PNEUMONIAE CHALLENGE AND CAN MODULATE MACROPHAGE INFLAMMATORY RESPONSES IN VITRO

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Background and Aims:

Regulatory T cells (Tregs) are a population of anti-inflammatory cells that may protect against excessive inflammatory responses. We aimed to investigate whether Tregs are recruited to the site of S. pneumoniae challenge, and whether Tregs can modulate the macrophage inflammatory response to S. pneumoniae in vitro.

Methods:

Intradermal injection of UV-killed S. pneumoniae into the forearm of healthy volunteers, followed by flow cytometry assessment of local T cell responses. Measurement of cytokine responses to S. pneumoniae in cell culture of monocyte-derived macrophages (MDMs) with or without incubation with Tregs.

Results:

In the human challenge model, there was a 5-fold increase in the CD3+ T cells present at the site of injection from 4 to 48 hours. There was a 10-fold increase in the number of Tregs and their proportion of all CD4+ cells increased from 13% to 40%. In vitro, pre-incubation with Tregs (isolated from PBMCs using flow cytometry sorting) reduced the TNFα inflammatory response of MDMs to co-culture with S. pneumoniae. Transwell experiments showed the suppressive effect on MDM TNFα production required contact between the MDMs and Tregs. In conclusion, in humans a S. pneumoniae challenge rapidly recruits Tregs to the site of infection, and in vitro co-culture experiments demonstrate that Tregs can modulate the MDM TNFα response to S. pneumoniae.

Conclusion

These results suggest a potential role for Tregs in limiting inflammatory responses in S. pneumoniae infection that could be important for disease pathogenesis by reducing associated consolidation, barrier breakdown and septic shock.
ISPPD-0398
DIAGNOSIS OF CHILDHOOD PNEUMOCOCCAL PNEUMONIA IN NEPAL USING HOST RNA EXPRESSION SIGNATURES

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Background and Aims:

Current diagnostic tests for pneumonia aetiology lack sensitivity and/or specificity. We hypothesised that host RNA expression could discriminate between pneumococcal infection and other infectious aetiologies in children with pneumonia.

Methods:

We collected clinical data and blood samples in RNA-stabilising tubes from consecutive children admitted with pneumonia to Patan Hospital, Kathmandu, Nepal; and healthy infant controls. Following whole transcriptome sequencing (Illumina HiSeq4000) 75bp paired end reads were aligned, gene counts calculated and differential gene expression determined between children meeting stringent a priori definitions of definite or highly probable pneumococcal pneumonia (PP) versus definite other bacterial pneumonia (DOB). A Pneumococcal Gene Score (PGS) was calculated based on the transcriptomic signature of differentially expressed genes, summating normalised expression differences.

Results:

554 children were enrolled. Samples from <48 h following admission were available from 11 children with PP and 8 children with DOB. Of the remaining children, 91 samples were sequenced, as were 25 samples from healthy infant controls. 65 genes were differentially expressed (false discovery rate 0.001) between PP and DOB. The PGS discriminated between PP and DOB with a sensitivity of 91% and specificity of 100% and was robust to "leave-one-out" cross-validation. Amongst samples from children with pneumonia of unproven aetiology, the probability of a "positive" PGS was correlated with an increased a priori probability of pneumococcal pneumonia.

Conclusion

In this case series a gene expression signature from whole blood accurately discriminated between PP and DOB pneumonia. However, further validation, particularly in infants and children with diverse severities of pneumococcal and non-pneumococcal pneumonia is needed.
E-POSTER SPOTLIGHT SESSION 2

ISPPD-0409
A NATIONWIDE OUTBREAK OF INVASIVE PNEUMOCOCCAL DISEASE (IPD) CAUSED BY STREPTOCOCCUS PNEUMONIAE SEROTYPE 2 (SP2) IN THE PCV13 ERA IN ISRAEL

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Background and Aims:

IPD caused by Sp2 is relatively rare and outbreaks were not reported post-PCV implementation. We describe a Sp2 IPD outbreak in Israel, in the PCV13 era.

Methods:

An ongoing, population-based, nationwide active surveillance, conducted since July 2009. PCV7/PCV13 were implemented in July 2009/November 2010, respectively. Sp2 IPD isolates were tested for antimicrobial susceptibility and 26.5% (27/102) for MLST.

Results:

Overall, 102/5,156 (2.0%) IPD episodes (2009-2017) were caused by Sp2. During 2016-2017, Sp2 caused 7.3% (48/656) of IPD episodes and was the most common IPD serotype in Israel (Figure 1).

Sp2 IPD rates (per 100,000) sharply increased 7-fold (0.08 in 2009-2010; 0.56 in 2016-2017). This increase was observed in both children and adults. (Figure 2) All Sp2 isolates were penicillin susceptible (MIC <0.06 μg/mL); bacteremic pneumonia comprised 77.5% (62/80 with available data). In 2014-2017, 84.6% of Sp2 IPD episodes were caused by a single ST-13578 clone, not previously documented worldwide. The outbreak is still ongoing.
Conclusion

We describe the first widespread Sp2 outbreak since PCV13 introduction worldwide, caused by an emerging clone. A further follow-up is needed to determine whether this is part of the serotype replacement phenomenon or a single outbreak event.
E-POSTER SPOTLIGHT SESSION 2

ISPPD-0481
PNEUMOCOCCAL CARRIAGE AND SEROTYPES OF INDIGENOUS CHILDREN IN A VACCINE RCT COHORT
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Background and Aims:
To observe Streptococcus pneumoniae carriage using aggregate data from 2012 - 2016 from the ongoing PREVIX-COMBO and BOOST vaccine trials in Northern Australia.

Methods:
Nasopharyngeal swabs have been collected from children aged 1, 2, 4, 6, 7, 12, 18 and 36 months. Pneumococci isolated through microbiological culture were tested for antimicrobial susceptibilities and serotyped by the Quellung method.

Results:
Preliminary data show capsular pneumococcal carriage rates increased from 33% of children at 1 month plateauing at ~70% from 4 to 36 months. At combined time-points, 85-88% of serotypes were non-vaccine types, with 55 different serotypes isolated. In 2012-14, 16F accounted for 19-22% of pneumococcal isolates, dropping to 12% in 2015, replaced by 11A (16%) as the most common carriage type. Multi-drug resistance (MR) peaked at 12% of isolates in 2014, with a dominant 7B clone (97% of MR-isolates), dropping to 8% in 2015 (55% MR-7B). Azithromycin resistance ranged from 22-36% of isolates in 2012-5, with 15A the most common resistant type. Penicillin resistance remained steady at 2-3% 2012-4, increasing to 9% in 2015, most often in serotypes 11A and 16F.

Conclusion
This population continues to have high nasopharyngeal pneumococcal carriage rates, with a diverse range of largely non-vaccine types. There has been a rise in 11A carriage, replacing 16F as the most common type.
E-POSTER SPOTLIGHT SESSION 2

ISPPD-0561
RE-EMERGENCE OF INVASIVE PNEUMOCOCCAL DISEASE (IPD) CAUSED BY 12F SEROTYPE IN ADULTS, JAPAN: THE CHARACTERISTIC FEATURES OF DISEASE
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5National Hospital Organization- Mie Hospital, Department of Medicine, Tsu, Japan
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7Sapporo Medical University School of Medicine, Department of Respiratory Medicine and Allergology, Sapporo, Japan
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10Kagoshima University Graduate School of Medical and Dental Sciences, Department of Microbiology, Kagoshima, Japan
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Background and Aims:

Streptococcus pneumoniae serotype 12F is considered to be highly invasive. A previous study reported a transient predominance of 12F serotype as the cause of adult IPD around 2006 to 2007 in Japan. We recently found a re-emergence of 12F serotype-IPD between 2015 and 2016 though a nationwide IPD surveillance among adults in 10 provinces, Japan. The aim of this study is to characterize the clinical features of IPD cases caused by 12F serotype in comparison to IPD cases caused by other serotypes among adults.

Methods:

A total of 881 cases, registered in an enhanced IPD surveillance among adults between April 2013 and March 2017, were analyzed. The characteristics of 61 IPD cases by serotype 12F were compared with those of 820 IPD cases by the other serotypes using an univariate analysis.

Results:

The 12F serotype IPD cases were reported in Niigata, Yamagata and other prefectures in 2015 and 2016. All cases were sporadic. Significantly differences found between IPD cases by serotype 12F and the other serotypes were the median age (p=0.03), age group older than 65 years (OR 0.58, 95%CI 0.33-0.99), the proportion of underlying disease (OR 0.02, 95%CI 0.33-0.95), and fatal outcome in age older than 65 years (OR 0.17, 95%CI 0.05-0.59).

Conclusion
The 12F serotype IPD is likely to occur in younger adults without underlying diseases, and the fatal outcome is less often in age older than 65 years. This epidemiological pattern supports a high invasiveness of serotype 12F.
E-POSTER SPOTLIGHT SESSION 2

ISPPD-0602
UNDERSTANDING THE LINKS BETWEEN NON-INVASIVE AND INVASIVE PNEUMOCOCCAL DISEASE IN CHILDREN WITH SEVERE PNEUMONIA THROUGH COMPARATIVE GENOMICS

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2Centre of Disease Control and Prevention, Respiratory Diseases Branch, Atlanta, USA
3Emory University, Global Health, Atlanta GA, USA
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5University of Auckland and Centre for International Health- University of Otago, Paediatrics, Dunedin, New Zealand

Background and Aims:

Severe pneumonia is a major cause of mortality among infants in The Gambia. Towards understanding the relationship between pneumococcal isolates from non-sterile specimens and invasive pneumococcal disease (IPD), we performed comparative genomics on paired pneumococci from infants with severe pneumonia.

Methods:

Whole genome sequencing was performed on 26 pneumococci isolated from non-invasive sites [nasopharyngeal swab (NPS) and/or Induced sputum (IS)] and/or IPD [blood or lung aspirate (LA)], in infants with severe pneumonia from the PERCH study. Phylogenetic and pan genome analyses were performed and visualised using Phandango.

Results:

For 4 patients the same genotype was isolated from non-invasive and sterile sites. However the invasive and non-invasive isolates differed in the core genome [range: 3 to 23 single nucleotide polymorphisms (SNPs)], and the invasive isolates had unique accessory genes compared to their paired non-invasive isolates. Among these 4 patients, one had the same genotype in NPS, IS and blood: the non-invasive isolates differed from each other by 3 SNPs but they differed from the invasive isolate, which had unique accessory genes, by 11 and 12 SNPs respectively. Unrelated non-invasive and invasive genotypes were found in 6 patients: one patient had identical genotypes (5 SNPs) from blood and LA. The final patient also had the same strain in blood and LA (2 SNPs).

Conclusion

Our data suggests that non-invasive strains may acquire important mutations and accessory genes as they transit to cause severe pneumonia. Our data also suggested a genotypic bottleneck in non-invasive and monoclonality of invasive diseases isolates from different invasive sites.
E-POSTER SPOTLIGHT SESSION 2

ISPPD-0740

COMPARISON OF ONE-MONTH WITH TWO-MONTH PCV10 PRIMING INTERVAL ON PNEUMOCOCCAL CARRIAGE AMONGST NEPALESE CHILDREN

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Background and Aims:

Pneumococcal conjugate vaccines (PCVs) reduce pneumococcal disease burden through direct immunological protection and by preventing transmission through the reduction of nasopharyngeal (NP) carriage. The WHO had previously recommended a two month interval between priming doses of PCVs however, due to programmatic reasons PCV10 was introduced into Nepal in 2015 using a 6 and 10-week priming schedule followed by a booster at 9 months. We investigated the impact of different priming schedules on NP carriage of pneumococci.

Methods:

We conducted an open-label, parallel group, randomised controlled trial in healthy infants aged 40-60 days in Kathmandu, Nepal. Participants were randomised to receive PCV10 at either 6 and 10 weeks (6+10) or 6 and 14 weeks (6+14) of age, followed by a 9-month booster in both groups. Nasopharyngeal swabs were collected from participants, processed according to WHO guidelines, and serotyped by Quellung reaction. Overall pneumococcus and vaccine-type carriage prevalence were analysed at 6 weeks and 10 months of age.

Results:

Analysis showed no difference between the two groups (6+10 vs 6+14) in overall pneumococcal carriage at 6 weeks 31/152 vs 29/152 (p=0.89) and at 10 months 79/142 vs 91/144 (p=0.23) nor in vaccine-type carriage (denominator is all children swabbed) at 6 weeks 5/152 vs 2/152 (p=0.45) and at 10 months 13/142 vs 12/144 (p=0.84).

Conclusion

There was no evidence of a difference in carriage prevalence after immunisation according to the two different vaccine schedules (6+10 vs 6+14 weeks). To evaluate long-term impact ongoing surveillance of pneumococcal carriage prevalence is needed.
Background and Aims:

Recent studies have showed the impact of PCV13 pneumococcal vaccine globally. The present study characterised population structure, strain type and genomic cluster (GC) diversity, antibiotic resistance and accessory genome dynamics of carried pneumococci sampled pre- and post-PCV13 introduction (2011) in northern Malawi.

Methods:

Population genomics was used to analyse 660 whole genomes from pneumococcal carriers of all ages pre-vaccination (2009-2010 [n=482]) and 3 years post-vaccination (2014 [n=178]).

Results:

Moderate reduction of vaccine type (VT) serotypes occurred in <5y (Gini-Simpson’s D:0.886-0.865, P=0.068), while serotype and sequence type diversity remained unchanged among non-VTs (NVTs). Compared to pre-vaccination era, VT serotypes decreased consistently across GCs in <5y olds (49·46-27·12%, P <0.0001) post-vaccination but not in ≥5y olds but individually none showed significant reductions. Conversely, NVTs serotypes 7C (0·80-
6.15%, OR=6.84, P=0.001), 15B/C (2.66%-9.23%, OR=3.64, P=0.004) and 23A (0-2.31%, OR=11.78, P=0.02) clonally expanded in <5y while 28F emerged both in <5y (0.5.38%, OR=24.32, P=0.0001) and ≥5y olds (0-6.25%, OR=9.32, P=0.03). Phylogenetic analysis showed that clonal expansion of previously masked NVTs rather than capsule-switching drove their upsurge post-vaccination. Antibiotic resistance rates were low and remained unchanged post-vaccination but interestingly, genotypically-predicted penicillin MICs decreased (P<0.01) driven by post-vaccination reduction of serotype 3-ST700 (GC12). Despite high stability of the accessory genome post-vaccination, frequency of certain genes (e.g. macB and kfoC) changed (P<0.0001) reflecting frequency-dependent selection.

**Conclusion**

These findings signify remarkable population-wide vaccine-induced changes as the equilibrium serotype distribution is gradually re-established after serotype replacement is complete. Monitoring for consequential genotypic and phenotypic changes in pneumococci requires continued surveillance and genomic analyses.
E-POSTER SPOTLIGHT SESSION 2

ISPPD-0770
EFFECT OF PCV10 AND PCV13 ALTERNATIVE SCHEDULES ON PNEUMOCOCCAL CARRIAGE IN VIETNAM: RESULTS FROM A PHASE II/III TRIAL
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Background and Aims:

Reduced dose PCV schedules could be cost-effective for national vaccination programs, but their efficacy is unknown. In a Phase II/III trial, we evaluated the effect of various infant schedules of PCV10 and PCV13 on pneumococcal carriage in 18 month olds in Ho Chi Minh, Vietnam.

Methods:

Nasopharyngeal swab samples were collected according to WHO guidelines. Pneumococci were detected by lytA qPCR and molecular serotyping conducted by microarray.

Results:

Table 1: Carriage prevalence (95%CI) at 18 months of age

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Number</th>
<th>All Pneumococci</th>
<th>PCV10 types</th>
<th>Non–PCV10 types</th>
<th>3/6A/19A types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synflorix 3+1</td>
<td>137</td>
<td>22.6 (15.9–30.6)</td>
<td>6.8 (3.2–12.5)</td>
<td>12.9 (7.7–19.8)</td>
<td>5.3 (2.2–10.6)</td>
</tr>
<tr>
<td>Synflorix 3+0</td>
<td>122</td>
<td>22.1 (15.1–30.5)</td>
<td>8.3 (4.1–14.8)</td>
<td>14.2 (8.5–21.7)</td>
<td>4.2 (1.4–9.5)</td>
</tr>
<tr>
<td>Synflorix 2+1</td>
<td>220</td>
<td>18.6 (13.7–24.4)</td>
<td>5.5 (2.8–9.3)</td>
<td>14.1 (9.8–19.4)</td>
<td>2.7 (1.0–5.8)</td>
</tr>
<tr>
<td>Synflorix 1+1</td>
<td>189</td>
<td>19.0 (13.7–25.4)</td>
<td>8.5 (4.9–13.4)</td>
<td>11.1 (7.0–16.5)</td>
<td>5.3 (2.6–9.5)</td>
</tr>
<tr>
<td>Schedule</td>
<td>Number</td>
<td>All Pneumococci</td>
<td>PCV10 types</td>
<td>Non–PCV10 types</td>
<td>3/6A/19A types</td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
<td>-----------------</td>
<td>-------------</td>
<td>-----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Prevnar 2+1</td>
<td>220</td>
<td>23.6 (18.2–29.8)</td>
<td>6.0 (3.2–10.1)</td>
<td>17.1 (12.4–22.8)</td>
<td>3.7 (1.6–7.2)</td>
</tr>
<tr>
<td>Control</td>
<td>375</td>
<td>28.3 (23.8–33.1)</td>
<td>14.2 (10.8–18.3)</td>
<td>14.0 (10.6–18.0)</td>
<td>5.5 (3.4–8.3)</td>
</tr>
</tbody>
</table>

Compared to unvaccinated controls, PCV10 carriage was lower for each schedule—including for the reduced dose group (2 doses; given at two and six months). There were no differences observed between PCV10 and PCV13 2+1 schedules. Administration of a booster dose reduced PCV10 carriage.

**Conclusion**

Carriage of PCV10 serotypes declined for most schedules and both vaccines. Future analyses conducted at 24 months will provide insight into long-term effects of reduced dose schedules and booster doses.
E-POSTER SPOTLIGHT SESSION 3

ISPPD-0286
DEFINING THE LINEAGES OF THE PNEUMOCOCCAL SPECIES: A LARGE SCALE, MULTI-CONTINENT WHOLE GENOME ANALYSIS

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³National Institute for Communicable Diseases, Centre for Respiratory Diseases and Meningitis, Johannesburg, South Africa
⁴Malawi-Liverpool-Wellcome-Trust, Clinical research programme, Blantyre, Malawi
⁵MRC Unit The Gambia, Vaccines and Immunity Theme, Serekunda, The Gambia
⁶University of the Witwatersrand, Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, Johannesburg, South Africa
⁷Emory University, Rollins School Public Health, Atlanta, USA
⁸University of Edinburgh, Queens Research Institute, Edinburgh, United Kingdom
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Background and Aims:

Understanding pneumococcal genetic variation is increasingly important for studies of conjugate vaccine impact and beyond. Genotyping methods, such as MLST, are incomplete representations of population structure, and published whole-genome studies have used clustering nomenclature specific to their datasets. We aimed to provide a portable definition of pneumococcal lineages, highlighting key lineages of global clinical relevance and genomic signatures of successful lineages.

Methods:

We assessed 12,439 genomes, representing 29 countries, in Africa (65%), North America (13%), Asia (10%), South America (9%), and Europe (3%). Isolates were from carriage (40%) or disease (60%). Global pneumococcal sequence clusters (GPSCs) were defined using kmer-based genome-wide similarity. Odds ratios were used to estimate invasiveness of GPSCs from countries submitting carriage and disease isolates. Recombination was assessed using Gubbins.

Results:

We resolved 351 lineages (GPSCs), down to singleton isolates. Ninety GPSCs accounted for 90% of the collection. GPSCs containing >200 isolates had high geographical Simpson’s Diversity. The largest lineage, GPSC1, revealed three clinically-recognised clones (PMEN32-CC230, PMEN37-CC199, PMEN1-CC81) share detectable common ancestry, and represent three successful trajectories of a single lineage. Recombination frequency per lineage was...
associated with serotype switch frequency (p<0.0001). GPSCs with high invasiveness odds ratios had low genetic diversity, measured by median-SNP distance.

Conclusion

Depth and geographical breadth of sampling allowed assignment of isolates to GPSCs, which likely represent much of the current global population of pneumococci. These definitions allow high resolution context for subsequent analysis of serotype dynamics, invasiveness, comparisons of lineages and population structure between studies, and elucidation of the mechanisms promoting successful lineages.
IS STREPTOCOCCUS PNEUMONIAE SEROTYPE 3 MASKING PCV13-MEDIATED HERD IMMUNITY IN ADULTS HOSPITALIZED WITH COMMUNITY ACQUIRED PNEUMONIA?

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Background and Aims:

The 13-valent pneumococcal conjugate vaccine (PCV13) has recently been shown effective against pneumococcal community acquired pneumonia (CAP-Spn). In Canada, the benefits of PCV13 for adults were unclear, given anticipated herd immunity from routine infant immunization with PCV13 since 2010. This study aimed to describe the clinical outcomes and serotype distribution in Canadian adults hospitalized with CAP-Spn from 2010 to 2015.

Methods:

Active surveillance for CAP was performed in adult hospitals across five Canadian provinces from 2011 to 2015, collecting patient demographics and outcomes. CAP-Spn cases were identified using sputum or blood culture, or using a PCV13-specific urine antigen detection (PCV13-UAD). Serotype was assigned using Quellung reaction, PCR, or PCV13-UAD.

Results:

A diagnostic test for S. pneumoniae was performed on 6687 CAP cases. S. pneumoniae positivity decreased from 22.1% in 2011 to 10.2% in 2014, but increased to 14.3% in 2015. PCV13 serotypes followed a similar trend, dropping from 17.7% in 2010 to 6.2% in 2014, but increasing to 8.5% in 2015. The decline in PCV13 serotypes was attributed to serotypes 7F and 19A (18.5% to 11.6% and 27.2% to 18.6%, respectively); however, the proportion of serotype 3 increased over time (15.5% to 34.9%). The burden of CAP-Spn remained unchanged in terms of requirement for mechanical ventilation, intensive care unit admission, and 30-day mortality.

Conclusion
CAP-Spn remains a significant cause of morbidity and mortality in hospitalized Canadian adults. Herd immunity afforded by serotypes 7F and 19A appears to be masked by a concomitant increase in serotype 3.
E-POSTER SPOTLIGHT SESSION 3

ISPPD-0373

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3Government of Fiji, Ministry of Health and Medical Services, Suva, Fiji
4Children's Hospital No. 2, N/a, Ho Chi Minh City, Vietnam
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6National Children's Hospital, N/a, Hanoi, Vietnam
7Government of Mongolia, Ministry of Health, Ulaanbaatar, Mongolia
8International Union Against Tuberculosis and Lung Disease, Child Lung Health Division, Paris, France
9Medical Research Council Unit, Pneumococcal Surveillance Project, Fajara, The Gambia
10London School of Hygiene and Tropical Medicine, Department of Infectious Disease Epidemiology, London, United Kingdom

Background and Aims:

WHO updated the 2005 definition of severe childhood pneumonia so that lower chest wall indrawing ceased to be a sign requiring hospitalisation. The epidemiology of severe pneumonia using the 2005 and 2013 WHO definitions, and the impact these different definitions have on pneumonia epidemiology is described.

Methods:

Pre-PCV data were obtained from hospitalised pneumonia studies in children 2-23 months old from 7 sites in 6 countries. Pneumonia was reclassified as severe using both WHO definitions. The percentage and incidence of all-cause pneumonia hospitalisations that were severe (table) or had radiological pneumonia (not shown), according to each definition, were summarised.

Results:

There were 24,287 pneumonia hospitalisations. Between 64.5% and 97.4% of sites reported chest wall indrawing.

<table>
<thead>
<tr>
<th></th>
<th>Fiji</th>
<th>Laos</th>
<th>Mongolia</th>
<th>Vietnam</th>
<th>Malawi</th>
<th>The Gambia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage (and number) of pneumonia hospitalisations due to severe pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>67·4% (2193/3254)</td>
<td>81·8% (555/678)</td>
<td>76·6% (2337/3051)</td>
<td>59·2% (155/262)</td>
<td>50·0% (190/380)</td>
<td>71·1% (11163/15709)</td>
</tr>
<tr>
<td>2013</td>
<td>56·5% (1838/3254)</td>
<td>56·6% (384/678)</td>
<td>46·6% (1422/3051)</td>
<td>27·1% (71/262)</td>
<td>42·9% (163/380)</td>
<td>21·2% (3327/15709)</td>
</tr>
</tbody>
</table>
### Annual incidence (95% CI) of severe pneumonia hospitalisations per 100,000 children <24m

<table>
<thead>
<tr>
<th>Year</th>
<th>Definition</th>
<th>2005 (95% CI)</th>
<th>2013 (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1671·4 (1595·1, 1750·5)</td>
<td>1370·4 (1301·3, 1442·2)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3003·3 (2995·7, 3010·3)</td>
<td>1827·4 (1819·7, 1834·3)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5034·4 (4358·7, 5780·9)</td>
<td>4319·0 (3692·8, 5017·1)</td>
<td>&lt;0·001</td>
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<td>5305·4 (4928·3, 5703·8)</td>
<td>2062·8 (1830·3, 2316·8)</td>
<td>&lt;0·001</td>
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</table>

**Conclusion**

Without any pneumonia intervention, hospitalised pneumonia will decline if the 2013 WHO definition has been adopted during the observation period.
E-POSTER SPOTLIGHT SESSION 3

ISPPD-0597
SHAM VACCINATION WITH PENTAVALENT VACCINE (DPT-HepB-Hib) TO ESTIMATE BIAS IN OBSERVATIONAL EFFECTIVENESS STUDIES OF PNEUMOCOCCAL CONJUGATE VACCINES.
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Background and Aims:
Non-randomised observational studies of vaccine effectiveness are susceptible to bias/confounding. Prior to conducting a study of Pneumococcal Conjugate Vaccine we estimated the magnitude of this bias by assessing the effectiveness of Pentavalent vaccine (DPT-HepB-Hib) on vaccine-neutral outcomes.

Methods:
This was a retrospective birth cohort study of children born after 31st December 2009 followed until 31st December 2016 nested in a demographic, clinical and vaccine surveillance system in Kilifi, Kenya. Exposure was first dose of the pentavalent vaccine. Outcomes were hospitalization for conditions not targeted by the vaccine or all-cause mortality. Children entered risk at age 6 weeks. They exited risk at 5 years, at out-migration or death. Using Cox Regression, we calculated hazard ratios adjusting for potential confounders which included sex, mother’s age, parity, distance to hospital and location of birth.

Results:
There were 56,454 children contributing 114,138 person years including 519 deaths and 3,103 hospital admissions. Pentavalent vaccine was associated with hospitalization (HR 1.73, 95% CI 1.52-1.96) but was protective against all-cause mortality (HR 0.52, 95% CI 0.43-0.62) and inpatient mortality (HR 0.71, 95% CI 0.52-0.98).

Conclusion
Children who have been vaccinated with Pentavalent vaccine are more likely to be brought to hospital when sick, less likely to die following hospital admission, and much less likely to die in the community – suggesting a degree of parental involvement in health. The magnitude of this bias, which did not decline with adjustment, makes interpretation of non-randomized vaccine effectiveness studies difficult.
E-POSTER SPOTLIGHT SESSION 3

ISPPD-0638
EXPLAINING DEPARTURES FROM NEUTRALITY IN PNEUMOCOCCAL COLONIZATION PATTERNS: PATHOGEN INTERACTIONS VS HOST HETEROGENEITY

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Background and Aims:

In the epidemiology of multi-strain pathogens, it is common to attribute non-neutral co-colonization patterns to interactions between pathogen strains – e.g. competition if the frequency of co-colonized hosts is less than expected, and facilitation if co-colonization is more frequent than expected under a model where strains circulate independently.

Methods:

Mathematical models are developed to confront this with alternative explanations based on host heterogeneity in risk to acquire pneumococcal carriage.

Results:

We show that, in theory, pathogen interactions and host heterogeneity can explain the same departures from neutrality.

Conclusion

We propose practical study designs to quantify the contribution of each process to overall deviations from neutral expectations in pneumococcal colonization patterns.
E-POSTER SPOTLIGHT SESSION 3

ISPPD-0647
INDIRECT EFFECT OF SIX YEARS OF CHILDHOOD PCV10/13 VACCINATION ON INVASIVE PNEUMOCOCCAL DISEASE IN THE ELDERLY OF 10 EUROPEAN COUNTRIES: IMPLICATIONS FOR ELDERLY VACCINATION
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⁶ECDC, Disease Program, Stockholm, Sweden

Background and Aims:
SpIDnet and I-MOVE+ networks conduct population-based surveillance for invasive pneumococcal disease (IPD) in elderly at 13 sites (10 countries). Since 2010-11, childhood pneumococcal conjugate vaccination (PCV) is implemented with PCV13 in six sites, PCV10 in two and both PCV10/13 in five. We estimated the indirect effect of childhood PCV10/13 vaccination on elderly IPD to support decision-making on pneumococcal vaccination policies, including PCV13 and 23-valent vaccines (PPV23).

Methods:
We calculated IPD incidence rate ratios (IRR) in ≥65 year-olds, by site, comparing the last PCV10/13 year (2016) to 2009 (pre-PCV10/13). We computed pooled IRR and 95% confidence intervals (CI) using random-effects meta-analysis, and the indirect effect as (1-IRR)*100.

Results:
After six PCV10/13 years, elderly IPD incidence caused by any, PCV7 and PCV13 non-7 serotypes declined by 11% (95% CI: -1 to 20), 79% (68-86) and 41% (19-58), respectively. The incidence of non-PCV13 serotypes, PPV23 non-PCV13 and non-vaccine serotypes increased by 66% (38-99), 59% (42-79) and 77% (38-128), respectively. In 2016, PCV13 and PPV23 non-PCV13 serotypes caused 30% and 47% of IPD. PCV13 non-7 IPD incidence declined 54% in PCV13 sites and increased 19% in PCV10 sites.

Conclusion
Declines in PCV13 serotype IPD incidence in the elderly indicate an indirect effect of childhood PCV10/13 but reduce the proportion of IPD in the elderly that can be prevented by PCV13 in that group. The rise in non-PCV13 serotype incidence, suggesting serotype replacement, increased the proportion of elderly IPD caused by serotypes unique to PPV23. Decision-making on elderly pneumococcal vaccination must take into account the indirect effect of the childhood PCV programme.
CASE-CONTROL STUDY TO EVALUATE PNEUMOCOCCAL VACCINES EFFECTIVENESS AGAINST INVASIVE PNEUMOCOCCAL DISEASE (IPD) AMONG U.S. MEDICARE BENEFICIARIES ≥65 YEARS OLD

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Background and Aims:

PCV13 and PPSV23 in series were recommended for all U.S. adults >65 years in 2015. We evaluated effectiveness of PCV13 and PPSV23 against IPD among Medicare beneficiaries >65 years old to assess this new policy.

Methods:

We linked records for IPD cases (pneumococcus isolated from sterile sites) identified through Active Bacterial Core surveillance with Medicare beneficiaries. Isolates were serotyped and classified as PCV13, PPSV23, and non-vaccine types. We matched controls to cases on age, residence census tract, and length of Medicare enrollment; we included all eligible controls. Vaccination histories were obtained through Medicare. We estimated vaccine effectiveness (VE) as one minus the IPD odds ratio for vaccinated (PCV13, PPSV23, or both) vs. unvaccinated persons using conditional logistic regression, adjusted for sex and underlying conditions.

Results:

From 2,246 IPD cases identified in 2015-2016, 1,017 (45%) were matched to Medicare beneficiaries. We included 699 eligible cases and 10,152 controls. PCV13-types (+6C) and PPSV23 serotypes accounted for 164 (23%) and 350 (50%) cases, respectively. Fourteen percent, 22%, and 8% of cases and 18%, 21%, and 8% of controls received PCV13 only, PPSV23 only, or both vaccines, respectively. PCV13-only VE against PCV13-types was 36%
VE was 26% (95% CI -58, 65%) against serotype 3 and 67% (95% CI 11, 88%) against other PCV13-types (+6C). PPSV23-only VE against PPSV23-types was 15% (95% CI -16, 37%). Neither vaccine showed effectiveness against non-vaccine types.

**Conclusion**

PCV13 was effective in preventing IPD caused by PCV13-types when excluding type 3; no effectiveness was demonstrated against serotype 3.
E-POSTER SPOTLIGHT SESSION 3

ISPPD-0774
NASOPHARYNGEAL PNEUMOCOCCAL CARRIAGE AMONG AMERICAN INDIAN CHILDREN AND ADULTS DURING ROUTINE USE OF THE 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV13)

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Background and Aims:

American Indians in the southwest US experience high rates of invasive pneumococcal disease and, historically, have had high pneumococcal carriage prevalence. We evaluated carriage during routine PCV13 use among children and recent PCV13 introduction among adults >65 years.

Methods:

American Indians aged <5 and >=18 years were enrolled continuously from October 2015-September 2017. Nasopharyngeal swabs were collected and oropharyngeal swabs from adults only. Pneumococci were isolated by broth enrichment culture and serotyped by cps gene sequencing supplemented with Quellung. PCV13 history was obtained by chart review.

Results:

Nasopharyngeal carriage was identified in 49.5% (297/600) of <5-year olds, 8.9% (53/597) of 18-64-year olds and 6.0% (18/299) of >=65 year olds. Oropharyngeal carriage was identified in 0.3% (2/602) of 18-64-year olds and 1.0% (3/299) of >=65 year olds. PCV13-type carriage prevalence was 5.0% (30/600) in <5-year olds, 1.5% (9/602) in 18-64-year olds, and 1.0% (3/300) in >=65 year olds. PCV13-types 3, 9V, 19A, 19F and 23F were identified; serotypes 3 (n=16, <5 years; n=3, 18-64 years; n=1, >=65 years) and 19F (n=10, <5 years; n=6, 18-64 years; n=2, >=65 years) predominated. 97% of <5-year olds and 75% of >=65 year olds had received >=1 PCV13 dose.

Conclusion

Low levels of PCV13-type carriage persist (3, 19F) during routine PCV13 use at high-coverage. Ongoing surveillance is important to determine how this is related to the known continuing occurrence of PCV13-type disease. Carriage prevalence was unexpectedly low among adults when assessed by oropharyngeal swab culture. More sensitive detection methods may reveal a higher prevalence for adults.
ISPPD-0093
CIRCULATING PNEUMOCOCCAL SEROTYPE-SPECIFIC ANTI-POLYSACCHARIDE IGG (CPSS-IGG) MAY NOT PREDICT PROTECTION AGAINST NASOPHARYNGEAL CARRIAGE ACQUISITION IN TODDLERS

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Background and Aims:
A recent human challenge study suggested that serotype-specific memory B-cells are associated with protection against pneumococcal carriage, but CPSS-IgG are not. Data from our study lend support to this finding.

Methods:
A prospective, randomized controlled study. Subjects received 3 PCV7 doses (2, 4, 6 m) with or without booster at 12 m (3+1, 3+0, respectively). Controls received 2 PCV7 doses (12, 18 m; 0+2).

Nasopharyngeal/oropharyngeal pneumococcal cultures were obtained at all 10 study visits. Serum CPSS-IgG concentrations were measured at 7, 13 and 19 m.

Results:
544 subjects: 3+1 (n=178), 3+0 (n=178); 0+2 (n=188). CPSS-IgG concentrations were similar at 7 m in 3+0 and 3+1 groups. At 13 and 19 m, antibody concentrations were significantly higher in the 3+1 than in the 3+0 group (Figure 1). Despite the differences in serum antibody concentration, PCV7+6A serotypes acquisition was similar for groups 3+1 and 3+0 at all ages during 7-30 m, and lower than the 0+2 controls (Figure 2).

Conclusion:
PCV7 administered at 3+0 and 3+1 resulted in similar protection against vaccine-serotype carriage, up to 30 months of age, when infant doses were administered 2 m apart. This suggests that besides circulating IgG, protection against pneumococcal nasopharyngeal carriage acquisition may also depend on other mechanisms, possibly memory B-cells stimulation.
Figure 1. Comparison between ELISA IgG geometric mean concentrations (GM, µg/ml) at ages 7, 13 and 19 m between groups 3+1, 3+0 and 0+2. The values are given with 95% confidence intervals.

Figure 2. Comparison of cumulative incidence (per 100 children) of new pneumococcal NP:OF acquisitions between the 3+1 and 3+0 groups. These 2 groups were互 compared to the 0+2 group, who received no PCV7 during the first year of life, but received 2 doses in the second year of life.

All P-values were adjusted for ethnic groups (Jewish vs. Bedouin children).
- α P-values between the 3+1 and 3+0 groups
- β P-values between the 3+1 and 2+0 groups
- γ P-value between the 3+0 and 2+0 groups
E-POSTER SPOTLIGHT SESSION 4

ISPPD-0161
COMPARING APPROACHES FOR INFERRING PNEUMOCOCCAL TRANSMISSION NETWORKS USING SIMULATED AND REAL DATASETS
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Background and Aims:

Pneumococcus transmission normally occurs through contact with respiratory droplets from asymptomatic carriers. Nasopharyngeal colonisation can then follow and is a prerequisite to invasive disease. Transmission risk factors are still not fully understood. In order to gain a better understanding, it is important to accurately reconstruct pneumococcal transmission networks. This will allow for the identification of genetic determinants associated with transmission.

Methods:

We make use of both simulated and real whole genome sequences of S. pneumoniae from a densely sampled population in the Maela refugee camp in north west Thailand, to investigate the ability of different methods to identify networks of disease transmission. Additionally, we investigate the utility of using information on the within host diversity of infected hosts to improve estimates of transmission networks.

Results:

Pneumococcal transmission inference is hampered by the pathogens high rate of recombination, variable carriage rates, and high prevalence. Recently, the number of methods to infer transmission networks has grown significantly. The way in which each method handles the various difficulties in phylodynamic inference has a significant impact on the resulting networks inferred. The difficulties encountered included appropriately accounting for, within host diversity, missing cases, epidemiological information, multiple samples, and mixed infections.

Conclusion

Simulation is an important step in determining which approaches are best suited to inferring pneumococcal transmission networks. These results will help to inform future work in analysing large densely sampled pneumococcal datasets.
E-POSTER SPOTLIGHT SESSION 4

ISPPD-0250
PERSISTENT HIGH PREVALENCE OF NON-VACCINE PNEUMOCOCCAL SEROTYPE CARRIAGE TO AGE 24 MONTHS IN PAPUA NEW GUINEAN CHILDREN VACCINATED WITH 10-VALENT OR 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINES
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Background and Aims:
In Papua New Guinea (PNG) pneumococcal conjugate vaccine (PCV) in infancy has limited impact on PCV serotype-specific carriage at age 9 months. We investigated pneumococcal carriage at 10-24 months in a study comparing the safety and immunogenicity of PCV10 and PCV13 with or without a pneumococcal polysaccharide vaccine (PPV) booster.

Methods:
262 infants were randomized to receive either PCV10 or PCV13 in a 1-2-3-month schedule, with further randomization within each group to receive or not receive PPV at 9 months. All children had a PPV challenge dose at age 23 months. We cultured 557 nasopharyngeal swabs collected at ages 10, 23 and 24 months. Pneumococci were serotyped using Quellung reaction.

Results:
Pneumococcal carriage rates were 82-98%, with no significant differences between groups at ages 10, 23 and 24 months. PCV10 serotype carriage prevalence was 17-24% in PCV10 recipients and 9-15% in PCV13 recipients at 10-24 months. Prevalence of PCV13 non-PCV10 serotypes was 5-8% in PCV13 recipients and 10-14% in PCV10 recipients. At age 10 months, prevalence of non-PCV serotypes was 61% in PCV13 recipients compared to 47% in PCV10 recipients (p=0.04). 54 different pneumococcal serotypes were identified. In order of frequency the most common serotypes in PCV10 recipients were 23F, 6A, 19A, 19F (vaccine type, VT) and 35B, 16F (non-vaccine type, NVT); while 19A, 9V, 6B (VT), 6C and 16F (NVT) were most frequent in PCV13 recipients.

Conclusion
In PNG, high pneumococcal carriage rates, particularly carriage of NVT, persist to age 24 months following infant PCV schedules.
E-POSTER SPOTLIGHT SESSION 4

ISPPD-0281
PNEUMOCOCCAL SEROTYPE AND DRUG RESISTANT GENE PREVALENCE AMONG PCV NAÏVE CHILDREN IN VIETNAM: BASELINE CARRIAGE SURVEY BEFORE PCV REDUCED DOSING SCHEDULES STUDY


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Background and Aims:

Pneumococcal conjugate vaccines (PCV) have reduced the burden of vaccine-type pneumococcal disease. A PCV reduced dosing schedule study is underway in Nha Trang, Vietnam. Here we present prevalence of pneumococcal serotypes and antimicrobial resistance genes in the nasopharynx before PCV introduction.

Methods:

The study is being conducted in 27 communes of Nha Trang city, central Vietnam. Communes are randomized to various PCV schedules and 60 children 4-11mth and 60 children 14-23mth, and their mothers are randomly recruited yearly for collection of nasopharyngeal (NP) specimens. The baseline NP survey we describe here was obtained in October 2016. Pneumococcal carriage was screened by lytA qPCR followed by serotyping using microarray method.

Results:

Of 6296 samples tested, pneumococci prevalence was 24%, 38% and 3% in infants, toddlers and mothers, respectively. The most common serotypes were 6A, 19F, 6B and 23F. Of the pneumococci detected, the proportion belonging to PCV10 serotypes was 44%, 48%, and 37% for each age group, and for PCV13 serotypes 77%, 78%, and 53%, respectively. Serotypes carried by mothers were typically the same as those carried by their children. 100% of PCVs serotypes and 88% of non-vaccine types, carried at least one antimicrobial resistance gene against erythromycin, tetracycline or chloramphenicol.

Conclusion

PCV10 and PCV13 serotypes were the most frequently carried serotypes in this PCV naïve population. Rates of carriage of antimicrobial resistance genes were found to extremely high. Annual NP carriage surveys post PCV introduction will be obtained to assess changes in serotype distribution and presence of antimicrobial resistance genes.
E-POSTER SPOTLIGHT SESSION 4

ISPPD-0420
SEROTYPE 3 IS THE LEADING CAUSE OF COMPLICATED PEDIATRIC PNEUMOCOCCAL PNEUMONIA IN PORTUGAL EVEN AMONG PCV13 VACCINATED CHILDREN (2010-2015)
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Background and Aims:

Despite the use of the 7-valent conjugate vaccine, there are reports of increasing incidence of pleural effusion and empyema, here referred as pediatric complicated pneumococcal pneumonia (PCPP). Some serotypes seem to be more frequently associated with PCPP including 1, 3, 5, 7F and 19A, found in the 13-valent conjugate vaccine (PCV13). We aimed to characterize the serotypes of pneumococci causing PCPP and to evaluate the role of molecular techniques in the enhanced detection of this important pathogen in pleural fluid samples.

Methods:

Samples from pediatric patients, recovered in Portugal in 2010-2015 were cultured and Streptococcus pneumoniae was identified and serotyped. In culture negative cases, samples were analyzed by conventional and RT-PCR for detection of S. pneumoniae and serotyping.

Results:

Only 17 cases were identified by culture. Molecular methods identified S. pneumoniae in most culture negative samples (n=92/135). The most frequent serotypes were 3, 1 and 19A together accounting for 62% (n=68) of the cases. A total of 19 cases due to PCV13 serotypes were detected among 22 PCV13 age-appropriately vaccinated children, mostly caused by serotype 3.

Conclusion

The dominance of the additional serotypes included in PCV13 among PCPP continues even with PCV13 use, including cases among age-appropriately vaccinated children, indicating PCV13 vaccine failures in preventing PCPP, particularly that caused by serotype 3.
Background and Aims:

‘Accessory’ genes, including many capsule synthesis and antibiotic resistance loci, are found in only a subset of pneumococcal strains. Conversely, the strains themselves can be defined by the distinctive set of these accessory genes they contain. Understanding the distribution of such genetic variation is critical in analysing pneumococcal epidemiology and ecology.

Methods:

Pneumococcal strains, and accessory genes, were identified across four population genomic datasets, three of which included post-PCV7 surveillance.

Results:

Despite the four studied populations having very different strain compositions, accessory gene frequencies were strongly correlated across them all. Functional annotation of over a thousand accessory genes revealed many were likely subject to negative frequency-dependent selection (NFDS) - the situation in which genes are most beneficial to a cell when they are rare in a population - through interactions with other bacteria, hosts, or mobile elements. As well as being conserved between locations, these frequencies were maintained following the introduction of PCV7. A novel model of NFDS was therefore developed in which strains frequencies changed so as to preserve the accessory gene frequencies. Fitting this to the post-vaccine population dynamics observed in three genomic datasets generated similar, reproducible estimates of NFDS’s influence on pneumococcal evolution. Simulations with these parameters replicated the stable frequency of strains unperturbed by vaccination, patterns of serotype switching, and clonal replacement.

Conclusion

This framework highlights the importance of both the starting pneumococcal population, and the role of multiple mechanisms of competition between strains, in determining the post-vaccine serotype replacement process.
E-POSTER SPOTLIGHT SESSION 4

ISPPD-0555
USE OF QUALITY IMPROVEMENT TOOLS TO IMPROVE COVERAGE OF PCV-10 IN A RURAL DISTRICT OF PAKISTAN
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Background and Aims:
Quality improvement tools have been widely used to improve health services globally. Aim of this study was to improve routine immunization services by increasing PCV-10 coverage using Quality Improvement tools in a rural district of Pakistan.

Methods:
A Quasi-experimental study was conducted in Thatta and Sajawal districts. Baseline and endline surveys were conducted using 30*7 cluster method in intervention and adjacent control district to assess change in coverage of PCV-10 among children of age 4-12 months. EPI staff and supervisors of the 16 catchment facilities were trained on use of quality improvement tools including process mapping, cause and effect analysis and plan-do-study-act (PDSA) cycles during April-July 2015. Weekly follow up interviews were conducted with EPI staff to assess progress on individual plans and use of PDSA approach in delivery of EPI services.

Results:
13 out of 16 facilities developed PDSA. Each facility staff developed specific aims to address issues hindering low coverage of PCV-10. Follow up interviews revealed system level issues including: lack of funds from district health office to conduct outreach activities in remote areas; staff shortage; non-availability of platform for information education and communication (IEC); and mismatch between specified targets and actual population. Coverage of PCV-10 three doses was significantly higher in intervention compared to control district with difference-in-difference of 7.7% (p=0.002).

Conclusion
It appears that PDSA at facility level has the potential to identify workable change ideas to improve vaccine coverage. However, it might not be able to address systemic deficiencies where inputs from district and provincial leaderships are required.
E-POSTER SPOTLIGHT SESSION 4

ISPPD-0777
SEROTYPE SPECIFIC OPSONOPHAGOCYTOSIS POST PRIMARY SERIES AND POST-BOOSTER FOLLOWING ALTERNATIVE PNEUMOCOCCAL VACCINATION STRATEGIES IN VIETNAM
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2Pasteur Institute, Ho Chi Minh City, Vietnam
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4Department of Paediatrics, University of Melbourne, Melbourne, Australia
5London School of Tropical Medicine and Hygiene, London, United Kingdom

Background and Aims:
Streptococcus pneumoniae causes severe infant infections. Our recent trial in Ho Chi Minh City, Vietnam compared the functional serotype specific responses following five different PCV schedules.

Methods:
Infants were randomised to receive PCV10 in a 3+1, 3+0, 2+1 or 2-dose schedule, or PCV13 in a 2+1 schedule. Functional antibody to 13 serotypes was measured in blood samples collected one month post-primary series and one month post-booster. OPA titres are presented for paired samples to the 10 serotypes common to both vaccines.

Results:
There was a significant increase in OPA titre for all serotypes in paired samples from the 3+1, 2-dose and both 2+1 groups (p<0.004), with the exception of serotype 14 in the 3+1 group where the increase was non-significant. There was a significant decrease (p<0.004) in OPA titre from post-primary series to 10 months of age in the 3+0 group. The post-primary series OPA titre was higher in groups that received more doses of PCV.

Conclusion:
The functional antibody response reflects the number of doses in the primary series. The functional antibody response increases significantly post a booster dose and wanes rapidly when no booster dose is given.
E-POSTER SPOTLIGHT SESSION 5

ISPPD-0160
IMPACT AND EFFECTIVENESS OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE AGAINST INVASIVE PNEUMOCOCCAL DISEASE CAUSED BY SEROTYPE 19A PNEUMOCOCCUS IN EUROPEAN CHILDREN: RESULTS OF SPIDNET MULTICENTRE STUDY
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Background and Aims:
Using surveillance data on invasive pneumococcal disease (IPD) in 13 sites from nine European countries, we measured the effectiveness and impact of 13-valent pneumococcal conjugate vaccine (PCV13) against serotype 19A IPD in children under 5 years-old.

Methods:
To measure PCV13 effectiveness, we compared the vaccination status of 19A IPD (cases) to that of non-PCV13 IPD (controls) reported between 2012 and 2016. We calculated the pooled effectiveness as (1-vaccination odds ratio)*100, adjusted for age, underlying conditions, notification year and site. To measure the impact, we calculated incidence rate ratios (IRR) comparing 19A IPD incidence in each PCV13 years 2011-2016 to the average incidence during PCV7 period, by site. We used random effects meta-analysis to estimate the pooled impact as (1-IRR)*100.

Results:
The effectiveness of at least one dose PCV13 against serotype 19A IPD was 84% (95% confidence interval (CI): 72-91) in 2-59-month-olds (n=1364) and of full vaccination 91% (95%CI: 76-96) among 12-59-month-olds (n=477). After PCV13 introduction, the incidence of 19A IPD ranged between 0.4 and 5.5/100,000 in 2011 and between 0 and 3.1/100,000 in 2016. The incidence of 19A IPD post-PCV13 introduction gradually decreased by 48% (95%CI: -12 to 76) in 2012 and 81% (95%CI: 67-89) in 2016.

Conclusion:
Our results suggest a good individual and population protection of the PCV13 against 19A IPD in children under 5 years-old. Serotype 19A persists in the population at a low incidence and we need further studies on PCV13 duration of protection and for identifying other factors that prevent elimination of this serotype in this age group.
Background and Aims:
We incorporated whole genome sequencing (WGS) into surveillance procedures to predict features of invasive pneumococcal disease (IPD) isolates.

Methods:
We performed WGS on 5284 isolates (~90% of cases) recovered during 2015-2016 through Active Bacterial Core surveillance (ABCs) to quantify serotypes, antimicrobial phenotypes, multilocus sequence types (MLSTs), and other features.

Results:
We identified 44 serotypes, 26 accounting for 98% of isolates. Eleven PCV13 serotypes accounted for 1248 (23.6%) isolates, with serotype 3 the most common (653/5284, 12.4%). Of 305 isolates from children <5yrs, 60 (19.7%) were PCV13 serotypes, including 57 of serotypes 19A, 19F, or 3. Twenty-one strain complexes were potentially indicative of PCV13-serotype genetic recipients recently “switching” to non-PCV13 serotypes. CC156, formerly primarily associated with ABCs 9V and 19A strains, accounted for 32 penicillin-resistant CC156 serotype 35B, 11A, 13, or 31 isolates. Within-PCV13 serotype exchanges included two multi-resistant serotype 3/ST271 variants that shared identical cps region and PBP type, presumably descending from the same serotype 19F/ST271 recipient. PBP typing predicted 22.3% (1179/5285) penicillin-nonsusceptibility (MICs >0.12µg/ml), with higher penicillin MICs (2-8 µg/ml) predicted in 7.9% (420/5284) of isolates that were primarily (368/420, 87.6%) serotypes 35B and 19A. Most penicillin-nonsusceptible isolates were macrolide-resistant (785/1179, 66.6%); 406/785 were erm gene positive and clindamycin-resistant.

Conclusion
Population-based genomic characterization of IPD isolates allows monitoring of features important for strain success. There are many recently-identified non-vaccine serotype “switch-variants”, some of which are expanding.
E-POSTER SPOTLIGHT SESSION 5

ISPPD-0361
PNEUMOCOCCAL CONJUGATE VACCINE INTRODUCTION AND UPTAKE TIMELINES FOR GAVI-SUPPORTED COUNTRIES
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Background and Aims:

Introduction of pneumococcal conjugate vaccines (PCV) into low and middle-income countries has been described as a success in accelerating vaccine access. Analyzing introduction timelines can help identify ways to accelerate PCV and other new vaccine introduction and uptake timelines.

Methods:

We measured timelines for major vaccine introduction milestones from first licensure through country uptake for PCV and five other vaccine preventable diseases (VPDs) across 45 vaccine products, three delivery platforms, and 73 Gavi-supported countries. We calculated median times between milestones across VPDs and countries. Results are presented for all licensed PCV vaccines and PCV10/PCV13 only.

Results:

Time from first product licensure to first Gavi-supported country introduction was slower for PCV (10.8 years) than the median time across all VPDs (5.4 years, n=6), but faster if considering only PCV10/PCV13 (2.0 years). Only Meningitis A vaccines reached first introduction more quickly (campaign = 0.6 years; routine = 1.6 years). PCV country introductions were more frequently delayed than other VPDs (in 96% of countries). PCV uptake rates from time of first WHO prequalified product have outpaced other routine immunizations, reaching 50% of the Gavi-cohort of surviving infants in 7.2 years (11.1 years across all VPDs, n=3). Only inactivated poliovirus vaccines were faster (2.1 years) than PCV (6.1 years) when considering uptake from first Gavi-supported introduction.

Conclusion

PCV introductions are accelerated compared to other VPDs if considering only PCV10/PCV13 timelines. This analysis highlights that having the right target product profile and achieving other introduction milestones prior to licensure can fast-track new vaccine introductions.
**E-POSTER SPOTLIGHT SESSION 5**

**ISPPD-0385**

**IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINES ON PNEUMOCOCCAL MENINGITIS IN ENGLAND AND WALES, 2000 – 2016.**

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**Background and Aims:**

The introduction of pneumococcal conjugate vaccines (PCV) was associated with reduction in incidence of invasive pneumococcal disease (IPD) especially IPD caused by the vaccine serotypes. Its impact on meningitis in the United Kingdom has not been assessed.

**Methods:**

Public Health England conducts enhanced surveillance for IPD and provides a national reference service for serotyping pneumococcal isolates in England and Wales. Data were extracted for isolates from confirmed IPD cases between 1st July 2000 and 30th June 2016, covering the 2000/01 to 2015/16 epidemiological years. Incidence rate ratio (IRR) and case fatality rate (CFR) were calculated.

**Results:**

There were 80,313 laboratory-confirmed IPD cases over the 16-year surveillance period, including 4,160 cases (4.9%) with meningitis. Of the 4,108 with reported age, 1,611 (39.2%) cases were reported in children aged <5y, 1,729 (42.1%) in 5-64 year-olds and 768 (18.7%) cases in 65+ year-olds. PCV7 introduction in September 2006 had no impact on the overall incidence of pneumococcal meningitis (0.55/100,000 during 2000/01-2005/06 vs 0.56/100,000 during 2008/09-2009/10) because of serotype replacement disease. PCV7 replacement with PCV13 in April 2010, however, led to a 48% (95% CI, 38-62%) reduction in pneumococcal meningitis incidence by 2015/16. The overall CFR was 17.5% (631/3,611, increasing from 10.7% (150/1408) in <5y to 17.3% (262/1517) in 5-64y and 31.9% (219/686) in 65+ year-olds.

**Conclusion**

The impact of PCV on pneumococcal meningitis has been less prominent than for other IPD presentations and case fatality remains high; a different strategy is, therefore, required to reduce the burden and outcomes of pneumococcal meningitis.
E-POSTER SPOTLIGHT SESSION 5

ISPPD-0433
IMPACT OF 10-VALENT PNEUMOCOCCAL VACCINE INTRODUCTION ON ALL-CAUSE MORTALITY AMONG CHILDREN IN KILIFI, KENYA

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Background and Aims:

In a trial in The Gambia, 9-valent Pneumococcal Conjugate Vaccine (PCV) reduced all-cause mortality among children aged 3-29 months by 16% (95% CI 3-28%). We estimated PCV10 impact on all-cause mortality in a routine setting with substantial impact against carriage, invasive pneumococcal disease and pneumonia.

Methods:

In Kilifi, Kenya, 10-valent PCV was introduced in 2011. A 2-dose catch-up campaign targeting children aged <5 years reached 63% with ≥1 dose. We used mortality and population data from Kilifi Health and Demographic Surveillance System to calculate age-specific mortality rates and estimate PCV10 impact using poisson regression adjusted for secular trends and excluding the introduction year.

Results:

Between 2003-2016, we observed 4643 deaths among 589,306 child years of observation (cyo). The table shows mortality rates/1000 cyo and mortality rate ratios (MRR) adjusted for secular trends using either calendar year or annual malaria incidence.

Conclusion

In contrast to the Gambian PCV9 trial results, we found no obvious changes in mortality attributable to PCV10 introduction, after adjusting for secular trends. A PCV10-specific effect was observed in neonates; although this could be attributable to indirect vaccine protection it is more likely due to specific improvements in newborn care.
<table>
<thead>
<tr>
<th>Age group</th>
<th>Pre-PCV10 mortality</th>
<th>Post-PCV10 mortality</th>
<th>MRR</th>
<th>Adj MRR (year)</th>
<th>95% CI</th>
<th>Adj MRR (malaria)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-28 days</td>
<td>198.0</td>
<td>57.7</td>
<td>0.29</td>
<td>0.82</td>
<td>0.68-0.99</td>
<td>0.77</td>
<td>0.64-0.92</td>
</tr>
<tr>
<td>29d-24m</td>
<td>10.15</td>
<td>6.02</td>
<td>0.59</td>
<td>1.45</td>
<td>1.20-1.77</td>
<td>0.95</td>
<td>0.83-1.09</td>
</tr>
<tr>
<td>2-4 years</td>
<td>3.36</td>
<td>1.77</td>
<td>0.53</td>
<td>2.05</td>
<td>1.54-2.75</td>
<td>1.01</td>
<td>0.84-1.21</td>
</tr>
</tbody>
</table>

Trend in mortality rate among neonates 0-28 days

Trend in mortality rate among children aged 29 days to 4 years

PCV intro year
E-POSTER SPOTLIGHT SESSION 5

ISPPD-0611
LONG-TERM EFFECT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) ON VACCINE-TYPE PNEUMOCOCCAL CARRIAGE IN CHILDREN UNDER FIVE YEARS OLD IN MOZAMBIQUE


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Background and Aims:
Pneumococcal carriage is a pre-requisite for invasive disease. In April 2013, Mozambique introduced the 10-valent pneumococcal conjugate vaccine (PCV10) into its immunization program using a three-dose schedule at 2, 3, and 4 months old.

Methods:
We evaluated three cross-sectional surveys; one pre- (2012-2013) and two post- (2014-2015 [period 1]; 2015-2016 [period 2]) PCV10 introduction. We recruited HIV-infected children <5 years from Maputo, Nampula, and Manhiça HIV clinics, and HIV-uninfected children from a demographic surveillance area in Manhiça. Nasopharyngeal swabs were collected and cultured for pneumococci. Isolates were serotyped by Quellung. We compared VT-carriage prevalence from the pre- and post-PCV10 periods by HIV status and vaccination status (fully vaccinated vs. unvaccinated).

Results:
For HIV-uninfected children, VT-carriage prevalence declined from 35.2% (108/307) pre-PCV10 to 21.2% (36/170 vaccinated) in period 1 (P=0.001) and to 11.6% (35/303 vaccinated) in period 2 (P<0.001). For HIV-infected children, VT-carriage prevalence declined from 33.9% (140/413) to 20.2% (27/134 vaccinated) in period 1 (P=0.003) and to 19.3% (40/207 vaccinated) in period 2 (P<.001). Among HIV-uninfected children, prevalence of PCV13 unique serotypes (3, 6A, 19A) increased from 11.4% (35/307) pre-PCV10 to 21.2% (36/170 vaccinated) (P=0.004) and to 16.8% (51/303 vaccinated) (P=.05) in periods 1 and 2 respectively; there were no significant changes in HIV-infected children. In period 2, VT-carriage decreased by 45.5% (P<0.001) and 29.8% (P=0.002) among unvaccinated HIV-uninfected and -infected children, respectively.

Conclusion
Despite observed direct and indirect effects of PCV10, VT-carriage prevalence continues to be common three years post-PCV10 introduction, especially in HIV-infected children.
E-POSTER SPOTLIGHT SESSION 5

ISPPD-0754
SHARP INCREASE OF SEROTYPE 24F AMONG INVASIVE PNEUMOCOCCAL DISEASE AND CARRIAGE IN CHILDREN SIX YEARS AFTER PCV13 IMPLEMENTATION IN FRANCE
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2Robert Debré Hospital, Microbiology, Paris, France
3GPIP, pediatric infectious disease research group, Paris, France
4National Reference Center for Pneumococci, Microbiology APHP HEGP, Paris, France

Background and Aims:

Before PCVs implementation, serotype 24F was rarely found in both carriage and invasive pneumococcal diseases (IPD). However, among non PCV13 serotypes, serotype 24F was shown to have one of the highest disease potential. We aimed to analyze the trends for this serotype in carriage and IPD in post PCV13 era.

Methods:

We cross-checked 3 databases from national surveys on nasopharyngeal carriage, pneumococcal meningitis (PM) and other IPD. We conducted a quasi-experimental, population-based interrupted time series analysis based on nationwide prospective cohorts in France, from 2001 to 2016.

Results:

Among pneumococcal nasopharyngeal carriers (n=5,953), the proportion of serotype 24F increased from 1.1% in pre-PCV13 to 3.6% in post-PCV13, with a concomitant increase in penicillin non-susceptibility. Among PM and other IPD (n=2,095), serotype 24F increased from 3.8 % and 3.6% pre-PCV13 to 21.2% and 13.5% in 2016, respectively. In 2016, serotype 24F is ranking first in IPD . Time series model estimated that PM incidence due to serotype 24F increased by 46.6% per month (95% CI [22.6; 70.5], p=0.0002) during 2015 and 2016, representing a cumulative 1,117% increase (95% CI [543; 1,692]) in 2015 and 2016.
Conclusion

Six years after PCV13 implementation, serotype 24F sharply emerged in both carriage and PM with a change in penicillin non-susceptibility rate. Our results suggest that this emerging serotype could represent a real threat among pneumococcal disease.
LONG-TERM IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN KENYA: NASOPHARYNGEAL CARRIAGE AMONG CHILDREN IN A RURAL AND AN URBAN SITE SIX YEARS AFTER INTRODUCTION

Background and Aims:

Kenya introduced the 10-valent pneumococcal conjugate vaccine (PCV10) in 2011, using three primary doses and, in select areas, catch-up campaigns. Surveys conducted 1-2 years post-introduction showed a stable prevalence of pneumococcal colonization, with declines in vaccine-type carriage. However little is known about PCV10 long-term impact in Kenya.

Methods:

We conducted a cross-sectional survey of pneumococcal carriage among children <5 years in November-December 2017 in Kibera (Nairobi informal settlement, no catch-up) and Asembo (rural western Kenya, 2-dose catch-up for children 1-4 years), using the same methods and settings as prior annual surveys from 2009-2013. Participants were randomly selected from an on-going population-based surveillance platform. Nasopharyngeal swabs were frozen in skim milk-tryptone-glucose-glycerin media within 4 hours and underwent broth enrichment before culturing. Isolates were serotyped by Quellung.

Results:

We enrolled 504 children, including 252 from each site. From Asembo, 6 (2.4%) samples had poor growth; pneumococcus was isolated from 146 (59.3%) of the remaining 246. Of 162 Kibera samples cultured to date, 3 (1.9%) had poor growth, and 130/159 (81.8%) grew pneumococcus. These prevalences reflect a decline from the pre-PCV10 and early-post-PCV10 periods (Figure). Serotyping is underway.
Conclusion

Six years post-PCV10 introduction, the prevalence of pneumococcal carriage among children appears to have decreased. The reasons for such decline are unclear, as consistent methods were used for each survey and pneumococcal vaccines do not typically reduce overall carriage prevalence.
E-POSTER SPOTLIGHT SESSION 5

ISPPD-0773
PNEUMOCOCCAL COMMUNITY ACQUIRED PNEUMONIA (CAP) IN HOSPITALIZED NATIVE AMERICAN ADULTS
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Background and Aims:
Native Americans experience a high burden of CAP. PCV13 has been used in adults ≥65yrs since 2015. Data on etiology can guide prevention and treatment.

Methods:
We enrolled adults hospitalized with CAP and age-group matched controls on Navajo and White Mountain Apache tribal lands. Urine from cases and controls was tested for pneumococcus by conventional urine antigen detection (UAD; BinaxNOW) and serotype-specific UAD (SSUAD) for 24 serotypes (PCV13 types plus 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F). Blood culture (bcx) and chest radiographs (CXRs) were obtained from cases at the provider’s discretion. Radiographic pneumonia was determined by clinical interpretation of CXRs.

Results:
Between March 2016–June 2017, we enrolled 497 cases (355 [71%] CXR+) and 269 controls. Among CXR+ cases with testing for pneumococcus, it was detected in 91/348 (26%) (Table). The commonest serotypes were 3 (16/72 [22%] cases with serotype available), 8 (15%) and 20 (11%). PCV13 serotypes comprised 14/45 (31%) cases of pneumococcal CAP among those ≥65yrs; 12/14 had previously received PCV13. SSUAD was positive in all 14 cases with a bcx serotype included in the SSUAD (sensitivity 100%; serotype concordance 100%).
Conclusion

SSUAD improved detection of pneumococcal CAP. Pneumococci, including PCV13 types, remain a major cause of CAP in Native American adults. New vaccines or other strategies are required to prevent pneumonia caused by serotypes not contained in currently available vaccines.
E-POSTER SPOTLIGHT SESSION 6

ISPPD-0150
FEASIBILITY OF BACTERIAL CARRIAGE EVALUATION USING PARENT-COLLECTED NASAL SWABS SENT BY MAIL
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Background and Aims:

Most carriage studies are based on cross-sectional samples or longitudinal studies with relatively sparse sampling points. In the Observational Research in Childhood Infectious Diseases (ORChID) study, weekly nasal swabs were collected to document the epidemiology of viral and bacterial respiratory infections in infants. Here we report on the feasibility and quality of the methods for bacterial detection.

Methods:

The ORChID study was a prospective birth cohort study conducted in 2010-2014 in Brisbane, Australia. Pregnant women were recruited, and their healthy newborns were followed until their second birthday. Parents collected weekly anterior nasal swabs from the enrolled child, and mailed these to the laboratory. Specimens were visually inspected for mould, and real-time PCR was used to detect bacteria and human DNA, a marker of specimen quality, using endogenous retrovirus 3 (ERV3).

Results:

We received 11,195 (68% of the maximum possible) swab samples from 158 children. Of 9,129 scheduled parent-collected swabs with full data on the quality indicators available, 8,206 (77.2%) were frozen in the laboratory within 4-days of swabbing. Delay in freezing was associated with observation of mould (16.1%; 1,470/9,129) and absence of ERV3 (not detected in 28.0%; 2,559/9,129). Any bacteria were detected in 49.9%, and pneumococci in 36.2%; but in higher proportions, 60.4% and 44.1%, respectively, in swabs with ERV3 detection.

Conclusion

The feasibility of frequent nasal swabbing by parents for bacterial carriage was confirmed and bacteria were detected in expected proportions. Attention to rapid freezing and including ERV3, as a marker of human DNA, increase bacterial detection.
Background and Aims:

Pneumococcal cell wall plays an important role in host pathogen interaction. On the host, Toll-like receptors (TLRs) identifies molecular components on pathogens and cause activation of host immune responses. The aim of the study is to investigate the effect of cell wall of various serotypes on Toll-like receptor signaling responses.

Methods:

S. pneumoniae strains of different serotypes (1, 3, 5, 19F, 23F, 14) were used. Their extracted cell walls were challenged against A549 human lung epithelial cell line. Expressions of 84 genes associated to Toll like receptor signaling pathways were performed by RT2 Profiler PCR Array. Fold differences in gene expression were determined using the 2-ΔΔCt method.

Results:

The host-pathogen interaction showed the involvement of TLRs, genes for pathogen specific responses, genes modulating TLR signaling, effectors, adaptors, and cytokines involved in downstream signaling and genes bridging innate to adaptive immunity. In response to different cell walls, chemokines (CCL2) and cytokines (IL1A/B IL6, IL8) were differentially expressed. Other downstream signaling molecule includes TNF, NF-κB CXLCL10, and CSF2/3. Regulation of the TLRs, pro-inflammatory cytokines (IL1A/B IL6, IL8), other downstream signaling molecules and adaptors showed serotypes 1, 3, 5 and 23F to be upregulated whilst serotype 14 showed downregulated expression.

Conclusion

Host pathogen interaction is dependent on the component of the cell wall component. Therefore, serotypic difference affects pathogenesis. Hence, the diversity of the serotypes to induce and regulate immune response would remarkably affect the efficacy of the available vaccines and the development of future targets would be necessary.
Background and Aims:

Persistent nasopharyngeal (NP) carriage of *Streptococcus pneumoniae* is associated with recurrence of acute otitis media (AOM) and prolonged middle ear effusion. Biofilm is found frequently in the middle ear in those with chronic otitis media, but the role of biofilm formation in persistent carriage remains uncertain. Our aim was to study whether *in vitro* biofilm formation distinguishes between pneumococcal strains that persist in the NP compared to those that do not.

Methods:

Clinical isolates were obtained from the NP of children (6-35 months) with AOM enrolled in a study of antimicrobial treatment vs. placebo. Children were followed for at least 2 months, and NP cultures were taken at follow-up visits. Persistent carriage was defined as detection of the same serotype of *S. pneumoniae* from the NP for ≥45 days. Biofilm formation was assessed by measuring optical density (OD) values in microtiter plates after crystal violet staining.

Results:

Persistent carriage was detected in 18% (31/177) of children. *In vitro* biofilm formation was significantly greater among persisting strains of *S. pneumoniae* compared with serotype matched, non-persisting strains [mean OD 0.367 (SD 0.109) vs. 0.292 (SD 0.066); P=0.01]. Overall bacterial growth did not differ between persisting and non-persisting strains [mean growth 0.656 (SD 0.163) vs. 0.609 (SD 0.157); P=0.38]. Repeat isolates from the same child demonstrated comparable *in vitro* results, suggesting that persisting strains were already better biofilm producers at the time of initial colonization.

Conclusion

*In vitro* biofilm formation distinguishes persisting strains of *S. pneumoniae* from those that are cleared from the NP.
E-POSTER SPOTLIGHT SESSION 6

ISPPD-0352
ASSOCIATION OF NASOPHARYNGEAL VIRAL RESPIRATORY INFECTION, SEROTYPE INVASIVE DISEASE POTENTIAL AND PNEUMOCOCCAL LOAD IN PEDIATRIC PATIENTS WITH INVASIVE PNEUMOCOCCAL DISEASE. A CASE-CONTROL STUDY.
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Background and Aims:
To evaluate different microbiological parameters that could potentially be associated with IPD

Methods:
Prospective case-control study matched by age, sex and seasonality including all IPD patients <18 years attended in 5 hospitals of Catalonia (2014-2016). Viral respiratory infection (18 virus tested), serotype invasive disease potential (IDP) and DNA pneumococcal load (DPL) in nasopharynx were analysed.

Results:
A total of 126 IPD patients were attended and 8 of them presented IPD risk factors. Ninety cases accepted to participate together with 90 healthy controls. Infection with Flu-A (6.7% vs. 0.0%; p=0.014) or RSV (5.6% vs. 0.0%; p=0.030) were significantly associated with IPD. Rhinovirus prevalence was high in both groups (35.5% vs. 31.1%; p=0.634). Sixty-seven patients had been exposed >24 hours to antibiotics and were excluded from subsequent analyses. A significant higher rate of pneumococcal carriage (82.6% vs. 58.9%; p=0.040) and nasopharyngeal colonization with high IDP serotypes (57.9% vs. 20.8%; p=0.003) was found in cases vs. controls. A similar DPL was observed in both groups (6.3 vs. 5.9 log10cp/mL; p=0.210). In cases, an increase in DPL was found comparing Flu-A infected patients vs. non-infected (7.9 vs. 6.0 log10cp/mL; p=0.037) while in controls, Rhinovirus infection was related to higher DPL (6.4 vs. 5.6 log10cp/mL; p=0.038). In absence of Rhinovirus infection, a significantly higher DPL was observed in cases compared to controls (6.84 vs. 5.64 log10cp/mL; p=0.018).

Conclusion
Nasopharyngeal colonization with highly invasive serotypes and Flu-A or RSV infection were significantly associated with IPD. Despite Rhinovirus infection increased nasopharyngeal pneumococcal load, it was not statistically related to IPD.
E-POSTER SPOTLIGHT SESSION 6

ISPPD-0397
RESPIRATORY MICROBIOME IN HIV AFFECTED AND HIV UNAFFECTED FAMILIES FROM EASTERN INDIA
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Background and Aims:
HIV infection increases risk of polymicrobial pneumonias. Bacterial and viral pathogens can co-infect the nasopharynx prior to development of pneumonia and their co-infection may vary in the context of HIV.

Methods:
We conducted a nested case control study within a larger prospective cohort study on the impact of pneumonia preventing vaccines in HIV infected families in West Bengal, India. 139 random banked nasopharyngeal swabs taken from 80 children and 59 parents with and without HIV before and after children received Hib and pneumococcal conjugate vaccines were subjected to multiplex quantitative RT-PCR for the detection of 21 respiratory viruses and four bacteria.

Results:
Samples from 40 children with HIV (median age 5), 40 children without HIV (median age 4), 30 parents with HIV and 29 parents without HIV showed Staphylococcus aureus as the most common bacteria found in children 42/80 (52.5%) followed by Streptococcus pneumoniae 29/80 (36.25%). The most common respiratory virus found in children was human rhino virus 15/80 (18.75%) followed by human adeno virus 7/80 (8.75%), boca virus 6/80 (7.5%), influenza b 3/80 (3.75%), respiratory syncytial virus 2/80 2.5%, corona 2/80 (2.5%) and human metapneumovirus 2/80 (2.5%). Children compared to adults had higher carriage of multiple viruses (p=0.029) and simultaneous carriage of pneumococcus and viruses (p=.003). Co-infection of rhino with pneumococcus (p=0.003) was more frequent in children. Adeno virus was more frequent in HIV affected families (p=0.02).

Conclusion
Pneumococcal co-infection with viruses was more commonly seen in children compared to adults regardless of HIV status.
E-POSTER SPOTLIGHT SESSION 6

ISPPD-0432
PHASE VARIATION OF PNEUMOCOCCAL POPULATIONS IN THE HUMAN NASOPHAYNX
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Background and Aims:

*Streptococcus pneumoniae* can alter the expression of genes associated with virulence and carriage through differential expression of the Type I Restriction Modification (RM) system SpnIII. Differential expression of this system, which can recognise 6 different unique DNA methylation-target sequences (A-F), has been linked to the opaque/transparent phenotype and also survival in mouse models of invasive disease. The Experimental Human Pneumococcal Carriage (EHPC) project offered a unique opportunity to track a colonising population over a defined time frame and to determine if SpnIII expression is selected for within the human nasopharynx.

Methods:

The EHPC project inoculates healthy volunteers with a dose of the carriage associated pneumococcal serotype 6B strain BHN418. Nasal wash samples are collected from these volunteers at days 2, 7, 14, and 21 post challenge. The bacteria recovered from colonised volunteers were analysed using a quantitative PCR protocol to determine the relative proportions of SpnIIIA-F. The experimental outcome was then compared to the outcome predicted if the expression of this system was random.

Results:

Analysis of samples from 40 carriage positive volunteers at a variety of time points showed that expression of SpnIII is highly variable between patients. The differences in expression of some variants shows that SpnIII expression is not random and some variants are significantly over (variant SpnIIID) or under-represented (variant SpnIIIE) in bacterial populations recovered after 21 days of carriage.

Conclusion

This implies that naturally occurring phase-variation may shape the bacterial population during carriage and impact pneumococcal colonisation of the human nasopharynx.
E-POSTER SPOTLIGHT SESSION 6

ISPPD-0584
ANTIBIOTIC RESISTANCE OF STREPTOCOCCUS PNEUMONIAE CAUSING PAEDIATRIC MENINGITIS IN WEST AND CENTRAL AFRICA, 2007-2016
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Background and Aims:

The World Health Organization (WHO) is supporting African countries to monitor pneumococcal antimicrobial resistance as part of surveillance for vaccine preventable invasive bacterial diseases. We report data collected between 2007 and 2016.

Methods:

Pneumococcal isolates were recovered from suspected meningitis patients aged 0-59 months in an on-going hospital-based surveillance across 10 West and Central African countries. Susceptibility to seven antibiotics was investigated by disk diffusion and resistance confirmed by E-test. Serotypes were determined by latex agglutination while sequence types (ST) and resistance genotypes (tetM, pbp, mef1, folA, catA) were inferred by whole genome sequencing.

Results:

A total of 185 isolates were analysed from 2007-2016. Of these, 143 (77.3%) were PCV-13 serotypes. ST618_serotype1 (10.3%), ST63_serotype14 (7.6%), ST303_serotype1 (5.9%) were the leading STs. Phenotypically, more than 50% of isolates were resistant to cotrimoxazole and tetracycline and there was >90% concordance with genotypic resistance genes, folA and tetM respectively. pbp and catA genes which predict resistance to penicillin and chloramphenicol, were identified in 20.5% and 9.7% of isolates respectively; these genes were associated with PCV serotypes as well as emerging non-vaccine serotype particularly 12F, which showed high levels of resistance. Almost all multidrug resistance isolates (4/5) belonged to PCV-13 serotypes.
Conclusion

Our data shows high antimicrobial resistance among PCV-13 serotypes. Finding suggests a projected decrease of antimicrobial resistance as PCV-13 is currently in-use in all countries included in this study. However, the emergence of serotype 12F with high antibiotic resistance is concerning and calls for re-evaluation of current vaccination programme.
E-POSTER SPOTLIGHT SESSION 6

ISPPD-0735
IFN-GAMMA MEDIATES SUSCEPTIBILITY TO POST RSV PNEUMOCOCCAL PNEUMONIA

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Background and Aims:

Secondary bacterial pneumonia is a common clinical complication that follows an influenza infection. However, this complication is not limited to influenza. We and others have demonstrated a significant relationship between infection with other respiratory viruses, including Paramyxoviruses RSV and hMPV, and pneumococcal pneumonia. The mechanisms responsible for increased susceptibility following these coinfections are not fully defined. We have now investigated the cause of increased susceptibility to secondary bacterial pneumonia after RSV infection.

Methods:

We employed a sequential murine RSV and S pneumoniae coinfection model. We intranasally infected mice with RSV and 7 days later, challenged intranasally with a low dose of the serotype 3 S pneumoniae strain, A66.1. To follow disease progression, mice were monitored for survival, bacterial burdens and inflammatory responses.

Results:

We observed that co-infected mice had impaired bacterial clearance, reduced innate immune responses and increased mortality compared to mice singly infected with RSV or S. pneumoniae. Further investigation revealed that greater susceptibility correlated with increased IFN-gamma levels. Using IFN-gamma deficient mice, we thus investigated if IFN-gamma was required for increased susceptibility to secondary pneumococcal pneumonia following RSV. We found that a deficiency of IFN-gamma resulted in reduced bacterial load and increased survival.

Conclusion

We conclude that IFN-gamma mediates increased susceptibility to pneumococcal pneumonia following RSV infection.
DIAGNOSIS AND TREATMENT

**ISPPD-0557**

EVALUATION OF THE SOFIA S. PNEUMONIAE FIA AND THE SOFIA LEGIONELLA FIA FOR DETECTION OF PNEUMOCOCCAL AND LEGIONELLA ANTIGEN IN URINE

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**Background and Aims:**

*Streptococcus pneumoniae* and *Legionella pneumophila* may cause community-acquired pneumonia. We evaluated the novel Sofia *S. pneumoniae* Fluorescent Immunoassay (FIA) and the Sofia *Legionella* FIA (Quidel, San Diego, USA) for detection of pneumococcal cell-wall polysaccharide antigen and *L. pneumophila* serogroup 1 antigen in urine.

**Methods:**

A total of 103 urine samples from adult patients (>18 years) with bacteremia (*S. pneumoniae, n*=47; other etiology, *n*=50) or confirmed *Legionella* pneumonia (*n*=6) were included. All samples were stored at -20°C until tested in a blinded procedure with both Sofia *S. pneumoniae* and Sofia *Legionella* FIAs and were not concentrated or filtrated prior to testing. The test results were interpreted by an automatically reader (Sofia Analyzer), invalid tests were retested, and were compared with those of BinaxNOW *S. pneumoniae* immunochromatographic test (ICT), BinaxNOW *L. pneumophila* ICT and ImmuView *S. pneumoniae* and *L. pneumophila* ICT.

**Results:**

The Sofia *S. pneumoniae* and the Sofia *Legionella* FIAs showed sensitivities of 68.1% and 100% and specificities of 92.3% and 97.9%, respectively, calculated on valid tests. The Sofia *S. pneumoniae* FIA showed a good inter-assay agreement with BinaxNOW *S. pneumoniae* ICT (κ=0.78) and ImmuView *S. pneumoniae* and *L. pneumophila* ICT (κ=0.78) for detection of pneumococcal antigen. The Sofia *Legionella* FIA showed a very good inter-assay agreement with BinaxNOW *L. pneumophila* ICT (κ=1.00) and ImmuView *S. pneumoniae* and *L. pneumophila* ICT (κ=1.00) for detection of *Legionella* antigen.

**Conclusion**

The Sofia *S. pneumoniae* and the Sofia *Legionella* FIAs performed similarly as other urine antigen tests on urine samples from infected patients with definite etiologies.

**ISPPD-0213**

CREATION, CHARACTERIZATION, AND ASSIGNMENT OF OPSONIC VALUES FOR A NEW PNEUMOCOCCAL OPA CALIBRATION SERUM PANEL FOR 13 SEROTYPES

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¹, ², ³, ⁴, ⁵, ⁶, ⁷, ⁸ Other institutions are not specified in the image.
Background and Aims:

Opsonophagocytic assays (OPAs) are useful for assessing the immunogenicity of pneumococcal vaccines, especially in the elderly. To reduce the variability in OPA results from different laboratories, sera with known OPA values are needed for assay calibration. Although a serum panel was created by the US FDA, those sera are in limited quantities and are not available. Therefore, a new panel (Ewha QC Sera Panel A) was created and an international collaborative study was conducted to determine consensus values for the 13 serotypes in PCV13.

Methods:

Sera were collected from 20 healthy adults after PPV23 vaccination, lyophilized, and aliquoted into >150 vials per serum. Four laboratories tested the sera five times, with reference serum pool 007sp included in each run. For each result, an unadjusted opsonic index (OI) and a normalized OI (based on 007sp performance) were calculated. The consensus values of both the unadjusted OIs and the normalized OIs were estimated using an ANOVA model.

Results:

The results for one laboratory differed significantly from those of the other laboratories and were therefore excluded from consensus value determination. Using data from the three remaining laboratories, consensus OIs (both unadjusted and normalized) were determined for each serum sample for 13 serotypes.

Conclusion

Ewha QC Serum Panel A will be useful for calibrating pneumococcal OPAs. The sera can be obtained by contacting Kyung-Hyo Kim (kaykim@ewha.ac.kr) or Si Hyung Yoo (yoosh1130@korea.kr) in Korean MFDS.

Acknowledgments

Study support: Ministry of Food and Drug Safety 15172MFDS275 and 17172MFDS275 (K-HK); US NIH contract HHSN272201200005C (MHN).
Background and Aims:

Current diagnostic tests for pneumonia aetiology lack sensitivity and/or specificity. We assessed whether antibodies from lymphocyte supernatant (ALS) – a test based on the acute, transient plasmablast response to infection – could be used to diagnose pneumococcal pneumonia in children.

Methods:

We took blood samples from consecutive children admitted with pneumonia, and 20 healthy controls. Peripheral blood mononuclear cells (PBMCs) were separated from whole blood, suspended to 1x 10^7 PBMCs/ml in culture medium and incubated for 48 hours, before harvesting of the supernatant (ALS). ALS concentrations to 5 pneumococcal proteins were assayed in a fluorescent multiplexed bead-based immunoassay, and the results analysed by an a priori estimate of the probability of pneumococcal pneumonia.

Results:

348 children were enrolled; 8 of whom had definite pneumococcal (DP) pneumonia, 7 had definite other bacterial (DOB) pneumonia, and the remaining children had unconfirmed pneumonia aetiologies. ALS to the optimum pneumococcal protein – PhtD (pneumococcal histidine triad D) – discriminated between DP and DOB pneumonia with 88% sensitivity and 71% specificity at an optimum threshold. Decreasing proportions of children had a “positive” ALS result to PhtD as the a priori probability of pneumococcal pneumonia decreased.

Conclusion

ALS to pneumococcal proteins may represent an alternative approach to the aetiological diagnosis of pneumonia in children. However, further challenges include replication of results, enrolment of greater numbers of children with confirmed infections (across age strata), and optimising the timing of sampling of transient plasmablast populations.

ISPPD-0374
SURFACE ENGINEERED NANOCAPSULES OF UMBELLIFERONE AS POTENT INHIBITOR OF NNRTI ALONG WITH ANTI-PNEUMOCOCCAL POTENTIAL BY INHIBITION OF PNEUMOCOCCAL CELL WALL DEGRADING VIRULENCE FACTOR
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Background and Aims: In number and causes of death Streptococcus pneumoniae is heading the table of mortality and morbidity when it comes community acquired infection ranking 6th in case of over all deaths. According to recent research, the risk is high in HIV patients when compared to non HIV and general population with more CD4 cells who are on
antiviral therapy. Thus, the present study deals with fabrication of umbelliferone nanoformulation which can able to target simultaneously both HIV and Pneumococcal infection. **Methods:**

UFG in docking model tested against Reverse transcriptase (HIV-1RT). Moreover, the inhibitory activity against the bacterial growth of *S. pneumonia* infection in mice (2.5-10 mg/kg) was also investigated. The RAW 264.7 macrophage cells were used to determine the cell viability using MTT assay. Docking was carried out with pneumococcal cell wall degrading virulence factor for determination of mechanism of action as antibacterial agent.

**Results:**

UFG nanoformulation showed smooth spherical small surface with relative narrow size distribution. UFG showed the utmost 87% inhibition of HIV-1 RT integrase catalytic with Ki= 85.56 nM. Additionally, UFG was effective in significant (p<0.05) way by reducing the burden of bacteria in blood, lungs and spleen after 24 and 48 hours of post infection together with higher survival rate and lower morbidity than those of non-treated group. Docking study confirmed that, UFG molecule extremely buried in the cavity of HIV-1 RT integrase catalytic domain via interacting with Thr66, Asn155, Asp116 and Glu152.

**Conclusion**

We can conclude that umbelliferone nanoformulation can able to target both HIV and Pneumococcal infection simultaneously.

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**ISPPD-0029**  
**PYOGENIC VENTRICULITIS DUE TO STREPTOCOCCUS PNEUMONIAE IN AN IMMUNOCOMPETENT GIRL: CASE REPORT**  
**G.S. Dhooria**

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**Background and Aims:**

Despite modern intensive care, antibiotic treatment, and the use of dexamethasone, the morbidity and mortality associated with Streptococcus pneumoniae meningitis remain high.

**Methods:**

We present here a 4 years old girl with *Streptococcus pneumoniae* meningitis, a vaccine preventable disease, whose course was complicated with development of hydrocephalus and ventriculitis.

**Results:**

A four years old girl, came in pediatric emergency in a moribund state with history of high grade fever, headache, vomiting for past one month and altered sensorium, refractory seizures 3 days prior to admission. She was treated with antibiotics, anticonvulsants, ventilator and inotropic support and other supportive care. Neuroimaging showed development of hydrocephalus and ventriculitis in addition to meningeal exudates. CSF and blood culture both came to be positive for streptococcus pneumonia. Immunodeficiency workup was negative. Hydrocephalus was treated with external ventricular drainage by neurosurgery team. Frank pus was drained. Tracheostomy was required for prolonged
ventilator dependence due to poor sensorium. She was shifted to local hospital after PICU stay of 2 weeks, who later survived with major sequalea.

Conclusion

Persistence of high grade fever, delirium, seizures in a clinically moribund patient of bacterial meningitis should raise suspicion of ventriculitis.

ISPPD-0430
PRECISE DETECTION OF CLOSELY RELATED SEROTYPES AND MULTIPLE SEROTYPES OF S. PNEUMONIAE BY MOLECULAR SEROTYPING MICROARRAY
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Background and Aims:

*Streptococcus pneumoniae* is a diverse pathogen with over 94 different serotypes. Accurate serotype determination is of importance to assess vaccine coverage and impact. Current typing methods are elaborate, expensive and inaccurate to type closely related serotypes. In addition, conventional methods have low sensitivity for detection of multiple serotypes. The study focus was to evaluate molecular serotyping by microarray for discrimination of closely related serotypes and detection of multiple serotypes with their relative abundance.

Methods:

19 invasive, 22 nasopharyngeal isolates and 11 oropharyngeal swabs from studies in India were included. 50 spiked samples were prepared using DNA extracted from 39 known strains belonging to 13 serogroups. The isolates were serotyped by Quellung. For microarray analysis, genomic DNA was extracted and hybridized to the Senti-SP v 1.5 microarray for serotype calls based on the cps gene content.

Results:

The invasive and NP isolates, showed 100% correlation of the serotype results by Quellung and microarray. The closely related serotypes in the spiked samples were accurately identified with their relative abundance by microarray. For the majority of OP samples, microarray analysis revealed that these contained a complex mix of related Streptococcal species. 3/11 OP samples contained pneumococcal serotypes and the remainders were other related species such as *S.mitis, S.parasanguinis, S.salivarius*.

Conclusion

The study demonstrates the utility of microarray to detect serotypes of isolates and clinical samples. The ability to accurately discriminate closely related serotypes, detect multiple serotypes, their relative abundance and also differentiate closely related species in NP/OP swabs could provide further insights in carriage studies.

ISPPD-0419
ONE ASSAY FOR ALL: A NOVEL MICROARRAY ASSAY FOR SEROTYPING OF
STREPTOCOCCUS PNEUMONIAE IN CULTURE NEGATIVE QMPCR POSITIVE SERUM SPECIMENS
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Background and Aims:

Serotyping of *Streptococcus pneumoniae* is of importance for disease management and vaccine studies. Current serotyping methods require culturing which is often negative. Serum provides a convenient and widely available source of pathogen detection. The difficulty in differentiating homologous strains and presence of host DNA are of hindrance for the adoption of molecular techniques. This study aimed to evaluate a microarray method to detect and serotype *S. pneumoniae* directly from serum specimens.

Methods:

Probes were designed using SureDesign software to identify, type, evaluate antibiotic resistance of *S. pneumoniae* and detect other respiratory pathogens. Unique probes and modified algorithms were used to identify homologous strains. Microbiome enrichment kit was used to selectively increase bacterial DNA from Serum specimens. 32 Homologous standard strains, 96 culture negative qmPCR positive, 16 culture positive and qmPCR positive serum samples were processed with in-house optimized microarray protocol using CY3 and CY5 dyes.

Results:

Our redesigned microarray chip identified serotype information accurately for all serum specimens and homologous strains. Excellent concordance with established serotyping methods (qmPCR and Sequencing) was seen with additional advantage of detecting other respiratory pathogens, multiple serotype carriage, their relative abundance levels and antibiotic resistance gene information. Optimized protocol with the use of two dyes, low running cost per sample was achieved.

Conclusion

Preliminary analysis suggest that our customized Pneumococcal microarray is a robust, economical assay for identification and typing of *S. pneumoniae* from culture negative qmPCR positive serum specimens, which can be used as a diagnostic tool in clinical setting.

ISPPD-0089
UTILITY OF REAL-TIME PCR ON DRIED BLOOD SPOTS FOR DETECTION OF STREPTOCOCCUS PNEUMONIAE IN FEBRILE NIGERIAN CHILDREN
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Background and Aims:


Streptococcus pneumoniae is a leading infectious cause of mortality in Nigeria. A major challenge in accurately determining the prevalence of pneumococcal disease is the lack of resources to process diagnostic specimens. Dried blood spot (DBS) testing has been demonstrated to be a promising method for diagnosis of infections in the developing world because of its low cost, minimal blood volumes involved, and ability for storage at ambient temperature.

Methods:

From September 2011-June 2015, children ≤5 years of age who presented to six hospital study sites throughout northern and central Nigeria with an acute febrile illness (temperature >38.5 °C) associated with difficulty breathing or altered consciousness were prospectively enrolled. Blood was obtained for culture using the automated BACTEC incubator system and also spotted onto filter paper. DBS DNA extractions were used as a template in real-time (rt)-PCR assays targeting the lytA gene, and RNase P amplification was used as a control to confirm recovery of human cellular DNA.

Results:

A total of 1,038 dried blood spots were analyzed. Rt-PCR detected S. pneumoniae from DBS in one culture-negative specimen from a high-risk group, 9 culture-positive specimens, and also in a culture-confirmed nonpneumococcal specimen and a healthy control. Six culture-positive isolates (40%) were missed.

Conclusion

While rt-PCR was able to detect S. pneumoniae in a culture-negative specimen in a high-risk patient, it missed a substantial number of culture-positive specimens. This limits the diagnostic utility of rt-PCR in this patient population and setting.

ISPPD-0049
PNEUMOCOCCAL PERITONITIS DIAGNOSED BY RT-PCR IN A MALNOURISHED CHILD
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Background and Aims:

Spontaneous bacterial peritonitis caused by Streptococcus pneumoniae is infrequent and commonly occurs when underlying abdominal diseases are present.

Methods:

We describe a culture-negative pneumococcal SBP in a malnourished child diagnosed by RT-PCR.

Results:

A 2-year old girl was admitted with recurrent high fever (39.5°C), vomit and inappetence for 3 days. She was severely dehydrated, hypoactive, tachycardic, tachypneic, and with distended and painful abdomen – no peritoneal inflammation signs were evidenced. Her family took a
vegan diet, presented with failure to thrive, undernutrition and incomplete primary immunization series. Complementary evaluation evidenced severe leucopenia (1150 WBC/µL), C-reactive protein=40.1 mg/dL, bowel edema at abdominal X-ray and ultrasound, without free liquid in abdominal cavity. As a refractory septic shock of abdominal origin was evidenced, high dose ceftriaxone, metronidazole and ampicillin were empirically initiated and she was transferred to the intensive care unit, where she required ventilatory support, multiple vasoactive drugs, hemodialysis and blood transfusions. Exploratory laparotomy was performed at the 2nd day of hospitalization, which identified a large amount of purulent secretion in the cavity, without signs of bowel perforation, acute appendicitis or any other apparent focus for the pyogenic infection. Sustained hemodynamic and ventilatory improvement occurred at the 15th day of antimicrobial course. Patient was discharged after 25 days of treatment, with no residual sequelae. Despite all negative cultures, RT-PCR collected from abdominal fluid five days after the laparotomy identified *Streptococcus pneumoniae*, which was negative in blood.

**Conclusion**

RT-PCR can improve sensitivity of identification of invasive pneumococcal disease, and is a useful tool for culture-negative infection

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**ISPPD-0395**

**PNEUMOCOCCAL LytA qPCR AS A NON-INVASIVE MOLECULAR DIAGNOSTIC FOR PNEUMOCOCCAL PNEUMONIA**

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**Background and Aims:**

We used nasopharyngeal samples from children with pneumonia to determine if higher pneumococcal density is associated with risk of pneumococcal pneumonia (as classified by a composite diagnostic standard) and to compare PCR with conventional culture for detection of pneumococcus.

**Methods:**

Between March 2014 and August 2016, 368 Nepalese children aged 2 months to 14 years admitted to Patan Hospital, Kathmandu, Nepal, with clinician diagnosed pneumonia had nasopharyngeal swabs analysed. DNA was extracted from the swab media and qPCR performed for pneumococcal autolysin (*lytA*). Pneumococcal pneumonia was defined as an abnormal CXR, a blood neutrophil level over the upper normal limit (7.5x10⁹/L), and carriage of either serotypes 1, 5, or 14, or any child with an abnormal chest x-ray and blood culture positive for pneumococcus.

**Results:**

The sensitivity and specificity for conventional culture detecting pneumococcus detected above the lower limit of qPCR detection (10² copies/ml) was 42.6% and 96.1% respectively.
A threshold of 568,921.2 copies/ml had a sensitivity of 72% and specificity of 72% when comparing children with pneumococcal pneumonia with those who did not meet the definition but had an abnormal x-ray.

Conclusion

The density of pneumococcal carriage amongst Nepalese children, can differentiate children with pneumococcal pneumonia from children who do not meet the diagnostic criteria but who have CXR changes. Further refinement of the composite diagnostic used in this study may allow increased optimisation of the qPCR assay as a diagnostic for pneumococcal pneumonia.

ISPPD-0706
RANDOMIZED TRIAL OF AMOXICILLIN VERSUS PLACEBO FOR FAST BREATHING PNEUMONIA
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Background and Aims:

World Health Organization (WHO) defined fast breathing pneumonia among children 2-59 months of age in low resource settings mandates outpatient antibiotic therapy with high dose amoxicillin. WHO itself recognizes limitations of this approach--non-specificity of the clinical diagnosis, large proportion due to viral infections and giving antibiotics where they are not needed, resultant disruption in microbiome, consequent poor growth along with the increased burden on scarce health resources. To fill the evidence gap, a double blind randomized placebo controlled non-inferiority trial using parallel assignment is conducted in low income squatter settlements of Karachi, Pakistan.

Methods:

Children 2-59 months old with fast breathing, without any WHO-defined danger signs and seeking care at primary healthcare center are randomized to receive either three days of placebo or amoxicillin. Primary outcome is difference in cumulative treatment failure between two groups (new clinical sign based on preset definitions indicating illness progression or mortality) on day 0, 1, 2 or 3 of therapy.

Results:

From September 2014 to August 2017, 89,838 children were triaged, 48,104 (53.5%) presented with cough or difficulty in breathing. 7,174 (8%) met the inclusion criteria i.e. having cough for less than two weeks with fast breathing. 3,682 were enrolled and received high dose amoxicillin or placebo. With per protocol rate of 96.3%, overall treatment failure is 132 (3.7%) with 2 deaths. There were 2 serious adverse events (severe diarrhea).

Conclusion

Overall rates of treatment failure in fast breathing pneumonia are low. Trial results will serve to support or refute use of antibiotics in this illness.
Background and Aims:

Sputum culture in the microbiological diagnosis of community-acquired pneumonia (CAP) has been considered worthwhile only if a high-quality (HQ) sample has been obtained, but evidence regarding pneumococcal etiology specifically is lacking. We evaluated the relevance of sputum quality assessment for sputum culture in the diagnosis of PncCAP.

Methods:

We studied radiologically confirmed CAP cases (N=323) from patients aged ≥65 years and compared sputum culture results with other pneumococcal tests (Table). Sputum quality was assessed microscopically after Gram-stain. Two sets of quality criteria were applied to delineate HQ from low-quality (LQ) sputa: leukocytes/epithelial cells ratio >5 and ≤2.5 epithelial cells per field (400-fold magnification) (HQ1) or a less stringent leukocytes/epithelial cells ratio >1 (HQ2).

Results:

A sputum sample was obtained and the quality assessed in 224 (69%) of the CAP cases; 47% of these were HQ1 and 76% HQ2. Encapsulated pneumococci (EPnc) were cultured at similar proportions in HQ1 and LQ1 sputa, if a pneumococcal test was positive, and less often in LQ1 than HQ1 sputa, if the other test was negative for pneumococcus (Table). Regardless of the result of the other diagnostic test, EPnc was found less often in LQ2 than in HQ2 sputa.
Conclusion

LQ sputum culture for demonstration of pneumococcal etiology of CAP may have low sensitivity rather than low specificity.

Acknowledgements: The study was conducted in collaboration with GlaxoSmithKline Biologicals SA.

ISPPD-0405
PHARMACODYNAMIC POTENTIAL AND EFFICACY OF CROCETIN IN IMMUNOCOMPETENT RAT MODEL OF PNEUMOCOCCAL PNEUMONIA
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Background and Aims:

There is growing concern over S. Pneumonia (pneumococcus) when it comes to community acquired pneumonia and may result in 15 to 25% of all reported cases in adults. The rise in mortality is observed from 5 to 20 -25% immunocompetent pneumonia patients. Crocetin is a strong and relatively accepted compound known for its antimicrobial properties mainly against bacteria from gram positive family including MRSA Streptococcus pneumoniae. This
work was an effort to scrutinize crocetin against the immunocompetent rat model of *pneumococcal pneumonia*.

**Methods:**

Molinspiration software was used for elucidation of Lipinski’s Rule of 5. Invivo activity of crocetin was compared with standard drug ceftriaxone as reference in immune-challenge rats with pneumococcal pneumonia infection. The infection in rats was made by 8x10⁷ CFU (intratracheally) of penicillin sensitive strain of S. pneumoniae for 5 days at a stretch. After that the rats were divided into different groups. The blood culturing of the all group rats were performed on regular interval (day 1, 3, 5 and 10) post infection for scrutinize the bacteremia.

**Results:**

The normal control group rats showed the cumulative mortality (100%), 56.4%, 21.8% against various doses of crocetin and 0% observed in the ceftriaxone group, respectively. The all group rats confirmed the significantly reduction in bacteria presence in bronchoalveolar lavage (BAFL) liquid on third day of infection than normal group rats. Crocetin and ceftriaxone treated rats confirmed the fewer bacterial organisms in the BAFL.

**Conclusion**

Our findings clearly suggest that crocetin has the better control of the progression of pneumococcal pneumonia.

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**ISPPD-0095**

**SELECTION OF PIPERACILLIN/TAZOBACTAM INFUSION MODE GUIDED BY SOFA SCORE IN CANCER PATIENTS WITH HOSPITAL-ACQUIRED PNEUMONIA: A RANDOMIZED CONTROLLED STUDY**

Y. Lyu¹

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**Background and Aims:**

This study aimed to select piperacillin/tazobactam infusion mode guided by Sequential Organ Failure Assessment (SOFA) score in cancer patients with hospital-acquired pneumonia (HAP) post-operation.

**Methods:**

Total 120 cancer patients with postoperative HAP were divided into two groups: improved administration group (L group) and conventional treatment group (Con group). Con group received Piperacillin/Tazobactam (TZP) in traditional infusion, and L group received prolonged infusion. Blood drug concentration was detected at different time points. Based on SOFA cut-off value of 9 the patients were re-grouped into M (mild) and S (severe) group.

**Results:**

%fT>MIC time was longer than 5 h in L group but was shorter than 4 h in Con group. Administration method (p = 0.033, OX value 2.796, B value 1.028, 95% CI 0.855 ~ 8.934) and SOFA score (p = 0.038, OX value 0.080, B value -2.522, 95% CI 0.007 ~ 0.874) were independent predictors of patient survival. In S group, compared to conventional treatment,
prolonged infusion mode had shorter days of antibiotics use and shorter ventilator time, and achieved longer survival, better clinical efficacy and lower 28-day mortality rate.

Conclusion

For cancer patients with SOFA score≥9, prolonged infusion mode of TZP could benefit the patients and obtain better clinical efficacy.

ISPPD-0505
DIRECT MULTIPLEX REAL-TIME PCR ASSAY FOR THREE MAJOR BACTERIAL MENINGITIS CAUSING AGENTS
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¹Child Health Research Foundation- Dhaka Shishu Hospital, Microbiology, Dhaka, Bangladesh
²Bangladesh Institute of Child Health- Dhaka Shishu Hospital, Microbiology, Dhaka, Bangladesh

Background and Aims:

Rapid diagnostic is key for timely management of bacterial meningitis. Predominant etiologies of meningitis are Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitidis. Current singleplex rt-PCR to detect these organisms directly from samples is an advancement in respect of time, cost and requirement of CSF volume. However, we developed a multiplex assay for all three pathogens in one reaction, to make the detection less time consuming, requiring less volume of CSF and reduce the cost.

Methods:

We used published primer and probe sequences of pneumococcus (lytA), Haemophilus (hpd) and meningococcus (sodC) with three florescence dye (sodC-FAM, lytA-Cy5 and hpd-HEX) combination to design a multiplex reaction. The cycle threshold (Ct) value of singleplex and multiplex assays were compared by using known DNA concentrations. Next, we compared samples with known etiology using both untreated CSF (2 µl) samples and extracted DNA samples (10 µl CSF).

Results:

Each direct assay was 100% specific in detecting the organisms directly from CSF. No significant difference was observed in Ct values between singleplex and multiplex assays. In the 45 tested clinical specimens with known etiology, we found 100% concordance between singleplex and multiplex assays.

Conclusion

This assay detects three major etiologies of meningitis simultaneously using only 2 µl of CSF with 2.5 turnaround time. It can be used as a rapid etiology detection tool, specifically in the areas with high prevalence of pre-hospital antibiotic usage.

ISPPD-0510
DETECTION OF PNEUMOCOCCAL SEROTYPES WITHIN SEROGROUPS 24 & 38/25: PCR SEROTYPING FOR CULTURE-NEGATIVE SPECIMENS
R. Malaker¹, A.M. Tanmoy², S. Saha¹, M. Hasanuzzaman¹, M. Islam¹, C.G. Whitney³,
Background and Aims:

Bangladesh has a significant burden of pneumococcal diseases and the 10-valent Pneumococcal Conjugate Vaccine was introduced in 2015. Diverse serotype distribution and their secular changes have been observed in the pre-vaccine era. Recently, an increase of serogroups 24 and 38/25 has been noticed, leading to fears of serotype replacement in the post-vaccine era. However, currently available conventional PCR primers cannot distinguish the serotypes within serogroups 24 and 38/25. Therefore, we designed primers to detect these serotypes in culture-negative samples.

Methods:

Six multiplex-compatible primers were designed manually from published sequences of capsular polysaccharide (cps) loci. Blastn was used to verify their specificity and OligoAnalyzer version 3.1 for physical properties. Specificity of the primers were confirmed using Quellung-confirmed isolates of serotypes 24A, 24B, 24F, 25A, 25F and 38. Cross-reactivity with 45 different predominant serotypes from invasive cases and human DNA were checked. Finally, their utilization was tested on culture-negative serogroup confirmed (24 and 38/25) clinical specimens.

Results:

These primers distinguish serotypes by yielding bands of different sizes for 24A (397bp), 24B/F (225bp), 25A/F (632bp) and 38 (802bp). Primers to separate 24B/F and 25A/F could not be designed due to high (99%) sequence similarity. These primers successfully differentiated three serogroup 24-confirmed culture negative cases into 24B/F and four serogroup 38/25-confirmed cases into three serotype 25A/F and one serotype 38.

Conclusion

Our work can contribute to generate comprehensive serotype data for pneumococcal surveillance and impact studies specifically in the post vaccine era when non-vaccine types will be of great importance.
Background and Aims:

We describe and evaluate the WHO CXR interpretation process from a PCV effectiveness study in Sylhet, Bangladesh.

Methods:

Eight physicians (CXR panel) were standardized to WHO CXR methodology and interpreted CXRs between May 2015-October 2017. Each CXR was randomized to two primary readers masked to all data. If primary readers were discordant for CXR interpretability or the presence or absence of primary endpoint pneumonia (PEP), then another randomly selected masked reader adjudicated the CXR (arbitrator). If the arbitrator disagreed with both primary readers, or concluded no PEP, then a masked expert reader finalized the conclusion. The expert reader also conducted blinded quality control (QC) on 20% of CXRs. We evaluated agreement between two primary readers and agreement between the expert QC reading and the final CXR panel interpretation using percentage, unadjusted kappa, and a kappa adjusted for prevalence and bias.

Results:

Among 9,689 CXRs, the panel concluded 18.9% as PEP, 80.1% as no PEP, and 1.1% as uninterpretable. Two primary readers agreed on CXR interpretability for 98% of CXRs (kappa; 0.26; adjusted kappa, 0.97). Among interpretable CXRs, two primary readers agreed on the presence or absence of PEP in 79% of CXRs (kappa, 0.35; adjusted kappa, 0.57). Expert QC readings agreed with the final CXR panel reading on the presence or absence of PEP in 93.1% of 1,429 interpretable CXRs (kappa, 0.73; adjusted kappa, 0.86).

Conclusion

Primary reader performance and expert QC results suggest CXR interpretations used to analyze PCV effectiveness in rural Bangladesh meet WHO standards.
Background and Aims:

In most parts of the world, isolating bacteria from clinical specimens of patients with invasive pneumococcal disease constitutes a major challenge and a major gap in local as well as global bacterial disease surveillance. We developed a new supplemented culture medium that can be used in lower-resource settings to enhance the isolation rate of fastidious organisms like pneumococci and to improve stability of specimens and isolates. The medium overcomes the short shelf life of blood-based media by the substitution of blood with lyophilized hemoglobin.

Methods:

The new medium containing hemoglobin and an additional supplement was compared to Tryptic Soy Broth (TSB)+5% sheep blood by simultaneously measuring the growth kinetics of clinical isolates of Streptococcus species in the two media using an automated microplate reader. Growth kinetics data were collected in triplicate from 3 independent experiments.

Results:

Growth curve and colony morphology data demonstrated that the new medium enhanced the growth of Streptococcus species. The average optical density of the bacterial culture was 0.4 to 0.8 units higher in the new medium compared to TSB+5% sheep blood. Moreover, a supplement contained in the medium prevented the autolysis of Streptococcus pneumoniae and improved its viability in supplemented TSB by an average of 1200 cfu/ml after 24 hours incubation at 37 °C, compared to non-supplemented TSB.

Conclusion

This new supplemented culture medium should prove useful for any bacteriology laboratory, since it will result in improved recovery of viable pneumococci and other fastidious bacterial species. This in turn will provide improved capacity for determining effective treatments.
Results:

There was a strong correlation between the summation of serotype-specific IgG and the percentage serotype coverage (% serotypes with >0.35μg/ml,p<0.0001, r^2=0.89). On an individual serotype basis low concentrations of responders and high concentrations of non responders were non informative and thus it was important to look at coverage. Holistically, significantly higher concentrations were observed for all 12 serotypes (Table1).

The concentrations of PN18C & 23F were statistically lower in individuals with low vs normal IgG, IgA or IgM (P<0.05). PN14 was significantly lower in individuals with low IgG or IgA (P<0.05), PN1 in individuals with low IgM (P<0.05) and PN3,4,5,6B,7F,9V and 19F in low IgG only (P<0.05).

Table 1: Median concentration and concentration ranges for serotype antibodies

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Non-responder (Range)</th>
<th>Responder (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PN1</td>
<td>0.12 (0.01-10)</td>
<td>1.09 (0.03-10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PN3</td>
<td>0.04 (0.01-4.43)</td>
<td>0.34 (0.01-10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PN4</td>
<td>0.06 (0.0-0.95)</td>
<td>0.32 (0.04-3.25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PN5</td>
<td>0.14 (0.01-6.76)</td>
<td>1.3 (0.23-10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PN6B</td>
<td>0.14 (0.01-10)</td>
<td>1.3 (0.08-10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PN7F</td>
<td>0.56 (0.01-7.33)</td>
<td>2.68 (0.57-10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PN9V</td>
<td>0.28 (0.01-7.63)</td>
<td>2.15 (0.15-10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PN14</td>
<td>1.16 (0.01-10)</td>
<td>7.7 (0.6-10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PN18C</td>
<td>0.29 (0.01-10)</td>
<td>6.06 (0.23-10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PN19A</td>
<td>0.47 (0.01-10)</td>
<td>4.08 (0.42-10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PN19F</td>
<td>0.33 (0-10)</td>
<td>4.03 (0.53-10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PN23F</td>
<td>0.21 (0.01-5.09)</td>
<td>2.3 (0.18-10)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusion

Significant differences were observed between the antibody concentrations and responses to pneumococcal serotypes.

**ISPPD-0449**
BUILDING A PREDICTION MODEL FOR RADIOGRAPHICALLY-CONFIRMED PNEUMONIA IN CHILDREN: FROM SYMPTOMS TO IMAGING.

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2Johns Hopkins School of Medicine, Pediatric Pulmonary, Baltimore, USA

Background and Aims:

Community acquired pneumonia (CAP) remains the most common infectious cause of morbidity and mortality in children world-wide. Current guidelines for diagnosis are neither sensitive nor specific. We sought to determine if improvements in the diagnostic yield of CAP in children followed when pulse oximetry, auscultation findings, and ultrasound imaging were added to clinical signs and symptoms.

Methods:
Children aged < 5 years with respiratory symptoms presenting to a tertiary hospital in Peru underwent clinical assessment and enrollment. The ability to predict radiographically confirmed pneumonia was assessed using logistic regression models under the following additive scenarios. Reported symptoms and clinical signs only, the addition of lung auscultation findings, the addition of pulse oximetry, and the addition of lung ultrasound findings.

**Results:**

Of the 830 children analyzed, 453 (54.6%) had clinical pneumonia and 221 (26%) were radiographically confirmed. The baseline prediction model, with only clinical signs and symptoms, yielded an Area Under the Curve (AUC) of 0.62 (95% CI 0.58-0.67). Adding lung auscultation findings improved the AUC to 0.73 (95% CI 0.69-0.77). The addition of oxyhemoglobin saturation did not improve the prediction model, with an AUC of 0.73 (95% CI 0.69-0.77). Finally, the addition of consolidation on lung ultrasound had the largest improvement in the predictive model (AUC of 0.85; 95% CI 0.82-0.89).

**Conclusion**

The addition of lung ultrasound and auscultation findings to clinical criteria improved the ability to diagnose radiographically-confirmed pneumonia. Implementation of these tools should be considered to improve diagnostic yield of pneumonia in resource-poor settings.

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**ISPPD-0518**

**TRAINING AND STANDARDIZING PHYSICIANS TO ULTRASOUND DIAGNOSIS OF PNEUMONIA IN CHILDREN AS PART OF A PNEUMOCOCCAL CONJUGATE VACCINE EFFECTIVENESS STUDY FROM SYLHET, BANGLADESH.**


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2. Johns Hopkins School of Medicine, Pediatric Pulmonology, Baltimore, USA
3. Johns Hopkins University Bangladesh, Health Systems, Sylhet, Bangladesh
4. Johns Hopkins University Bangladesh, Health Systems, Dhaka, Bangladesh
5. Johns Hopkins Bloomberg School of Public Health, Health Systems, Baltimore, USA

**Background and Aims:**

Lung ultrasound (LUS) is an emerging tool for the point-of-care diagnosis of pediatric pneumonia. We aimed to evaluate our ability to train and standardize physicians to use LUS, to diagnose pediatric pneumonia, as part of a pneumococcal conjugate vaccine (PCV) effectiveness study conducted in Sylhet, Bangladesh.

**Methods:**

Twenty-five physicians underwent a standardized teaching program to conduct and interpret LUS between May 2015 and October 2017. Each eligible child had LUS conducted by a study physician. A second physician, blinded to the first LUS results, interpreted the recorded LUS on the same day. Upon disagreement between the first and second readers, a blinded interpretation was done by an expert third reader. The inter-rater reliability among study physicians and between study physicians and expert readers, using Cohens kappa, was used to assess standardization.

**Results:**
We analyzed LUS data from 8,308 children enrolled into the PCV-10 study with clinical pneumonia. 29.9% of these children had evidence of sonographic pneumonia on LUS. Study physicians had high agreement (kappa of 0.85; 95% CI 0.84-0.86; adjusted kappa 0.88) when the first and second readers were compared. This agreement is slightly reduced, but still significant (kappa of 0.81; 95% CI 0.79-0.82), when both readers are compared to an expert reader.

**Conclusion**

LUS is a promising tool with the potential to improve diagnostic capabilities and may be directly applicable in field intervention trials of pediatric pneumonia. Our teaching program is able to train and standardize physicians to diagnose pneumonia on LUS with a high level of inter-rater agreement.

**ISPPD-0658**

**EVALUATION OF DRIED BLOOD SPOTS AMONG CHILDREN <5 YEARS OLD FOR STREPTOCOCCUS PNEUMONIAE DETECTION AND SEROTYPING IN RURAL MOZAMBIQUE**

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2Centro de Investigação em Saúde de Manhiça, Acute Respiratory & Invasive Bacterial Infections Research Unit, Manhiça, Mozambique

**Background and Aims:**

_S. pneumoniae_ is the leading cause of bacterial pneumonia and meningitis, yet collection of invasive specimens and diagnosis by culture or PCR remain challenging. Dried blood spots (DBS) have been used for detection of viral and parasitic diseases. However, little is known about its use for bacterial infections. We evaluated the use of DBS for pneumococcal and _Haemophilus_ detection.

**Methods:**

DBS and nasopharyngeal (NP) swabs were collected from ill children enrolled through pneumonia surveillance and from healthy children from Manhiça District. For DBS, blood was collected through finger prick and spotted onto Whatman paper. Culture and Quellung were done on NP swabs to identify and serotype pneumococcus. Quantitative PCR for _lytA_ (pneumococcus), _hpd_ (Haemophilus), and serotyping was done for DBS.

**Results:**

We enrolled 310 children, 190 ill and 120 healthy. Healthy children were more likely to be _lytA_-positive and _hpd_-positive on DBS than ill children (Table). DNA concentrations were adequate for serotyping for 50.4%(59/117) of positive DBS. Where results could be compared, we detected the same serotype/serogroup in the DBS and NP-swab for 77%(10/13) ill and 38%(11/29) healthy children.

Table: DBS and NP swab results

<table>
<thead>
<tr>
<th>Ill-children N=190</th>
<th>Healthy-children N=120</th>
</tr>
</thead>
</table>

193

**Conclusion**

We found more pneumococcal and *Haemophilus* DNA in healthy children’s DBS, suggesting that this test did not distinguish colonization from disease and is not likely to be useful for diagnosis.

**ISPPD-0520**

**SPATIAL MULTIPLEX SCREENING OF RESPIRATORY TRACK ASSOCIATED VIRAL, BACTERIAL AND FUNGAL PATHOGENS VIA MULTI-PARAMETER CUSTOMIZED QUANTITATIVE PCR MICROFLUIDICS CARDS**

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²Quantigen, Research & Development, Fishers- Indiana, USA

**Background and Aims:**

Syndromic testing with a rapid and complete diagnostic panel would be extremely useful for routine respiratory testing for patient care and public health surveillance. We have developed and validated a real-time PCR-based microfluidics card which can test up to eight samples within 3 h from sample to results. It can simultaneously detect up to 48 pathogens and controls.

**Methods:**

Phase 1 testing included analytical sensitivity testing (LoD), reactivity, specificity and reproducibility testing using synthetic controls and commercially available standards. For Phase 2, clinical samples including Nose-Throat Swabs and Nasopharyngeal Aspirates were tested for 28 viral, 12 bacterial and 1 fungal respiratory pathogen

**Results:**

All 41 targets together detected >95% of positives in phase 1. All tested assays showed excellent analytical sensitivity, with LoD ranging from 1 to 100 copies/µL. An overall specificity of >98% was found. Reproducibility showed a mean of >90%. For the clinical validation, a total of over 200 samples were tested, with an overall positivity rate of >50% and a co-infection rate of >10%.

**Conclusion**

This syndromic panel was analytically and clinically validated and will be implemented for routine respiratory testing.
ISPPD-0552
DETECTION OF Streptococcus pneumoniae IN CEREBROSPINAL FLUID FROM CLINICALLY DIAGNOSED CENTRAL NERVOUS SYSTEM INFECTION PATIENTS IN JAKARTA, INDONESIA
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2Eijkman Institute for Molecular Biology, Molecular Bacteriology, Jakarta, Indonesia
3Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital, Child Health, Jakarta Pusat, Indonesia

Background and Aims:
Bacterial meningitis is a life-threatening condition with a high rate of mortality, especially in developing countries like Indonesia, and is mostly caused by Streptococcus pneumoniae. However, there has been no pneumococcal meningitis study in Indonesia. Therefore, this study aimed to detect S. pneumoniae in CSF from clinically diagnosed Central Nervous System (CNS) infection patients obtained from Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia as a national referral hospital.

Methods:
The specimens were collected from 110 patients clinically diagnosed had CNS infection. Specimens were tested with direct microscopic examination using Gram stain, culture, and real-time PCR using lytA gene. Then, the isolated S. pneumoniae was serotyped by PCR. Disk diffusion was performed to determine the antimicrobial susceptibility of the isolate.

Results:
We detected 1 specimen was positive for S. pneumoniae with Gram stain and culture. Furthermore, serotyping and antimicrobial susceptibility test showed that the isolate was serotype 6B and non-susceptible to oxacillin and trimethoprim-sulfamethoxazole. To date, real-time PCR detection for 110 specimens is ongoing.

Conclusion
S. pneumoniae serotype 6B isolated in one patient with CNS infection was non-susceptible to oxacillin and trimethoprim-sulfamethoxazole.

ISPPD-0030
STREPTOCOCCUS PNEUMONIAE CAUSING INTRAABDOMINAL AND PELVIC INFECTION: A CASE SERIES
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2St Vincent’s Hospital, Department of Microbiology and Infectious Diseases, Sydney, Australia

Background and Aims:
We present a case series of pneumococcal abdominopelvic infections with associated *S. pneumoniae* bacteraemia, which is an under-recognized cause of gastrointestinal illness.

**Methods:**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Clinical disease</th>
<th>Medical and surgical history</th>
<th>Pneumococcal vaccination status</th>
<th>IUD present</th>
<th>Regular Medications</th>
<th>Bacteraemia</th>
<th>Positive microbiology for pneumococcus</th>
<th>Directed treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37F</td>
<td>Peritonitis, Salpingitis</td>
<td>SLE, LLETZ procedure</td>
<td>Unknown</td>
<td>No</td>
<td>Prednisone</td>
<td><em>S. pneumoniae</em> 13B</td>
<td>Pelvic pus PCR</td>
<td>Exploratory laparotomy</td>
</tr>
<tr>
<td>2</td>
<td>46F</td>
<td>Sigmoid colitis, pneumonia</td>
<td>Splenectomy, idiopathic</td>
<td>Pneumovax-23</td>
<td>No</td>
<td>Prednisone</td>
<td><em>S. pneumoniae</em> 23B</td>
<td>Urinary-Ag</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>3</td>
<td>41F</td>
<td>Enteritis, peritonitis</td>
<td>Thrombocytopenic purpura</td>
<td>Unknown</td>
<td>Yes</td>
<td>Metronizine</td>
<td><em>S. pneumoniae</em> 3</td>
<td>Blood-Ag</td>
<td>Ceftazolin Linomycin</td>
</tr>
<tr>
<td>4</td>
<td>49F</td>
<td>Enteritis</td>
<td>Proctoritis</td>
<td>Not vaccinated</td>
<td>No</td>
<td></td>
<td><em>S. pneumoniae</em> 3</td>
<td>Stool-Ag</td>
<td>Ceftriazone Metronidazole</td>
</tr>
</tbody>
</table>

**Results:**

The mode of entry of *S. pneumoniae* into the peritoneal cavity is contentious, possible routes including hematogenous spread and transmural intestinal translocation. The female preponderance raises the possibility of translocation from the female genital tract as an important route of invasive disease. Risk factors include an indwelling intrauterine device (IUD), long-term steroid use or immunocompromise.

Empiric therapy for pneumococcal disease may include penicillin, amoxicillin, moxifloxacin or a third-generation cephalosporin. In patients presenting with clinical syndromes suggesting colitis, particularly if severe or affecting high-risk groups, ciprofloxacin or macrolides are commonly prescribed. These empiric regimens do not provide adequate coverage for *S. pneumoniae*. Though a rare pathogen in these settings, it is important to consider in the differential diagnosis, particularly if risk-factors for invasive pneumococcal infection are present.

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**ISPPD-0050**

DEVELOPMENT OF A SYNTHETIC DNA, NUVERSA, TO BE USED AS A STANDARD IN QUANTITATIVE PCR REACTIONS FOR MOLECULAR PNEUMOCOCCAL DETECTION AND SEROTYPING

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²Bill & Melinda Gates Foundation, Pneumonia, Seattle, USA
Background and Aims:

Quantitative (q)PCR assays have been developed for the identification and serotyping of pneumococcus. qPCR assays require genomic DNA from targets to prepare standards, which can be time consuming. In this study, a novel synthetic DNA molecule was developed as a surrogate for genomic DNA covering 94 serotypes of pneumococcus.

Methods:

Single-plex qPCR reactions (N=11) for individual serotypes/serogroups were developed and optimized. Specificity of reactions for specific target serotypes/serogroups was investigated using a collection of strains. A synthetic DNA (NUversa, ~8.2 kb) was then engineered to contain all available qPCR targets for serotyping and lytA. NUversa was cloned into pUC57-Amp-modified to generate pNUversa (~10.2 kb). Standards prepared from NUversa were compared to those prepared from genomic DNA.

Results:

Specificity of these new reactions was confirmed and, after optimization, the obtained limit of detection was between 2 to 20 genome equivalents/reaction. Molecular studies demonstrated that linearity [NUversa (R²>0.982); pNUversa (R²>0.991)] and efficiency of qPCR reactions using synthetic DNA were similar to those utilizing chromosomal DNA (R²>0.981). Quantification with plasmid pNUversa was affected, whereas quantification using synthetic NUversa was comparable to genomic DNA.

Conclusion

Novel single-plex reactions, together with published qPCR reactions, make it possible to detect and quantify 94 pneumococcal serotypes/serogroups. Furthermore, NUversa can be utilized as a control for the detection and quantification of pneumococcal serotypes using most, if not all, published single-plex qPCR reactions.
ISPPD-0304
EXPANDED MULTIPLEX REAL TIME PCR SCHEME TARGETING PNEUMOCOCCAL SEROTYPES AND KEY ANTIBIOTIC RESISTANT DETERMINANTS POST PCV-13 IN THE USA

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2Emory University, Public Health, Atlanta, USA

Background and Aims:

In the US, pneumococcal serotype distribution has changed since PCV-13 introduction in 2010. To address this change, additional assays targeting non-vaccine serotypes are needed to expand the current CDC triplexed real-time PCR (RT-PCR) scheme. Our aim was to develop and validate new serotyping assays as well as assays targeting key antibiotic resistance (AR) and pili genes in a quadriplex format.

Methods:

Primers and probes were designed for 42 new assays and validated using 94 S. pneumoniae serotype reference isolates, 200 previously characterized pneumococcal clinical isolates and 45 non-pneumococcal strains. Lower limits of detection were assessed using 10-fold serial dilutions of DNA.

Results:

The expanded sequential RT-PCR scheme consists of 14 quadriplex reactions that serve to identify 65 serotypes in 48 assays as individual serotypes/small serogroups, AR and pili genes. The assays are predicted to cover 100% of current invasive pneumococcal disease (IPD) isolates recovered through CDC’s ABCs based upon year 2013-2015 data. The oligonucleotides had high sensitivity of detection of <10 copies/reaction. Each oligonucleotide set was specific for a single serotype/serogroup and no cross reactions were found with other pneumococcal serotypes or non-pneumococcal species.

Conclusion

We developed a highly sensitive quadriplex RT-PCR assay for identifying S. pneumoniae serotypes/serogroups, as well as AR and pili genes. While the expanded sequential multiplex format is formulated specifically for use within the US based on serotype prevalence within our current IPD strain surveillance, it should be useful in any region of the world where a PCR approach is used for pneumococcal serotyping.

ISPPD-0239
COMPARISON OF DROPLET DIGITAL PCR AND QPCR FOR THE QUANTIFICATION OF THE AUTOLYSIN GENE (LYTA) OF STREPTOCOCCUS PNEUMONIAE

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Background and Aims:

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Quantitative droplet digital polymerase chain reaction (ddPCR) is a novel technique providing absolute quantification of target nucleic acids without the need for reference material. There are few reports of the use of ddPCR for detection of clinical pathogens such as *Streptococcus pneumonia*. Quantification of target pathogens using ddPCR may be more precise than with qPCR. This study compared the diagnostic potential of ddPCR and qPCR for precision and absolute quantitation of the autolysin gene (*lytA*).

**Methods:**

Replicates of ten-fold serial dilution of ATCC 496196 *Streptococcus pneumonia* strain were extracted and amplified to establish a qPCR assay for autolysin gene (*lytA*) diagnosis on a CFX96 platform. The assay was transferred and optimized on ddPCR and performance compared. Twelve replicate runs of samples with known molecular weight/copy numbers of pneumococcal genomes were analyzed on both platforms and measurements compared to evaluate the accuracy by mean differences. Controls were included in all runs.

**Results:**

The qPCR assay had a broader dynamic range compared to the ddPCR assay with saturation experienced for ddPCR at higher concentrations. The qPCR had lower sensitivity compared to ddPCR with a limit of detection at Ct value of 36 corresponding to 1.39 copies/µL and 0 copies/µL respectively. The ddPCR assay showed a lower coefficient of variation compared to the qPCR especially in low target concentration. Comparison of the means generated on both platforms showed, there was no statistical significant difference in the means (P= 0.30159).

**Conclusion**

DdPCR assay offers high precision and accuracy compared to qPCR assay in quantitative detection *Streptococcus pneumonia*.

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**ISPPD-0554**

**ANTIMICROBIAL SUSCEPTIBILITY PROFILE OF INVASIVE PNEUMOCOCCAL ISOLATES IN INDIA**

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**Background and Aims:**

*Streptococcus pneumoniae* is a highly recombinant species, their expansion being determined by antibiotic and vaccine pressure. We sought to determine antimicrobial susceptibility patterns of invasive isolates of *S. pneumoniae* from children <5yrs across India.

**Methods:**
Between 2015-2017, we obtained invasive pneumococcal isolates from 288 <5yrs children presenting with pneumonia, meningitis or sepsis (blood=234, CSF=24, pleural/ascitic fluid=30) from 16 sites across 9 states in India. Only one sample per child was used; meningeal isolates were obtained from children with a clinical diagnosis of meningitis. We reconfirmed culture and antimicrobial susceptibility testing by E-test method in our reference laboratory according to standard CDC and CLSI protocols.

**Results:**

Susceptibility profile of all isolates were penicillin 91%, cefotaxime 97%, erythromycin 43% and cotrimoxazole 24%, levofloxacin 94%, vancomycin and linezolid 100%.

Among PCV13-type (220) vs non-vaccine type isolates (68), resistance to at least one drug was seen among 85% and 73% respectively. The most common serotypes that showed penicillin resistance were 19F (20%), 14 (28%), 6B (16%) and 6A (16%).

Among meningeal (40) and non-meningeal isolates (248), vaccine-serotype penicillin-resistant isolates were 21 (53%) and 4 (2%), respectively. Multidrug resistance (resistant to penicillin, erythromycin and cotrimoxazole) was seen among 5% of all isolates.

Meningeal serotypes that were MDR (9/40) were all vaccine types as follows: 14 (n=4), 6B (n=2), 19F (n=2), 19A (n=1).

**Conclusion**

The study anticipates that PCV13 can protect against at least 90% of resistant invasive pneumococcal disease. Sustained pneumococcal antimicrobial surveillance in the vaccine era will inform policy vaccine rollout.

**ISPPD-0325**

**CHILDREN’S CLINICAL CHARACTERISTICS WITH LOCAL AND SYSTEM INFECTION OF STREPTOCOCCUS PNEUMONIAE AND ANTIBIOTIC RESISTANCE FROM SICHUAN, SOUTH-WEST CHINA**

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**Background and Aims:**

To study the clinical characteristics of children with septicemia, meningitis, otitis media and pneumonia infected by Streptococcus pneumoniae(S.pn) and the antibiotic resistance in south-west China.

**Methods:**

A retrospective analysis was performed on the clinical data of 52 children(0-12 years,60%<2 years) with S.pn detected in bloodstream(n1=12,23.1%), cerebrospinal fluid(CSF,n2=8,15.3%), both in bloodstream and CSF (n3=15,28.8%), earcanal secretions(n4=10,19.2%), and bronchoalveolar lavage-fluid(BALF,n5=7,13.5%) between 2011 and 2017.

**Results:**
Of the 52 cases, 41 cases (78.8%) had elevated white-blood-cell (WBC) count, and WBC count in septicemia ($x_{WBC1} = 23.1 \times 10^9/L$) and meningitis complicated by septicemia (Meningitis&Septicemia, $x_{WBC3} = 21.0 \times 10^9/L$) were higher than otitis-media ($x_{WBC4} = 10.7 \times 10^9/L, P < 0.05$) and pneumonia ($x_{WBC5} = 11.8 \times 10^9/L, P < 0.05$), and lower red-blood-cell (RBC) count ($x_{RBC1} = 3.9 \times 10^{12}/L$) than septicemia ($x_{RBC1} = 4.4 \times 10^{12}/L, P < 0.05$), otitis-media ($x_{RBC4} = 4.3 \times 10^{12}/L, P < 0.05$), and pneumonia ($x_{RBC5} = 4.6 \times 10^{12}/L, P < 0.01$). Forty-eight cases (92.3%) had elevated serum C-reactive protein (CRP) levels ($x = 77.0 mg/L$). In meningitis patients, all 23 children had an elevated nucleated-cell count ($x = 1790 \times 10^6/L$), and CSF protein $> 1000 mg/dL$ was noted in 19 children (82.6%, $x = 1827 mg/L$). Forty-seven cases (90.4%) were cured, 3 cases (5.8%) were cured with sequelae, and 2 cases (3.8%) died. The drug-sensitivity analysis showed S. pn from meningitis had more resistance rates to penicillin (85.6%) and cefotaxime (42.9%) than S. pn from septicemia (9.1%, $P < 0.05$), otitis media (10.0%, $P < 0.05$), and pneumonia (5.0%, $P < 0.05$), and S. pn from Meningitis&Septicemia had more resistance rates to penicillin (46.7%) than S. pn from pneumonia (5.0%, $P < 0.05$). S. pn from all sources had high resistance rates to erythromycin (90.4%), clindamycin (86.2%), sulfath (71.2%), and tetracycline (50.0%), but they were sensitive to amoxicillin (92.3%), chloramphenicol (98.1%), vancomycin (98.1%) and levofloxacin (100%).

Conclusion

System infection caused by S. pn lead a severer inflammation response than local infection, and grave infection leads to increased blood cell destruction. Aggressive S. pn strains are more resistant to antibiotics, and rapid detection of drug susceptibility is urgent.

**ISPPD-0252**

PEDiatric Pneumococcal Meningitis, serotype distribution and antibiotic resistance at the Eastern Highlands Provincial Hospital, Papua New Guinea between 1997 and 2015


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**Background and Aims:**

*Streptococcus pneumoniae* (pneumococcus) is the leading cause of bacterial pneumonia and meningitis in children worldwide, particularly in low-income countries. We report on serotype distribution and antimicrobial susceptibility of pneumococci isolated from cerebrospinal fluid (CSF) from children in Goroka, Papua New Guinea (PNG) between 1997 and 2015. The 13-valent pneumococcal conjugate vaccine (PCV13) was introduced in 2015.

**Methods:**
CSFs were collected from children aged 0-14 years admitted to Eastern Highlands Provincial Hospital with clinically suspected meningitis. Pathogens were identified by bacterial culture and latex agglutination. Antimicrobial susceptibility was determined by disc diffusion and minimum inhibitory concentration. Pneumococcal serogrouping/typing was conducted by Quellung reaction.

Results:

325 (8%) of 4,309 CSFs were positive for *S. pneumoniae*, 74% (242) of which were from children aged >12 months. Thirty-seven different serogroups/types were identified, including all PCV13 types and 24 non-vaccine types. In order of frequency, the most common serogroups/types were 2, 5, 7F, 46, 14, 4, 23F, 8 and 24F. PCV13 would have covered 35% of pneumococcal meningitis cases. Of 279 pneumococcal isolates, 16%, 12%, 4% and 1% were resistant to penicillin, cotrimoxazole, chloramphenicol and erythromycin respectively; all isolates were susceptible to ceftriaxone. Resistance to >2 antibiotics was observed in 9% of isolates.

Conclusion

In the PNG highlands, pneumococcal meningitis was due to a diverse range of serogroups/types, including non-vaccine types. Vaccination is an important preventative strategy, particularly in the face of rising antibiotic resistance. However, effectiveness of PCV13 needs monitoring, vaccines covering all pneumococcal serotypes are needed and complementary preventative strategies should be explored.

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ISPPD-0781

INCIDENCE AND SEROTYPE DISTRIBUTION OF PNEUMOCOCCAL PNEUMONIA IN BANGLADESHI CHILDREN UNDER 5 YEARS OF AGE

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Introduction Pneumonia is the leading cause of mortality in children under 5 years of age worldwide, mainly in developing countries, and is most often caused by *Streptococcus pneumoniae*. Therefore, pneumococcal conjugate vaccines (PCVs) for infants have been introduced in many national immunisation programmes, the Netherlands' included, and their use has been recommended worldwide. In 2015, a 10-valent PCV has been introduced in Bangladesh’s national immunisation programme. No data, however, are available on pneumococcal serotype incidence and virulence in Bangladesh. This study aims to identify pneumococcal serotypes causing pneumonia in children under 5 in Bangladesh.

Methods From 1533 children aged 0 to 59 months with an indication of upper respiratory infection or pneumonia, one serum sample was obtained at the moment of diagnosis and another ≥14 days later. We measured the serotype-specific pneumococcal antibody response using a multiplex immunoassay panel of 25 specifically selected serotypes (1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12A, 12F, 14, 15B, 18C, 19A, 19F, 20, 22F, 23F, 33F and 45). Calculating the fold increase of the antibody response between the second and first
serum sample allowed us to determine the causative serotype for infection in the participants, and yielded information regarding the serotype distribution in the region.

Results A serotype-specific pneumococcal antibody response was detected in 31% of the children. The 10 most frequently identified serotypes are 11A, 22F, 3, 2, 19F, 45, 15B, 19A, 33F, and 9N. Comparing these serotypes to those included in the Synflorix 10-valent PCV, used in both Bangladesh and the Netherlands, shows that only one of the 10 most prevalent serotypes is included in the 10V PCV.

Conclusions Our findings demonstrate that the 10-valent PCV used in Bangladesh yields low coverage of the most prevalent identified serotypes and serogroups. Although the identified serotypes do not all cause invasive disease, we can state that conducting more research into the prevalent serotypes in the region could lead to more protective vaccines.

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ISPPD-0443

IMPROVED DETECTION OF STREPTOCOCCUS PNUEMONIAE BY MOLECULAR TECHNIQUES DURING A FATAL OUTBREAK OF MENINGITIS IN NORTHERN NIGERIA, 2017.

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Background and Aims:

Outbreaks of meningitis occur periodically in Northern Nigeria. Although Neisseria meningitidis is the most common cause of meningitis outbreaks, Streptococcus pneumoniae, may also be a cause. A fatal outbreak of meningitis occurred in 3 states in Northern Nigeria from December 2016 to May 2017. This study aimed at determining the prevalence of S. pneumoniae during the outbreak of meningitis in Northern Nigeria

Methods:

Active surveillance of suspected meningitis cases who met the WHO case definition was conducted at Zamfara, Federal Capital Territory and Yobe States between December 2016 and May 2017. Cerebrospinal fluid samples were collected and analysed by Culture, Rapid Diagnostic Test (Pastorex®) and Polymerase Chain Reaction (PCR) for detection of N. meningitidis, S. pneumoniae and H. influenzae.

Results:
CSF was collected from 217 suspected meningitis cases. The most sensitive method for pathogen detection was PCR (n=97, 44.7%) followed by RDT (n=34, 15.6%) and Culture (n=16, 7.3%). Neisseria meningitidis (n=124, 57.1%) was the predominant cause of meningitis based on all three techniques; followed by S. pneumoniae (n=16, 7.3%) and then Haemophilus influenzae (n=2, 0.9%). Five S. pneumoniae cases were serotyped by PCR which gave three serotype 19F, one serotype 1 and one serotype 5.

Conclusion

Our data underscores the urgent need for improved healthcare and laboratory infrastructure for effective outbreak intervention in West Africa. Molecular techniques are important tools in determining the etiology of meningitis outbreaks. Efforts should be geared towards early and improved diagnosis of all bacterial agents including S. pneumoniae using molecular techniques to ensure improved treatment outcome of patients.

ISPPD-0692

COMPARATIVE GENOMICS OF SEROTYPE 20B ISOLATES FROM INVASIVE DISEASE BEFORE AND AFTER PCV10 INTRODUCTION IN SOUTHERN BRAZIL

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Background and Aims:

*Streptococcus pneumoniae* serotype 20B is a relatively uncommon serotype of low invasive pneumococcal disease (IPD) potential. However, following the introduction of PCV10 in Southern Brazil, we observed an increase in cases of IPD caused by this serotype. Herein we perform comparative genomic analysis to elucidate the genomic epidemiology and pathogenicity features related to the rise of this serotype in IPD.

Methods:

Isolates collected from 2007 to 2013 in three hospitals in Southern Brazil were subjected to serotyping by multiplex PCR. Whole genome sequencing of serotype 20B isolates was performed using an Illumina sequencer. SNP calling was done using CLC Genomics 10 and the pan-genome was analyzed using Roary.

Results:

Serotype 20B was significantly more frequent (p=0.0382) in the post vaccine period (16/435) than in the pre-vaccine period (4/163), with a peak (11/171) in 2011. All patients were adults (age 32-85) with a wide range of underlying diseases. Serotype 20B isolates were characterized as ST8889, a SLV of ST235 and carried the tet(M) gene. The average number of SNPs in comparison to the oldest isolate was 22.42±3.03 SNPs, excluding one pre-vaccine era isolate that presented 81 SNPs. Gene content analysis showed a total of 2029 and 2278 genes for core and pan-genomes, respectively.

Conclusion
Serotype 20B IPD cases in Southern Brazil are caused by a clonal lineage of *S. pneumoniae* that seems to be capable of preferentially disseminating among adults. The genomic determinants of pathogenicity of this opportunistic clone are currently being elucidated.

Financial support: CAPES, CNPq, FAPERGS

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**ISPPD-0407**

**THE EMERGENCE OF STREPTOCOCCUS PNEUMONIAE SEROTYPE 2 (SP2), ST-13578 CLONE, CAUSING A WIDESPREAD INVASIVE PNEUMOCOCCAL DISEASE (IPD) OUTBREAK IN ISRAEL**

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**Background and Aims:**

A nationwide IPD outbreak caused by the previously rare Sp2 was observed during 2014-2017 in Israel. We aimed to analyze the population structure and evolutionary dynamics of Sp2 during 2009-2017.

**Methods:**

A nationwide, active surveillance is being conducted since 2009. Serotype Sp2 was determined by PCR and Quellung reaction. Sp2 isolates from IPD cases during 2009-2017 were analyzed by PFGE, MLST and whole genome sequence (WGS). Antimicrobial profiling was performed by broth micro-dilution.

**Results:**

Overall, 102 Sp2 IPD cases were identified (July 2009 through June 2017); 27 (26.5%) isolates were analyzed by MLST. During 2016-2017, Sp2 caused 7.6% of all-IPD, a 7-fold increase compared with 2009-2010, and ranked first among IPD isolates. During 2009-2014, all sequenced Sp2 IPD were caused by the globally reported ST-1504 clone (pubMLST). (Figure 1, Figure 2) The predominant outbreak strain among 2015-2017 isolates was ST-13578, not previously observed worldwide before 2015. WGS analysis confirmed that ST-13578 isolates were clonal, genetically distinct from ST-1504. All tested strains were penicillin-susceptible (MIC <0.06 μg/mL).
Conclusion

ST-13578, an emerging Sp2 clone, was identified as the cause of an ongoing large IPD outbreak in Israel. Further follow-up is required to determine the unique characteristics of this clone.
Background and Aims:

A total of 886 suspected cases of meningitis were reported in BAR between 2nd December 2015 and 26th February 2016. Overall 135 cases of meningitis were confirmed by culture, rapid test and/or quantitative PCR (qPCR). QPCR identified Streptococcus pneumoniae serotype 1 (78%) as the predominant pathogen.

Methods:

Whole genome analysis was performed on a convenience sample of 11 serotype 1 strains isolated from the CSF of meningitis patients and one throat swab isolate recovered during the outbreak period. Using Gubbins a phylogenetic analysis was performed to compare the outbreak isolates to 108 West African sequence type ST217 and ST303 context genomes.

Results:

The outbreak was caused by a novel clade of ST303 serotype 1 that emerged from the West African ST303 clade primarily through recombination. Cases associated with the novel clade were most prevalent in the outbreak epicentre and among children >5 years and adults. The novel clade was likely circulating in the affected communities before the outbreak and presented evidence of on going spreading. We found no evidence of alteration to the capsular polysaccharide genes within the novel clade to suggest vaccine escape. However, we identified recombination events unique to the novel clade in areas of the genome implicated in fitness, immune evasion and virulence, which may have contributed to the ability of the clade to cause the outbreak.

Conclusion

These findings are significant because they show that despite the availability of an effective conjugate vaccine recombination can potentially drive outbreaks of S. pneumoniae by facilitating the rapid acquisition of advantageous genes.

ISPPD-0671
Rapid Minion Metagenomic Profiling of Pneumococcal Isolates from a Recent Meningitis Outbreak in Northern Nigeria: Full Genomic Characterisation


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Background and Aims:

The MinION® sequencing platform, a portable low-cost device with real-time analysis workflows makes the device attractive for in-field deployment during outbreak of infectious diseases in remote regions of the developing countries. We employed the MinION® platform for shotgun metagenomic sequencing directly from CSF samples as well as cultured pneumococcal isolates from a recent meningitis outbreak in Zamfara State, Nigeria.

Methods:

DNA was extracted from both CSF and S. pneumoniae isolates cultured from patients with meningitis. Libraries were prepared with the PCR free 1D ligation. The Rapid Library preparation kit is a simple 10-minute procedure that prepares DNA for one-dimensional sequencing. We used the ONT Metrichor analysis platform and the workflow for 'Whats In My Port' (WIMP) to analyse the MinION sequencing data in real time.

Results:

We showed that deep sequencing directly from CSF samples revealed very few reads that aligned to the pneumococcal genome. Sequencing cultured pneumococcal isolates from the same patient’s CSF samples resulted in >30% of the total number of reads and >80% of the classified reads identified S. pneumoniae. Galaxy long reads Nanopore assembly pipeline mapped a high number of reads with a high coverage of S. pneumoniae and Neisseria Spp genomes.

Conclusion

Our data using the MinION®, a fast, portable, low cost sequencing device, and with real time analysis workflows provided a rapid genomics solution in the classification and species identification of a recent meningitis outbreaks in Nigeria.
Background and Aims:

As part of efforts to assess pneumococcal conjugate vaccine (PCV10) effectiveness, we conducted a baseline nasopharyngeal carriage survey of *Streptococcus pneumoniae* in rural (Kumbotso, Kano) and urban (Pakoto, Ogun) Nigeria.

Methods:

In December 2016 and February 2017, we recruited 876 (Kano) and 924 (Ogun) participants, collected demographic and clinical data, and cultured nasopharyngeal swabs to identify pneumococci. We calculated crude and age-standardised carriage prevalence (against the 2013 INDEPTH network’s standard population).

Results:

Overall crude carriage prevalence in Kumbotso (74% [95%CI:71-77]) was higher than in Pakoto (50% [95%CI: 47-53]).

| Study location | Age group (years) | N  | %   | N  | %   | N  | %   | N  | %   | N  | %   |
|               |                  |    |     |    |     |    |     |    |     |    |     |
| Kumbotso (rural) | 0-4     | 295 | 145 | 76 | 66 |
|                | 5-17    | 288 | 79  | 77 | 53 |
|                | 18-34   | 71  | 31  | 20 | 26 |
|                | ≥50     | 6   | 2   | 9  | 27 |
| Pakoto (urban)  | 0-4     | 52  | 71  | 29 | 19 |
|                | 5-17    | 79  | 31  | 20 | 26 |
|                | 18-34   | 53  | 33  | 6  | 32 |
|                | ≥50     | 50  | 28  | 32 | 23 |

The age-standardized prevalence of pneumococcal carriage was 66% in Kumbotso and 40% in Pakoto. The most commonly identified serotypes were 19F, 6A and 23F.

Conclusion

Pneumococcal carriage prevalence is high in Nigeria. An infant PCV10 programme may not quickly eliminate transmission of PCV10-serotypes given their prevalence in older children and adults. Therefore, a high vaccination coverage is essential for full protection of children.
The long-term sustainability of expensive Pneumococcal conjugate vaccines (PCV) in low income countries (LICs) is threatened by the absence of robust local effectiveness data. Surveillance for invasive pneumococcal disease (IPD) is expensive and complicated. However, repeated cross-sectional surveys of carriage prevalence are feasible and affordable in LICs and these can be used in mathematical models to extrapolate changes in IPD attributable to PCV. These models are critically dependent upon measures of serotype-specific invasiveness.

Methods:

In a systematic review, we searched electronic databases for published articles from 01/01/40 to 31/01/17 reporting IPD and carriage data from the same population. Using serotype-specific numbers of IPD cases and serotype-specific numbers of pneumococcal carriers at each site we estimated the pooled odds ratio for invasion for each serotype standardised against serotype 14 in a random-effects model and quantified heterogeneity.

Results:

Of 16 relevant articles- 10 were from HICs, 4 from Africa, 1 each from Oceania and South America. Although some heterogeneity was apparent, the range and direction of ORs were largely similar for vaccine (VT) and non-VT serotypes in LICs and HICs. Serotypes 5 and 1 were the most invasive regardless setting (figure 1).

Conclusion
Our results can be used in models of PCV effectiveness based on changes in VT-carriage in LICs. With continued PCV use, non-vaccine type (VT) may become increasingly implicated in IPD according to their rank order of invasiveness.

ISPPD-0159
STABLE DYNAMICS OF STREPTOCOCCUS PNEUMONIAE OVER 10 YEARS IN PRE-PCV ISRAEL
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Background and Aims:

Streptococcus pneumoniae (SP) carriage studies are important understand the level of circulating vaccine type (VT) and non-vaccine type (NVT) SP before the introduction of vaccination programs. It is generally not known how stable these levels are over time and subsequently how many carriage studies are necessary to completely characterize the dynamics in populations. Here we show that both VT and NVT carriage levels are stable over ten years in populations of Jewish and Bedouins in Southern Israel.

Methods:

Eight carriage surveys were carried out in Jewish and Bedouin populations in Southern Israel between 1997 and 2008. We reanalyze these studies to estimate age dependent SP carriage, among children under two years of age, in the decade prior to PCV introduction.

Results:

We estimate overall SP carriage at 6 months of age to be stable around 0.35 in the Jewish and 0.7 in the Bedouin populations (see Figure). Similarly, we find VT carriage at 6 months to be stable in both the Jewish and Bedouin populations at around 0.2 and 0.4, respectively.

Figure: stable carriage prevalence in Jewish and Bedouin populations in Southern Israel.
Conclusion

The relative stability of SP carriage in two disparate populations in Southern Israel over 10 years supports the possibility that only a single carriage survey in a new population is sufficient to characterize SP dynamics. This has important consequences for rolling out new vaccine programs across the globe.

ISPPD-0662
SPATIOTEMPORAL DYNAMICS OF STREPTOCOCCUS PNEUMONIAE IN RURAL PAKISTAN
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Background and Aims:

Knowing how S. pneumococcus (SP) carriage varies in time and space aides in rollout of new vaccination programs through identifying potential ‘hotspots’ of transmission as well as estimating the level of herd-protection induced by those vaccination programs. Largely, these spatiotemporal dynamics are underexplored in developing settings.

Methods:

An ongoing NP carriage survey near Karachi, Pakistan randomly selects 60 infants per month and gathers information on illness indicators, socioeconomic status, and household demographics, and records the spatial coordinates of each individual. These data were modeled as spatial point patterns and space-time clusters were identified using Ripley’s K function.

Results:

Significant clusters were observed over the study area across three years. Over time, the physical distance between children vaccinated with PCV and vaccine-type SP carriage increased, giving an indirect estimate of herd immunity induced by PCV.

Conclusion:

Clear spatiotemporal patterns of SP carriage exist in rural Pakistan, and are associated with PCV vaccinated individuals, indicating the need for uniform vaccination coverage when introducing it to new populations.

ISPPD-0104
SEROTYPES AND ANTIBIOTIC SUSCEPTIBILITY OF STREPTOCOCCUS PNEUMONIA ISOLATES FROM INVASIVE PNEUMOCOCCAL DISEASE IN ALGERIA (2006-2016).
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Background and Aims:
In the present study, 148 strains of S. pneumoniae were isolated from patients with invasive infections in the University Hospital Benbadis from Constantine, Algeria, across the period 2006-2016. Antibiotic susceptibility and multi-drug resistance were investigated and serotype distribution was analyzed. Furthermore, the theoretical coverage of the 13-valent conjugate vaccines was evaluated.

Methods:

From 2006 to 2016, a total of 148 non-duplicate invasive S. pneumoniae isolates were identified. Isolates were obtained from cerebrospinal fluid (CSF), blood, and pleural fluid. All isolates were originally identified, and antibiotic resistance was determined by disk diffusion test (CLSI 2014). A total of 9 antibiotics were tested including. The minimum inhibitory concentration of penicillin, amoxicillin, and cefotaxime were determined using the E test method. The serotypes were determined by agglutination by latex particles and/or by the Neufeld test.

Results:

Among the 148 isolates, 55.4% were non-susceptible to penicillin (PNSP), 47.97% were resistant and 7.43% were intermediate (MIC range 0.5-4 μg/ml). Resistance rates to other antibiotics were as follows: erythromycin 31.75%, cotrimoxazole 52%. All the strains were susceptible to vancomycin, levofloxacin, and linezolid. The predominant serotypes were 14 (23.68%), 19F (18.42%), 6B stage, the rate of this serotypes were 14 (19.56%), 19F (15.21%), 6B (15.21%) and 23F (8.69%). The theoretical coverage of CV13 added up to 74%.

Conclusion:

Continual surveillance of antibiotic susceptibility and serotype distribution is recommended in order to plan future treatment and preventive strategies. The expanded coverage offered by PCV13 will provide additional protection against pneumococcal diseases in Algeria. Pneumococcal vaccination has been introduced in the national immunization program in Algeria since April 2016.

Background and Aims:

Streptococcus pneumoniae is a major cause of meningitis, septicaemia, and pneumonia in The Gambia. Pneumococcal carriage is a prerequisite for disease and children in The Gambia are reservoirs for pneumococcal serotypes. The effect of PCV7 on genomic epidemiology of pneumococcus in the nasopharynx has not yet been described in The Gambia. Here, we present baseline genomic data on the epidemiology of pneumococcal carriage in rural Gambia prior to the introduction of PCV7.
Methods:

Nasopharyngeal swabs (NPS) collected from participants aged 0-25 years as part of a carriage surveillance in The Gambia in 2009 were cultured on Gentamicin Blood Agar (GBA) and presumptive S. pneumoniae was confirmed by Optochin test (Oxoid) and subjected to whole genome sequencing (WGS). The phylogeny of the isolates was visualised in the context of accessory genome clustering using micro react.

Results:

Commonly carried serotypes in our dataset were 6A/6B, 19F/19A, 3, 23F and 34. There was a high level of diversity amongst 6A isolates as isolates clustered divergent clades with distinctive clustering of accessory genome. Within Serotype 3 isolates belonging to the same serotype, formed monophyletic clades. Nine non-typeable were placed as outliers on the tree. However one non-typeable clustered with serotype 14 isolates. Similarly ST910 isolates from serotypes 17F, 15B and 23A formed a unique clade.

Conclusion

We observed a high level of diversity between and within serotypes. The impact of PCV13 on the evolution of pneumococcal carriage in Basse can be determined based on this data and ongoing carriage surveillance.

ISPPD-0184
PNEUMOCOCCAL DISEASE IS A CAUSE OF DEATH IN COSTA RICA
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Background and Aims:

Worldwide reported pneumococcal disease (PD) mortality is 8-30%; mortality in Costa Rican population is not known.

We pretended to determine the case-fatality rate of pneumococcal disease in Costa Rican Social Security Hospitals.

Methods:

Descriptive study of adult patients with microbiological culture-positive Streptococcus pneumoniae disease seeking care at two tertiary care hospitals in Costa Rica between the years 2014-2016. Information on demographics, clinical presentation, underlying comorbidities, and risk factors for PD was analyzed for each case.

Results:

We included 181 culture-positive patients, and we found that a total of 70 died (39 deaths per 100 cases of PD). Mortality in patients ≥ 65 y/o was higher than in younger patients (OR=2.5; 95%CI 1.2-4.9). Regardless of age, high-risk patients had a higher mortality than patients without risk factors for PD (OR=5.0; 95%CI 1.03-48.22). Out of known risk factors for PD, those with an increased risk of death were: chronic heart disease (OR=2.9; 95%CI 1.3-6.3),
cirrhosis, HIV infection, and asplenia. Findings in mortality for invasive and non-invasive PD, and for healthcare-associated and community-acquired PD were similar.

**Conclusion**

We conclude that the case-fatality rate for adult patients with PD was higher than that reported in other countries, despite invasiveness or infection origin at time of clinical presentation. These findings call for a future analysis of the causes of death in this population.

**ISPPD-0180**

SEROTYPE DISTRIBUTION OF STREPTOCOCCUS PNEUMONIAE AND POTENTIAL IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINES IN CHINESE CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**Background and Aims:**

To update the research evidence for the serotype distribution and to estimate the potential impact of pneumococcal conjugate vaccines (PCVs) before the license of PCV13 in mainland China, we performed this systematic review and meta-analysis.

**Methods:**

This meta-analysis were conducted on the pneumococcal serotype distribution publications concerning the pediatric patients <18-year in mainland China from 2000 to 2016. The literature was searched in PubMed, Ovid-EMBASE, Web of Science, CNKI and Wanfang. Heterogeneity and publication bias were tested by I², meta-regression, Egger’s and Begg’s test. The pneumococcal serotype and PCV serotype coverage rates were pooled using the random-effects model in Stata SE 12.0.

**Results:**

In total, 50 publications were included. Of included 896 invasive pneumococcal strains, the most common serotypes were 19F 23.4%, 19A 22.4%, 14 16.3%, 23F 6.6%, and 6B 4.9%; the pooled coverage for PCV10 serotypes was 61.4%, that for PCV13 was 87.4% and that for PPSV23 was 86.4%. Of the 7577 non-invasive strains, the most common serotypes were 19F 25.5%, 19A 8.4%, 23F 7.9%, 14 6.6%, and 6A 4.9%; the pooled coverage for PCV10 serotypes was 43.2%, that for PCV13 was 55.7% and that for PPSV23 was 53.4%. The major changes of pneumococcal serotypes from 1996 to 2016 in mainland China were the increasing of serotype 19A and 19F since 2000-2004.
Conclusion

The most common pneumococcal serotype of children in mainland China was 19F. The serotype coverage rates of PCV13 and PPSV23 were high in mainland China.
Our review highlights how critical uncertainties in the relationship between carriage and transmission can contribute to disparate outcomes of predictive models. This work reiterates the importance of incorporating accurate biological assumptions about the role of asymptomatic carriers in models of infectious diseases, informed by detailed population based surveys of the carriage state.

ISPPD-0071
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Background and Aims:
This study aimed to evaluate the importance of pneumococcus in invasive bacterial infections, and to analyze the serotypes of pneumococci isolated from invasive infections among children after introduction of PCV10 and PCV13 into the national immunization program in 2014.

Methods:
This is a retrospective study of children under 18 years of age who were diagnosed as invasive bacterial infections at 25 tertiary hospitals located throughout the Republic of Korea from September 2013 to December 2016. Pneumococcal isolates from patients with invasive pneumococcal disease were collected prospectively from January 2014 to February 2017. Serotypes of pneumococci were determined by Quellung reaction, polymerase chain reaction, or sequencing of cps genes.

Results:
A total of 806 cases of invasive bacterial infections among immunocompetent children were identified and 101 cases (12.5%) were caused by pneumococcus. Pneumococcus was the most common pathogen in the 3-23 month group (38.2%) and the 24-59 month group (41.9%). A total of 92 isolates were available for serotyping. Most common serotypes were 10A (17 isolates), followed by 12F/A (10 isolates) and 15A (9 isolates). Three isolates (3.3%) were PCV7 serotypes, two isolates (2.2%) were PCV10 additional serotypes, and ten isolates (10.9%) were PCV13 additional serotypes. Overall, 83.7% (76 isolates) were nonvaccine serotypes.

Conclusion
Pneumococcus was the most common cause of invasive bacterial infections among children aged 3-59 months. The percentage of vaccine serotypes causing invasive pneumococcal diseases was decreasing.

ISPPD-0437
PEDIATRIC INVASIVE BACTERIAL DISEASE FROM 66 COUNTRIES REPORTING TO THE GLOBAL SENTINEL SITE INVASIVE BACTERIAL VACCINE-PREVENTABLE DISEASE (IB-VPD) SURVEILLANCE NETWORK (2008-2016)
A. Cohen²
Background and Aims:

In 2008, the World Health Organization (WHO)-coordinated Sentinel Site Invasive Bacterial Vaccine-preventable Disease (IB-VPD) Surveillance Network was established to standardize the monitoring of the global burden and etiology of IB-VPD, primarily in low- and middle-income countries. Data are described on meningitis and pneumonia cases identified between 2008 and 2016.

Methods:

WHO received case-based clinical and laboratory surveillance data from participating sentinel hospital surveillance sites. Case-patients were patients aged <5 years admitted to sites meeting a standardized case definition for meningitis or pneumonia/sepsis. Cerebrospinal fluid and/or blood was obtained and tested by culture and rapid diagnostic tests at the hospital and polymerase chain reaction assay at local, national, or regional reference laboratories.

Results:

From 2008 to 2016, 171,011 suspected meningitis and 73,008 suspected pneumonia/sepsis cases were reported from 263 surveillance sites in 66 countries. Of 6423 (4%) meningitis cases with a pathogen identified, 3,734 (58%) were pneumococcus, 1,170 (18%) Haemophilus influenzae, and 1,519 (24%) meningococcus. Of 544 (1%) pneumonia/sepsis cases with a pathogen identified, 405 (74%) were pneumococcus, 133 (24%) Haemophilus influenzae, and 6 (1%) meningococcus. Pneumococcal serotype was determined for 681 (38%) pneumococcal cases detected in 2014-6. Globally, serogroup 6 (15%) and serotypes 19A (12%) and 19A (8%) were the most prevalent types.

Conclusion

Pneumococcus was the most commonly identified cause of pediatric invasive bacterial disease globally in low and middle income countries. Serotypes 19A and 14 and serogroup 6 were the most commonly identified types.

ISPPD-0364
GLOBAL AVAILABILITY OF PNEUMOCOCCAL SEROTYPE DISTRIBUTION DATA IN RECENT YEARS
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Background and Aims:

Serotype distribution data are important to assess vaccine impact and whether there are emerging serotypes not covered by existing pneumococcal conjugate vaccines (PCVs). This study aimed to report availability of serotype data and identify data gaps.

Methods:
An electronic database was created to capture serotype data from original studies with pneumococcal isolate collection and typing from around the globe, published in recent years (2012 - 1Q2017). Primary sources of data were full publications retrieved from PubMed/Medline and EMBASE databases. Key exclusion criteria were publications before 2012, language not English, and studies with number of isolates < 50. Data extracted included country and region, population characteristics, and disease type (ie, invasive pneumococcal disease vs non-invasive pneumococcal disease including acute otitis media [AOM] and nasopharyngeal carriage).

Results:

A total of 308 publications met the inclusion criteria: 56 from Africa/Mediterranean, 69 from Asia-Pacific, 115 from Europe, 25 from Latin America-Caribbean, and 43 from Northern America. A large proportion of the data originated from distinct countries (e.g., Spain, USA, Israel), whereas data were scarce for several populous countries (e.g., Indonesia, Pakistan, Nigeria, Bangladesh). There were more data from the pediatric than the adult population. Data from AOM and pneumonia cases were much fewer than those from IPD and nasopharyngeal carriage.

Conclusion

Although a large body of published serotype distribution data is available, data gaps exist for resource limited countries in specific geographic areas, and for AOM and pneumonia.

ISPPD-0656
PNEUMOCOCCAL SEROTYPE DISTRIBUTION: A SNAPSHOT OF RECENT DATA IN PEDIATRIC POPULATIONS AROUND THE WORLD, 2016-17
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2Analytica Laser, Value Access, Montreal- QC, Canada

Background and Aims:

Despite availability of pneumococcal conjugate (PCV) and polysaccharide (PPV23) vaccines, pneumococcal disease remains a global health problem due to persistent and emerging serotypes.  systematic literature review is conducted to monitor recent changes in serotype distribution among children.

Methods:

Reviews of Medline, EMBASE and Cochrane reviews were performed from February 2016 to April 2017, using the terms serotype, serogroup, pneumococcus*, streptococcus pneumoniae; serotype distribution data for children under the age of 6 years were extracted and summarized.

Results:

Serotype data were available in 33 original articles covering varying periods, including 26 from areas/periods where pediatric PCV was part of immunization programs. Most (21) publications covered nasopharyngeal carriage, 7 covered invasive pneumococcal disease (IPD) only, 4 acute otitis media only and 2 non-IPDs. Globally, pooled results suggested the 6 most prevalent serotypes were PCV13-specific: serotype 19A ranked in the top 10 in all regions, including first in both Europe and Asia-Pacific while serotype 14 was most prevalent.
overall in Latin America and the Africa/Eastern Mediterranean region. In the US, the most prevalent serotype was 15B, not a PCV-13 serotype. Serotypes 22F and 33F were among the top list of serotypes in IPD and were 1.6% and 0.8% prevalent, respectively, in carriage/non-IPD. Non-vaccine serotypes were highly prevalent, varied by countries/regions, and were detected in 37.7% (U.S.) and 25.7% (Europe) for IPD and non-IPD studies combined.

Conclusion

PCV specific serotypes continue to be carried globally in children; non-PCV serotypes tend to be more common as penetrance of PCV increases.
Background and Aims:

Given the rapid decrease in DNA sequencing cost in recent years, researchers now face new challenges regarding management of the amount of data provided by these new technologies. In this context, we aimed to create an online tool to perform serotyping, MLST, resistance and virulence genes detection of pneumococcus, that would bring an ease to use, management and with the ability to analyze a large number of isolates.

Methods:

The online tool was developed adapting pre-existing scripts that used PneumoCaT for serotyping and SRST2 to MLST, resistance genes and the virulence markers pspA, pspC, ply, pavA, lytA, phtA,B,D,E nanA,B,C, rrgA (pilus 1), sipA (pilus2), pcpA and psrp.

Results:

A novel open source tool was specifically created to automate the process of analyzing big quantities of short reads data. Serotyping, MLST and resistance genes are already functional. Validation is being conducted with a database with 111 isolates from Massachusetts Eye and Ear Infirmary and having a 100% congruence with previous methodologies used. To perform the analysis, the users allow the system to access their private account through Dropbox API, and do not need to upload large files. Another advantage is the ability to make more than one analysis at the same time on the same samples without any cost to the users.

Conclusion

An online tool for analysis of pneumococcus is being successfully created for serotyping, MLST and resistance genes detection. We intend to integrate virulence genes analysis and other new tools to this workflow in the coming months.
Background and Aims:

Community-acquired pneumonia (CAP) is the third leading cause of death worldwide, particularly among children aged ≤5 years and adults aged ≥50 years. The aim of this study is to compare the mortality rates for CAP in children (≤5 years) from the pre 13-valent pneumococcal conjugate vaccine (PCV13) introduction period and the following years of PCVs application in four Latin American (LA) countries.

Methods:

Annual CAP mortality rates (per 100,000 populations) were calculated before and after PCV13 introduction in the National Immunization Programs (NIPs) in Guatemala, Panama, Mexico and Uruguay. The data extracted for this analysis are in public domain official websites by country (ie, “health statistics”, “vital statistics”, “population statistics”, etc.). PCV coverage rates have been extracted from the World Health Organization (WHO) and Panamerican Health Organization (PAHO) website. The percent of CAP mortality rates change was calculated (proportion test has been used, P < 0.05 were considered statistically significant).

Results:

<table>
<thead>
<tr>
<th>CAP Mortality Rates n(100,000 population)</th>
<th>Pre-PCV</th>
<th>Post-PCV</th>
<th>Difference (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guatemala (PCV13)</td>
<td>139</td>
<td>123</td>
<td>-12</td>
<td>0.1381</td>
</tr>
<tr>
<td>Panama (PCV13)</td>
<td>49</td>
<td>38</td>
<td>-23</td>
<td>0.0350</td>
</tr>
<tr>
<td>Mexico (PCV13)</td>
<td>16</td>
<td>10</td>
<td>-38</td>
<td>0.0001</td>
</tr>
<tr>
<td>Uruguay (PCV13)</td>
<td>12.5</td>
<td>2.5</td>
<td>-80</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

1prePCV 2011/postPCV 2015, PCV coverage: 85% primary; 50% booster.
2prePCV 2010/postPCV 2015, PCV coverage: 90% primary; 80% booster.
3prePCV 2010/postPCV 2015, PCV coverage: 90% primary; 90% booster.
4prePCV 2009/postPCV 2015, PCV coverage: 95% primary; 90% booster.

Conclusion

After the PCV13 introduction in the NIPs, the CAP mortality rates significantly decreased in children ≤5 years old, demonstrating a very important impact on public health in the region.

ISPPD-0384

SEROTYPE PREVALENCE OF Streptococcus pneumoniae CARRIAGE IN CHILDREN UNDER 5 YEARS OF AGE IN SOUTHEAST ASIA : A SYSTEMATIC REVIEW

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Background and Aims:
Prevalence of pneumococcal carriage is very high among young children and the rates were varied across Asia. Wide range of studies in pneumococcal carriage in children has been conducted in recent years. However, summary of serotype prevalence from findings in Southeast Asia were still limited. We aimed to summarized published data on the serotype prevalence of \textit{S. pneumoniae} carried in the nasopharyx of children under 5 years of age in Southeast Asia.

**Methods:**

We performed a systematic review and meta-analysis for relevant studies on pneumococcal carriage from online journal databases published between January 2012 to December 2016.

**Results:**

Meta-analysis showed the pooled prevalence of PCV13-type in healthy children under 5 years of age in Southeast Asia was 56.76 (95% CI: 54.58% - 58.93%). The highest rate of PCV13-type was in Cambodia 70.20% (95% CI: 62.79% - 77.62%) and lowest rate was found in Indonesia 45% (95% CI: 32.56% - 57.53%). Pooled estimation of serotype 6A/B, 19F and 23F was 20.54% (95% CI: 13.91% - 27.17%), 11.79% (95% CI: 7.61% - 15.97%) and 11.84% (95% CI: 9.59% - 14.09%) respectively. Non-PCV13-type (NVT) prevalence was still relatively high with pooled estimation of 28.13% (95% CI: 22.54% - 33.72%) and highest rate was found in Indonesia 36.94% (95% CI: 25.63% - 48.24%).

**Conclusion**

PCV13-type prevalence was still high in Southeast Asia. At least half of \textit{S. pneumoniae} serotype circulating in children under <5 years of age were PCV13-type with serotype 6A/B, 19F and 23F being the most common.

ISPPD-0707

RACIAL DIFFERENCES IN INVASIVE PNEUMOCOCCAL DISEASE IN YOUNG CHILDREN

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**Background**

Invasive pneumococcal disease (IPD) remains an important cause of morbidity and mortality among children aged <2 years, particularly in black children. We previously described near elimination of racial differences post-PCV13. We sought to determine if these differences persisted six years after widespread use of PCV13.

**Methods**

We used population and laboratory-based IPD surveillance data for children <2 years from the CDC Active Bacterial Core Surveillance program (1998-2013) for Tennessee. The data were divided into 4 eras: Pre-PCV7 (1998-1999), Early-PCV7 (2001-2004), Late-PCV7 (2005-2009), and Post-PCV13 (2011-2016); and race-stratified into black and white. The transitional years 2000 and 2010 were excluded. Population based rates were calculated using census data, and IPD rates were compared using incidence rate ratios.

**Results**
Table 1 shows annualized IPD rates per 100,000, stratified by race and vaccine era.

<table>
<thead>
<tr>
<th>Vaccine Period</th>
<th>Total IPD Rate in Children &lt;2 years</th>
<th>IPD Rate in Black Children &lt;2 years</th>
<th>IPD Rate in White Children &lt;2 years</th>
<th>IRR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-PCV7</td>
<td>177</td>
<td>257</td>
<td>125</td>
<td>2.06</td>
<td>1.62-2.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early-PCV7</td>
<td>68.4</td>
<td>88.2</td>
<td>52.6</td>
<td>1.68</td>
<td>1.28-2.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late-PCV7</td>
<td>55.6</td>
<td>63.9</td>
<td>41.8</td>
<td>1.53</td>
<td>1.16-2.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-PCV13</td>
<td>22.7</td>
<td>25.4</td>
<td>15.3</td>
<td>1.66</td>
<td>1.11-2.48</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IRR: Incidence Rate Ratio; 95% CI: 95% Confidence Interval

Figure 1 demonstrates decreases in IPD rates over time with increased rates in black children compared to white children.
Conclusions
We observed persistent racial differences in the incidence of IPD, with black children aged <2 years having higher rates than white children aged < 2 years. Although PCV introduction has decreased the magnitude of racial differences, inequalities persist. Further studies should be conducted to better understand the etiology of these differences and which serotypes predominate post-PCV13.

ISPPD-0705
GENDER DIFFERENCES IN INVASIVE PNEUMOCOCCAL DISEASE
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Background and Aims:
We previously described higher rates of invasive pneumococcal disease (IPD) in males compared to females from 1998 to 2013. Although IPD rates declined after introduction of pneumococcal conjugate vaccines (PCV7 and PCV13), gender differences in IPD rates persisted in the first three years after PCV13 introduction. We sought to determine whether these differences persisted six years after widespread use of PCV13.

Methods:
We extracted population and laboratory-based IPD surveillance data from the CDC Active Bacterial Core Surveillance program for Tennessee. Data were divided into four eras: Pre-PCV7 (1998-1999), Early-PCV7 (2001-2004), Late-PCV7 (2005-2009), and Post-PCV13 (2011-2016); and age-stratified into <2, 2-17, 18-39, 40-64 and 65 years and older. The transitional years 2000 and 2010 were excluded. Population based rates were calculated using census data and IPD rates were compared using incidence rate ratios.

Results:
9828 IPD cases were identified. Overall IPD rates were higher among males than females in all age groups, especially among adults aged 40-64 (Figure 1). Rates continued to decline in both males and females after the introduction of PCV7 and PCV13. Significant gender differences were eliminated following PCV13 introduction in age groups 2-39, who had among the lowest IPD rates overall.
Conclusion

Males had persistently higher rates of IPD than females in TN. Additional study is needed to understand the reasons for these differences and their potential implications in vaccine-derived indirect protection.

ISPPD-0092
SEROTYPE DISTRIBUTION AND ANTIMICROBIAL RESISTANCE OF INVASIVE STREPTOCOCCUS PNEUMONIAE IN CANADA IN ADULTS ≥65 YEARS OF AGE, 2010 – 2016
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Background and Aims:

The 13-valent polyvalent conjugate vaccine (PCV13) introduced in 2010 for children resulted in reduction of invasive pneumococcal disease (IPD) caused by PCV13 serotypes in all ages.

Methods:

A total of 7,282 IPD isolates of IPD from people ≥65 years were serotyped from 2010–2016. Serotyping was performed by Quellung reaction using commercial antisera and antimicrobial susceptibilities were determined by broth microdilution.
Results:

Although incidence of IPD among children declined significantly from 18.2–10.8 cases per 100,000 between 2010–2016, only marginal declines from 23.4–20.3 cases per 100,000 have been observed in adults ≥60 years. In adults ≥65 years, PCV7 serotypes have remained relatively constant, declining from 9.1% (n=96) to 6.7% (n=72), however the additional 6 serotypes in PCV13 have declined significantly from 39.5% (n=418) to 18.6% (n=201) (p <0.05). Pneumococcal polysaccharide vaccine (PPV23) and non-vaccine (NVT) serotypes increased from 26.3% (n=278) to 36.2% (n=393) (p <0.05), and from 25.1% (n=266) to 38.4% (n=416) (p <0.05), respectively. There were no significant changes in antimicrobial resistance rates from 2010–2016: 24.1% of the IPD from adults ≥65 years were resistant to clarithromycin (n= 609), 10.0% to doxycycline (n=254), 11.8% to penicillin (n=299), 5.2% to cefuroxime (n=131), 6.6% to clindamycin (n=168) and 6.0% to trimethoprim-sulfamethoxazole (n=152).

Conclusion

PCV13 successfully reduced IPD caused by PCV13 serotypes directly in children, and indirectly in adults through herd immunity effects. IPD in adults ≥65 years has remained constant from 2010–2016, however there has been a shift in the epidemiology due to the emerging predominance of non-PCV13 serotypes.

ISPPD-0634

PNEUMOCOCCAL VACCINATION IN ICELAND: PHID-CV10 EFFECTIVENESS AGAINST AOM ASSOCIATED ANTIMICROBIAL PRESCRIPTIONS IN CHILDREN UNDER THREE YEARS OF AGE

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5Reykjavík, Iceland

Introduction: Acute otitis media (AOM) is the most common cause of antimicrobial prescriptions in the pediatric population. The ten-valent pneumococcal conjugate vaccine (PHiD-CV10) was introduced into the pediatric vaccination program in Iceland in 2011. The aim was to estimate vaccine effectiveness against antimicrobial prescriptions for AOM in children under three years of age.

Methods: Ten consecutive Icelandic birth-cohorts (2005-2014) were followed from birth until age three or the end of the study period (December 31, 2016). Birth-cohorts were grouped as vaccine non-eligible (VNEC, 2005-2010) or vaccine eligible (VEC, 2011-2014). All physician visits for AOM and all filled antimicrobial prescriptions were extracted from two national registers. Using national identification numbers, prescriptions were linked to physician visits if filled within three days of the visit. The cumulative proportion, incidence rate and incidence rate ratio of AOM related prescriptions were calculated. An Andersen-Gill model was used to model individual level data, accounting for repeated events and censoring. Vaccine effectiveness was calculated as (Hazard ratio-1)x100%.

Results: Included were 49,293 children with 145,639 person-years of follow-up and 56,378 filled prescriptions. The cumulative proportion of AOM related prescriptions by three years of age decreased from 55.6% to 49.5% and the incidence rate decreased significantly from
42.4 to 32.5 prescriptions per 100 person-years The PHiD-CV10 vaccine effectiveness against AOM related antimicrobial prescriptions was 19.8% (95%CI 14.8-24.6%).

Conclusion: In this whole-population cohort study, the introduction of PHiD-CV10 was associated with a 19.8% decrease in AOM related antimicrobial prescriptions in children under three years of age.

ISPPD-0637
PNEUMOCOCCAL VACCINATION IN ICELAND: PHID-CV10 EFFECTIVENESS AGAINST ALL-CAUSE ANTIMICROBIAL PRESCRIPTIONS IN CHILDREN UNDER THREE YEARS OF AGE

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Background and Aims:

Introduction: Antimicrobial resistance is a threat to public-health and antimicrobial consumption is the main contributer to resistance. The ten-valent pneumococcal conjugate vaccine (PHiD-CV10) was introduced into the Icelandic vaccination program in 2011. The aim was to estimate vaccine effectiveness of PHiD-CV10 against all-cause antimicrobial prescriptions in children under three years of age.

Methods:

Methods: Eleven consecutive Icelandic birth-cohorts 2005-2015 were followed until age three or the end of the study period (December 31, 2016). Birth-cohorts were grouped as vaccine non-eligible (VNEC, 2005-2010) or vaccine eligible (VEC, 2011-2015). All antimicrobial prescriptions filled by children under three years of age were extracted from the National Drug Prescription Database. Incidence rates and incidence rate ratios between VNEC and VEC were calculated. An Andersen-Gill model was used to model the individual level data, accounting for repeated events and censoring. Vaccine effectiveness was calculated as (Hazard ratio-1)x100%.

Results:

Results: Included were 53,150 children with 151,992 person-years of follow-up and 231,660 filled prescriptions. The overall incidence rate decreased significantly from 157 to 144 prescriptions per 100 person-years. The vaccine effectiveness against all-cause antimicrobial prescriptions was 6.8% (95%CI 2.7-10.7%). The observed reduction was primarily mediated through the vaccine’s effect on the first (HR 0.89, 95%CI 0.87-0.90), second (HR 0.95, 95%CI 0.93-0.97) and third (HR 0.97, 95%CI 0.96-0.99) prescriptions.

Conclusion

Conclusion: Introduction of PHiD-CV10 into the pediatric vaccination program in Iceland was associated with a 6.8% decrease in all-cause antimicrobial prescriptions in children under three years of age.
MODELING THE CLINICAL IMPACT OF SWITCHING FROM A LOWER TO HIGHER VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN COLOMBIA, FINLAND AND THE NETHERLANDS

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Background and Aims:

Widespread use of 10-valent (PCV10; Synflorix, GSK) or 13-valent (PCV13; Prevenar 13; Pfizer) pneumococcal conjugate vaccines (PCV) has resulted in an overall reduction of vaccine-type invasive pneumococcal disease (IPD) globally. However, serotypes not contained in the vaccines have emerged to replace those reduced by vaccination. Our objective was to model serotype dynamics and forecast future disease under each PCV program in Colombia, Finland and The Netherlands.

Methods:

Country-specific databases, supplemented with published data, informed historical incidence of IPD in Colombia (PCV7->PCV10; 2+1), Finland (PCV10; 2+1), and The Netherlands (PCV7->PCV10; 2+1). Observed age- and serotype-specific IPD trends from each country were used to forecast future IPD cases under continuous PCV10 use. UK serotype dynamics were used to model potential impact of a switch to a PCV13 program in each of these countries.

Results:

Over 5 years, switching to a PCV13 program was estimated to reduce overall IPD among 0-2 yo by an incremental 48% in Colombia, 50% in Finland, and 33% in the Netherlands, respectively, compared with continuation of the current vaccination strategy (Figure 1). In adults ≥65yo, there was expected decreases in overall IPD, due to herd effect, in Colombia (38.9%), Finland (22.2%), and the Netherlands (11.5%).

Conclusion

In Colombia, Finland and the Netherlands, switching from a PCV10 to PCV13 infant vaccination program could provide significant benefit in reducing the burden of IPD in children and older adults.
THE POTENTIAL IMPACT AND COST-EFFECTIVENESS OF CURRENT AND POTENTIAL PNEUMOCOCCAL CONJUGATE VACCINES IN INDIA

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Background and Aims:

Pneumococcal conjugate vaccination (PCV) has been introduced into India’s universal immunization programme (UIP) recently but on a limited scale. This study evaluates cost effectiveness of nationwide scale up of two available vaccines, PCV10 and PCV 13 compared to no PCV vaccination.

Methods:

The incremental cost-effectiveness (ICER) of introducing either PCV 10 or PCV 13 into India’s UIP compared to no vaccination was conducted using an age-stratified static cohort model. This model assesses the risk of different clinical presentations of pneumococcal disease at different ages, in both vaccinated and unvaccinated individuals. Besides the direct impact of PCV on vaccinated individuals, the model also considered potential indirect effects of PCV vaccination. The ICER for PCV-10 or PCV-13 introduction was estimated in terms of the incremental cost per DALY averted.

Results:

The ICER for PCV-10 and PCV-13 are US$ 295 and US$ 224 respectively from a societal perspective, and US$ 527 and US$ 470 from healthcare provider perspective. Adding either PCV-10 or PCV-13 to India’s UIP would avert around 62-78 thousand deaths and 681-827 thousand hospitalisations over thirty-year period. The potential reduction in pneumococcal disease through the vaccination programme would also save around US$ 979-1,227 million in healthcare costs and around US$ 3,748-3,659 million in societal costs over thirty year period.

Conclusion

Introducing PCV10 or PCV13 in India’s UIP appears to be highly cost effective compared to no vaccination both from health provider and societal perspective. The ICERs remains robust not only for the base case scenario but also for other conservative scenarios considered.

PNEUMOCOCCAL MENINGITIS IN NSW CHILDREN, A REVIEW SINCE THE INTRODUCTION OF PNEUMOCOCCAL CONJUGATE VACCINES.

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Background and Aims:

Streptococcus pneumoniae is the main causes of bacterial meningitis among children in New South Wales (NSW). Since the introduction of both the 7 valent (PCV7 2005) and the 13 valent (PCV13 2011) pneumococcal conjugate vaccines into the National children’s
immunisation schedule, the incidence of meningitis has decreased. Recently this decrease has been slightly lessened by an increase in replacement serotypes, particularly 3 and 19A.

Methods:

Describe the epidemiological, clinical, and microbiological characteristics of children diagnosed with pneumococcal meningitis following PCV introduction. Patient demographic, clinical data and microbiological data were collected.

Results:

During 2002 to 2017, 171 cases of pneumococcal meningitis were notified in children aged <15 years. The overall incidence of disease has declined from 1.23 per 100 000 pre vaccine to on average 0.68 per 100 000 population a decrease of 44%. Pre-introduction of PCV’s, 85% of disease was caused by serotypes contained in the PCV7. Post PCV7 and PCV13 only 23% and 25% of disease was caused by serotypes contained in the vaccine. Of these 30% of disease was caused by serotypes 3 and 19A. There were 9/171 vaccine failures, 70% of these have been since the introduction of PCV13, all were caused by serotypes 3 and 19A.

Conclusion

The incidence of meningitis in children is low in NSW and this trend has continued post introduction of PCVs. The majority of disease was caused by serotypes not contained in the vaccine. However post PCV13 introduction, both serotypes 3 and 19A have accounted for the bulk of disease incidence and vaccine failures.

ISPPD-0113
DISTRIBUTION OF STREPTOCOCCUS PNEUMONIAE SEROTYPES AMONG ISOLATES FROM NON-STERILE RESPIRATORY SOURCES FROM ADULTS 65 YEARS AND OLDER IN THE UNITED STATES, 2004-2016
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Background and Aims:

As older adults are at increased risk for pneumococcal disease, a cause of morbidity and mortality worldwide, it is important to monitor both burden of disease and serotype epidemiology in the setting of pediatric and adult pneumococcal vaccination. We therefore evaluated the serotypes and antibiotic susceptibilities of Streptococcus pneumoniae respiratory isolates collected through the Tigecycline Evaluation Surveillance Trial (TEST) between 2004-2016.

Methods:

782 S. pneumoniae from adults ≥65 years old were collected in the US from sputum (707), trachea (57), head/ears/nose (8), and other respiratory sites (10). Serotypes were determined by PCR and Quellung testing. Antimicrobial susceptibilities were determined by broth microdilution and interpreted following CLSI guidelines.
Results:

Prevalence of serotypes contained in the conjugate and 23-valent vaccines is shown below. Post-PCV13 (2010-2016), the most common serotypes in respiratory specimens were 19A (14.9%), 22F (9.1%), 3 (8.7%), 11A (8.4%), and 35B (7.3%). The highest percentages of erythromycin-resistant isolates were found among serotypes 19A, 6A, 15B, 15C, and 35B, while the highest percentage of penicillin-intermediate isolates was found in serotype 19A.

Conclusion

These data, although limited in numbers, suggest that the indirect effect from pediatric vaccination does not fully protect older adults from diseases caused by PCV13 serotypes, particularly 19A and 3. Direct vaccination of adults > 65 years with PCV13 may be useful in reducing the burden of adult respiratory disease caused by these serotypes.

ISPPD-0758
PREDICTION OF NASOPHARYNGEAL COLONISATION OF STREPTOCOCCUS PNEUMONIAE USING SUPPORT VECTOR MACHINES IN CHILDREN WITH AND WITHOUT HIV AND THEIR PARENTS
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Background and Aims:

Machine Learning techniques like Support Vector Machine (SVM) can be used in longitudinal studies to predict outcomes. We used a novel SVM method to predict nasopharyngeal colonization (NPC) in families who participated in a vaccine trial. Longitudinal data is a combination of binary and continuous variables, which can be analyzed optimally with SVM. The model chooses certain data points for a decision boundary between the predicted outcomes.
Methods:

We collected 1742 nasopharyngeal swabs during a prospective cohort study on the impact of PCV-13 immunization in families in West Bengal. An SVM model with a Radial Basis Function kernel was applied after appropriate pre-processing. The data was stacked vertically and standardized. Missing data was imputed using a K-Nearest Neighbours approach or the observation was excluded. Most outcomes were negative, requiring appropriate penalization. A decision tree-based classifier selected 15 variables with highest predicting power. We divided the data into training (85%) and testing (15%), and 5-fold cross validation was used for training the SVM, after which prediction was carried out.

Results:

The most important factors were child’s age and CD4 counts. We report the accuracy metrics as follows:

<table>
<thead>
<tr>
<th></th>
<th>Precision</th>
<th>Recall</th>
<th>f1-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0.77</td>
<td>0.86</td>
<td>0.81</td>
</tr>
<tr>
<td>Positive</td>
<td>0.48</td>
<td>0.33</td>
<td>0.39</td>
</tr>
<tr>
<td>Average</td>
<td>0.69</td>
<td>0.72</td>
<td>0.70</td>
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</table>

Using SVM, we predicted the prevalence of pneumococcal colonization in the children two months into the future to be 15.48%, at an f1-score of 0.70.

Conclusion

SVMs are an efficient tool in analyzing data from longitudinal studies and predicting future outcomes.

ISPPD-0294
DECREASING 30-DAY MORTALITY FOLLOWING INVASIVE PNEUMOCOCCAL DISEASE, NORTH EAST OF ENGLAND, 2006–2016
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Background and Aims:

Against changing incidence, serotype distribution and age profile of cases of invasive pneumococcal disease (IPD), we explored changes in mortality over the last decade in the North East of England (NEE).

Methods:

In the NEE, cases of laboratory-confirmed IPD were reported to the enhanced surveillance system between 1 April 2006 and 31 March 2016. Clinical, microbiological and demographic data of cases were obtained from primary and secondary care physicians and the national reference laboratory. The association between 30-day all-cause mortality and
epidemiological year was estimated after adjustment for significant predictors using multivariable logistic regression. Factors investigated included age group, sex, clinical risk group, clinical diagnosis and vaccine-type serotype subgroup.

Results:

A total of 2,510 episodes of IPD were reported over the study period (~9.7/100,000 population per epidemiological year). Of these, 486 died within 30 days of IPD specimen date (~1.9/100,000 population per epidemiological year). Increasing age group (<5, 5-64, >64), male sex, being in one or more clinical risk groups, and a clinical diagnosis of septicemia (compared to pneumonia or meningitis) were independently associated with an increased odds of mortality when adjusted for epidemiological year. A significant decline in mortality over time was observed following adjustment for significant predictors (adjusted odds ratio: 0.961; 95% confidence intervals: 0.928-0.996; p-value: 0.028). Vaccine-type serotype subgroup was not associated with mortality.

Conclusion

A small but significant decline in 30-day all-cause mortality following IPD has been observed in the NEE population between 2006 and 2016. Nonetheless, certain population groups remain at increased risk of dying following IPD.

ISPPD-0563
DEATH FROM PNEUMONIA IN CHILDREN UNDER 5: A CAUSE OF DEATH ANALYSIS OF A DEMOGRAPHIC SURVEILLANCE SYSTEM (DSS) POPULATION IN LOW RESOURCE SETTING IN PAKISTAN
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Background and Aims:

92,000 children die from Pneumonia in Pakistan annually. Like resource limited settings, estimates are modeled leaving data gaps reflected in uncertainty around estimates. We aim to identify leading causes of deaths among children under five recorded prospectively in DSS.

Methods:

In DSS, covering population `300,000 in peri-urban Karachi, Pakistan, all pregnancies, births, deaths & migrations are recorded and tracked through GIS. For all child deaths detailed verbal autopsies (VA) are conducted after two weeks. Each VA is independently coded by two trained physicians for cause of deaths (COD), in case of discordance, a third physician codes it. If no concordance between either three, a specialist finally assigns the COD.

Results:

There were 1442 child deaths from 2008-2012 in DSS. VA was available for 1292(90%). 721(56%) were neonatal while 571(44%) post-neonatal deaths. Among all deaths, Pneumonia was identified 3rd leading cause for post-neonatal deaths 97(8%, 95%CI,6-9), while 4th for neonatal deaths 54(4%,95CI,3-5). Among post-neonatal deaths pneumonia was killing 17%(95CI, 14-20) children remaining persistent over years. Pneumonia was most
lethal 122(81%,95%CI,74-88) of all pneumonia related deaths) in first 6 months of life. Boys were vulnerable both in neonatal 67%, 95%CI,53-80) and post-neonatal 52%, 95%CI, 41-62). Deaths from pneumonia at home were (54%, 95CI,45-62) and hospitals (29%, 95%CI,22-37). GIS highlighted areas with poor nutrition and living conditions had high burden and mortality.

Conclusion

The results confirm that pneumonia remains a major killer in children under 5 in Pakistan. Better implementation of existing preventive and treatment strategies with careful monitoring are required to achieve SDG including Goal#3.

ISPPD-0606
A SYSTEMATIC LITERATURE REVIEW AND NETWORK META-ANALYSIS FEASIBILITY STUDY TO ASSESS THE COMPARATIVE EFFICACY AND COMPARATIVE EFFECTIVENESS OF PNEUMOCOCCAL CONJUGATE VACCINES
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3GlaxoSmithKline, Medical Affairs, Wavre, Belgium
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Background and Aims:

Network meta-analyses (NMAs) allow for indirect comparison of multiple interventions, even when direct head-to-head studies do not exist. This feasibility study (GSK study identifier: HO-17-18418) evaluated whether NMA methodology can be used to evaluate comparative vaccine efficacy/effectiveness (VE) of pneumococcal conjugate vaccines (PCVs) in preventing invasive pneumococcal disease (IPD) in children ≤5 years old.

Methods:

A systematic search was performed in June 2017 using predefined strings and selection criteria in Ovid and Cochrane databases. Key outcomes extracted included VE against IPD of all serotypes and vaccine type IPD. A NMA feasibility assessment using standard approaches evaluated the possibility to synthesize study results to estimate the comparative VE of PCVs. Differences within and between direct treatment comparisons were considered and study quality was assessed using Cochrane Risk of Bias tool for randomized controlled trials (RCT) and Newcastle-Ottawa scale for observational studies.

Results:

5,292 unique publications were screened, of which 26, published between 2000-2016, were included in the NMA feasibility assessment (4 publications from 2 RCTs, 7 indirect cohort analyses, and 15 case-control studies). Preliminary NMA feasibility assessment highlighted a disconnected evidence network when only RCTs were considered and heterogeneity across study designs and reporting of data (e.g., age group analysed, dose and schedule of vaccines, level of vaccine exposure, and patient characteristics such as age, gender, immunocompromised status, and comorbidities).

Conclusion
Preliminary feasibility assessment suggests NMA methodology is inappropriate to indirectly compare VE of PCVs due to the network structure of the studies and to the heterogeneity between these studies evaluating PCVs.

**ISPPD-0088**

**CHANGING INCIDENCE OF PNEUMOCOCCAL BLOODSTREAM INFECTIONS IN CHILDREN ≤5 YEARS AT QUEEN ELIZABETH CENTRAL HOSPITAL, MALAWI (1998-2016)**

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**Background and Aims:**

Childhood pneumococcal disease remains a leading cause of morbidity and mortality in many low- and middle-income countries (LMICs), despite the introduction of pneumococcal conjugate vaccines (PCV).

**Methods:**

We reviewed bacteraemia surveillance data obtained from children ≤5 years hospitalized at Queen Elizabeth Central Hospital (serving 1.3 million people) between 1998-2016, spanning introduction of PCV13 in Malawi in November 2011. We describe changes in the incidence of pneumococcal bloodstream infections (BSI) by age group over time.

**Results:**

A total of 71,251 blood cultures were obtained from children ≤5 years between 1998-2016. Of these, 23,544 (33.04%) yielded a pathogen; 1,035 (1.45%) yielded *Streptococcus pneumoniae*. Incidence rates for children ≤5 years peaked in 121 per 100,000 children in 1999 and 118 per 100,000 children in 2005, and then decreased to 18-78 per 100,000 children between 2006-2010, even prior to introduction of PCV13 in Malawi. Further reduction in rates were documented post-introduction. Pneumococcal BSI was primarily in children aged 2-5 years (30.7-46.1%) but was also detected in infants <60 days (10.3-13.9%).

**Conclusion**

We have seen a decrease in incidence of pneumococcal BSI in children ≤5 years even prior to introduction of PCV in Malawi, occurring alongside improvements in nutrition, mother-to-child HIV transmission, malaria control and other health indices. Understanding mechanisms that were driving the decline in IPD in the pre-PCV period will help us improve control in the
vaccine era. Continued pneumococcal BSI among young infants indicates the need to identify additional approaches to protect this vulnerable group.

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**ISPPD-0075**

**HEALTH RELATED QUALITY OF LIFE ON PNEUMOCOCCAL PNEUMONIA IN SOUTH INDIAN POPULATION.**

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**Background and Aims:**

Community acquired pneumonia causes considerable morbidity and mortality. The objective of this study is to assess the health-related quality of life (HRQoL) associated with pneumococcal pneumonia in South India.

**Methods:**

A telephone survey was conducted to assess the impact of pneumonia using EuroQoL EQ-5D-3 L (EQ-5D) instrument. The study was explained and verbal consent was obtained.

Participant with laboratory confirmed pneumonia were included in the study. HRQoL was determined 1-2 weeks after hospital discharge and 1, 6 and 12 months thereafter. One year quality—adjusted life years (QALY) were estimated for the subjects.

**Results:**

We interviewed 2500 subjects who had laboratory confirmation of pneumonia. The exclusion of other laboratory confirmed subjects include non-participation, busy line or non-answering, wrong number, loss due to follow up, privacy issues and unwillingness to disclose disease issues. The EQ-5D 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) had a poorer scoring along with a lower visual analogue score. The one-year excess QALY loss attributed to community-acquired pneumonia was 0.17. Mortality in the post-discharge follow-up year was 9.3 % in community-acquired pneumonia patients.

**Conclusion**

Pneumonia illness had a substantial impact on a lower HRQoL and increased mortality.

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**ISPPD-0261**

**PERSISTANCE OF VACCINE SEROTYPES CAUSING INVASIVE PNEUMOCOCCAL DISEASE AFTER INTRODUCTION OF THE 13-VALENT VACCINE IN CALGARY, CANADA**

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**Background and Aims:**

After the introduction of PCV7 in 2002, IPD caused by PCV7 serotypes (STs) was nearly eliminated at all ages. We now report on invasive pneumococcal disease (IPD) trends in the PCV13 era.
Methods:

The Calgary Area *Streptococcus pneumoniae* Epidemiology Research (CASPER) team has conducted surveillance on IPD in Calgary since 1998. Here we report on the incidence and ST trends pre-PCV13 (2008-09) and post-PCV13 (2010-16).

Results:

The overall IPD incidence was 8.7 cases/100,000/year pre-PCV13. By 2016 there was no significant change with an incidence of 9.5 cases/100,000/year (Risk difference of 0.08 (95%CI -3.1 to 14.6) per 100,000). All PCV13 STs declined in children but PCV13 STs caused 24% of childhood IPD in 2016. In adults, a ST4 outbreak, predominantly in homeless persons, persisted from 2014 to 2016 (causing 15% of IPD in 2016). ST3 and ST19A remained common (9% and 7% of IPD cases in 2016, respectively).

**Figure 1.** Cases of IPD by serotype groups in post-PCV13 years highlighting serotype 3, 19A and 4

Conclusion

More than 6 years after PCV13 introduction in Calgary, vaccine ST IPD is uncommon in children. However, ST3 and ST19A remain common in adults and an outbreak of ST4 predominantly in homeless persons, suggests that the indirect herd effect of PCV13 given to children is not consistent in adults for all ST.

**ISPPD-0401**

POINT PREVALENCE SURVEY OF ASYMPTOMATIC NASOPHARYNGEAL COLONIZATION BY *STREPTOCOCCUS PNEUMONIAE* IN OLDER ADULTS IN CALGARY, CANADA

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Background and Aims:

PCV13 is part of the childhood vaccine schedule in Calgary, and more recently is recommended for older and immunocompromised adults as well. Colonization in adults is not well studied. Our current aim is to measure nasopharyngeal colonization in older adults in Calgary.

Methods:

The Calgary Area Streptococcus pneumoniae Epidemiology Research (CASPER) team approached residents and visitors, aged 65 years and older, in 49 senior centres during the 2017 influenza vaccine campaign. None were acutely ill at the time of participation. Informed consent was obtained and nasopharyngeal swabs were collected from participants for standard culture as well as molecular identification of S. pneumoniae. In addition, a brief survey was performed and consent to collect information on immunizations and medication use was obtained.

Results:

Data collection for this study concluded at the end of October 2017. There were 716 participants, 697 (97.3%) with complete data, 71.7% were female. The average age was 82.3 years with a range of 65 to 101 years. Overall, 36.2% reported themselves to be healthy, 44.5% reported 1-2 active health problems and 19.4% reported 3 or more active health problems. Data collection on immunizations and medications are ongoing. One swab was positive for S. pneumoniae by standard culture methods. Of note, a heavy growth of Staphylococcus aureus was identified in 11 participants. Molecular detection for S. pneumoniae is pending.

Conclusion

Pneumococcal nasopharyngeal colonization is rare among older adults who are not acutely ill in Calgary, Canada.
We retrospectively analyzed all patients with the principal ICD9 diagnosis codes of AOM in the Truven Health Marketscan® Claim Databases during 2008-2014. Incidence rates of healthcare utilization related to the index AOM episode were calculated using the total number of enrolled persons-years as denominator and those with AOM as numerator. AOM costs were calculated as mean payment per episode during 2013-2014.

**Results:**

The overall annual AOM related healthcare utilization per 1,000 persons-years was 60.5 (ranged 58.4-62.6) with a highest rate in children aged < 18 years (162.3 ranged 152.4-169.4) compared to adults (30.5 ranged 27.9-32.4) in the study period. The age specific rate of AOM related healthcare utilization per 1,000 varied and declined with increasing age (474.3 in <1 year, 503.9 in 1 year, 316.3 in 2-4 years and 94.9 in 5-17 years). Rates of healthcare utilization per 1,000 were 55.7 (ranged 52.0-58.8), 4.7 (3.7-6.3), 0.0 (0.0-0.1) for office or outpatient visit, ER/UC and hospitalization, respectively. The mean cost per AOM episode (US$) was $199 (95%CI: 198-200), $330 (328-331), $1,593 (1,422-1,764) for office or outpatient visit, ER/UC and hospitalization, respectively.

**Conclusion**

Our findings show that AOM still represents substantial burden of healthcare utilizations and costs in the US and need for effective preventive measures against AOM.

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**ISPPD-0174**  
HEALTHCARE UTILIZATIONS AND COSTS ASSOCIATED WITH PNEUMONIA IN THE UNITED STATES IN THE POST PNEUMOCOCCAL CONJUGATE VACCINATION PERIOD  
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**Background and Aims:**

Pneumonia is the leading cause of morbidity and mortality worldwide. *Streptococcus pneumoniae* remains the most frequent cause of bacterial pneumonia in post PCV period. The burden of pneumonia is not well defined in the US.

**Methods:**

The study data included 132,270,389 person enrolled in the Truven Health Marketscan® Claim Databases during 2008-2014. Incidence rates of healthcare utilization related to the index pneumonia episode were calculated using the total number of enrolled person-years as denominator and those with a principal ICD9 diagnosis of pneumonia as numerator. Costs of pneumonia were calculated as mean payment per episode during 2013-2014.

**Results:**

The overall annual healthcare utilization rate of pneumonia was 15.1 (ranged 13.5-16.6) per 1,000 person-years over the study period (ranged 2.0-2.4 for hospitalization, 2.2-2.8 for ER/UC and 8.9-11.6 for office or outpatient). Rates of pneumonia related healthcare utilization varied by age groups with higher rates in persons <1 year (29.7 per 1,000), 1 year
(47.9 per 1,000), 2-4 years (39.5 per 1,000) and >65 years (45.0 per 1,000). Of the 4,386,058 pneumonia episodes identified, 13.9% were in children <5 years and 24.2% were in elderly >65 years and 88.3% required office or outpatient visits. The mean cost per pneumonia episode was US$429 (95%CI: 425-434), $1,127 (1,120-1,134), $10,963 (10,823-11,102) for office or outpatient visit, ER/UC and hospitalization, respectively.

**Conclusion**

Our study documented that pneumonia still represents substantial burden of healthcare utilizations and costs in the US. Our data can help to guide new vaccination strategies and other interventions to reduce pneumonia.

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**ISPPD-0674**

**THE BURDEN OF PNEUMOCOCCAL DISEASE IN CUBAN BEFORE ROUTINE USE OF PNEUMOCOCCAL CONJUGATE VACCINE**

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¹Tropical Medicine Institute “Pedro Kouri”, Epidemiology, Havana, Cuba
²Finlay Vaccine Institute, Clinical Research and Impact Evaluation, Havana, Cuba

**Background and Aims:**

Cuba has a new heptavalent conjugate pneumococcal vaccine under advanced clinical development. The introduction in children 1-5 years old is scheduled in 2018. Estimates of disease burden are needed to inform about their use and impact. We reported the burden of pneumococcal cases and deaths in children younger than 5 years for 2015

**Methods:**

Mortality and morbidity attributable to pneumococcus were estimated for each of the three primary syndromes: pneumonia, meningitis, and invasive non-pneumonia, non-meningitis (NPNM). Disease incidence and case-fatality were calculate following the instructions of WHO estimation procedures for Global Burden of Diseases studies. The data was obtained from two domestic sources: National Bacterial Meningitis Surveillance System and the laboratory register from the National Reference Laboratory. Estimates were adjusted for HIV prevalence and access to health care. All analyses were conducted using Stata 14 (College Station, TX)

**Results:**

In 2015, about 970 severe cases (UR: 692 – 1209) were attended in Cuba due streptococcus pneumoniae infection and 39 deaths (UR: 23 – 59) were reported among children 1-59 months. Incidence rate of pneumonia severe cases was 149.16 (UR: 111.75 – 170.13) and CFR was 2% (UR: 1-2%). Over a period of one year, a total of 22 deaths were attributed to pneumococcal pneumonia (UR: 16-23), 9 to meningitis (UR: 14-19) and 8 to bacteremia (UR: 3-17). The CFR due pneumococcal meningitis achieved 18% (UR 8-37%)

**Conclusion**

Mobility and mortality reduction in children less than 5 could be achieved in Cuba with the accelerated pneumococcal vaccine introduction in preschool children

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**ISPPD-0543**
EMERGENCE OF A MACTEROLIDE RESISTANCE, ST6011 SEROTYPE 3 STREPTOCOCCUS PNEUMONIAE IN THE PCV13 ERA IN HONG KONG

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²The Chinese University of Hong Kong, Department of Microbiology, Hong Kong, Hong Kong S.A.R.

Background and Aims:

Hong Kong experienced an outbreak of invasive serotype 3 diseases despite the implementation of PCV13 vaccination. This study was conducted with the aim of characterizing the Serotype 3, Streptococcus pneumoniae present in the PCV 13 period, in Hong Kong.

Methods:

155, single patient, serotype 3 pneumococcal isolates obtained from clinical samples (87) and nasopharyngeal aspirates (68) during the pre-PCV, PCV7/10 and PCV13 periods were tested with PFGE and selected isolates were tested with MLST. Minimum inhibitory concentrations for selected antibiotics and PCR based detection of genetic markers for macrolide and tetracycline resistance were performed.

Results:

Two predominant clusters were identified. PFGE cluster 1 with representative MLST type 180 was found to decrease in proportion in while cluster 3 with representative MLST type 6011 was found to increase in the PCV 13 period (Table 1). All isolates of the emerging cluster was found to be resistant to erythomycin and tetracycline and harbored ermB.

Table 1: Clonal distribution before and after pneumococcal vaccination

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Pre-PCV (n,% )</th>
<th>PCV7/10 (n,% )</th>
<th>PCV13 (n,% )</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>25 (83.3)</td>
<td>50 (84.7)</td>
<td>36 (54.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>0</td>
<td>3 (5.1)</td>
<td>29 (43.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Time periods are Pre-PCV: Apr 05-Mar06; PCV7/10: Oct 09-Sep11; PCV13: Oct11-Sep13.

Conclusion

The persistence and the emergence of a relatively drug resistant cluster of serotype 3 in the post PCV 13 period is a reason for concern.

ISPPD-0694

VACCINE FAILURES FOLLOWING THE INTRODUCTION OF UNIVERSAL INFANT VACCINATION WITH PNEUMOCOCCAL CONJUGATE VACCINES USING A 3+0 SCHEDULE, QUEENSLAND, AUSTRALIA, 2005-2015

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²Australian National University, National Centre for Epidemiology and Public Health, Acton, Australia
³University of Queensland, UQ Centre for Children's Health Research, South Brisbane,
Australia

Background and Aims:

Publicly funded 7-valent pneumococcal conjugate vaccine (7vPCV) was introduced for all Australian infants at 2, 4, and 6 months of age in 2005 (3+0 schedule), and was replaced by 13vPCV in July 2011. A booster dose is available for Aboriginal and Torres Strait Islander children aged 12–18 months, as well as for children with medical conditions placing them at elevated risk of invasive pneumococcal disease (IPD). We aimed to describe the epidemiology of IPD among Queensland children aged younger than 5 years, with emphasis on cases of vaccine failure.

Methods:

Descriptive analysis of enhanced IPD surveillance data and vaccination records in children aged younger than 5 years, Queensland, 2005–2015. Vaccine failures were defined as those occurring in a child who completed a 3+0 primary PCV course (7v, 13v), where a serotype contained in all 3 PCV doses was identified as the infecting serotype.

Results:

Forty-three cases of PCV vaccine failure occurred from 2005 to 2015, the majority (74%) of which have occurred since the replacement of 7vPCV with 13vPCV. Since 2012, over 60% of vaccine failures were caused by serotype 19A, with 19F (19%) the next most common serotype. The median age of onset of vaccine failure was 22.2 months and the time since last PCV dose to onset of vaccine failure ranged from 4.5 to 51.6 months.

Conclusion

The number of 13vPCV vaccine failures were higher than expected. A dose of 13vPCV at or after 12 months of age should be considered to reduce the burden of vaccine failure IPD in children.

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ISPPD-0697
ESTIMATING THE RISK OF RECURRENT INVASIVE PNEUMOCOCCAL DISEASE, QUEENSLAND, AUSTRALIA, 1997-2015

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2Australian National University, National Centre for Epidemiology and Public Health, Acton, Australia
3University of Queensland, UQ Centre for Children’s Health Research, South Brisbane, Australia

Background and Aims:

Overseas evidence suggests that individuals with previous invasive pneumococcal disease (IPD) are at increased risk of future IPD. In Australia, certain groups with medical conditions at elevated risk of IPD are recommended and/or funded to receive pneumococcal vaccines, but those with previous IPD are not included. We sought to estimate the risk of recurrent IPD in Queensland, and explore the potential preventability of recurrent disease through pneumococcal vaccination.

Methods:
We conducted a retrospective cohort study of Queensland IPD notifications from 1997-2015, using time-to-event analyses to estimate recurrent IPD rates. Recurrence was defined as any repeat notification in an individual >30 days after the collection date of the initial notification. Cases surviving >14 days after illness onset contributed person-time at risk of disease from the illness onset date until death or end of the study period.

Results:

From 1997-2015, there were 6,075 notified cases of IPD reported in 5,955 individuals. Of these, 120 (2%) were recurrent episodes that occurred in 102 individuals. The annual rate of primary IPD during the study period was 7.8 per 100,000 and the recurrent IPD rate was 264.4 per 100,000 person-years. Forty-eight percent of individuals with recurrent IPD had no risk factor identified at the time of their first episode. Since 2012, one-third of recurrent episodes were caused by 13-valent pneumococcal conjugate vaccine serotypes.

Conclusion

Individuals with previous IPD are at substantially increased risk of future episodes that are potentially preventable through targeted use of pneumococcal vaccines. Those with previous IPD should be recommended and funded for pneumococcal vaccination.

ISPPD-0679
STREPTOCOCCUS PNEUMONIAE INVASIVE DISEASE RELATED SEROTYPES IN GUATEMALA CITY HOSPITALS
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2Hospital Roosevelt, Pediatrics, Guatemala, Guatemala

Background and Aims:

Invasive Pneumococcal Disease (IPD) is an important bacterial infection. Guatemala introduced PCV13 conjugated vaccine in 2013 in national immunization program. We report results from a surveillance study in two reference hospitals in Guatemala city.

Methods:

As part of a surveillance study in two Guatemala city reference hospitals we performed culture and RT-PCR for diagnosis of SN from sterile fluids, positive results were further tested by RT-PCR for 21 most common types in Latin America.

Results:

From March 2016 to September 2018, 225 patients were diagnosed with suspected IPD; 62 patients with meningitis, 41 sepsis, 39 other type of IPD were enrolled. 91 RT-PCR were screened by RT-PCR, with 36 positive cases (35% positivity rate). Serotypes and age distribution are showed on table 1 and 2.

TABLE 1: Diagnosis by Age

<table>
<thead>
<tr>
<th>UNDER 1-5 YEARS</th>
<th>5-25 YEARS</th>
<th>25-50 YEARS</th>
<th>50-65 YEARS</th>
<th>OVER 65</th>
<th>TOTAL</th>
</tr>
</thead>
</table>

243
Table 2: Serotype distribution by diagnosis

<table>
<thead>
<tr>
<th>SEROTYPE</th>
<th>PNEUMONIA</th>
<th>MENINGITIS</th>
<th>BACTEREMIA</th>
<th>PERITONITIS</th>
<th>SEPTIC ARTHRITIS</th>
<th>OTHER</th>
<th>TOTAL</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
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<td>2</td>
<td>3</td>
<td>2</td>
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<td>1</td>
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</tr>
<tr>
<td>19A</td>
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<td>1</td>
</tr>
<tr>
<td>3/19F/2</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td>1</td>
</tr>
<tr>
<td>5, 19A</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>7F/7A</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Other Non Vaccine Type</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion

Non vaccine serotypes are predominant in IPD in Guatemala after vaccine introduction.

ISPPD-0287
PREVALENCE OF PNEUMOCOCCI IN CONJUNCTIVAL FLORA AMONG VIETNAMESE CHILDREN


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4Pasteur Institute, Pathology, Nha Trang, Vietnam
5Murdoch Children’s Research Institute, Tropical medicine, Melbourne, Australia

Background and Aims:

*Streptococcus pneumoniae* a pathogen of keratoconjunctivitis and corneal ulcer, can exist as conjunctival flora. A Pneumococcal Conjugate Vaccine (PCV) reduced dosing schedule study was planned in Nha Trang, Vietnam. Therefore before PCV introduction, we investigated the baseline prevalence and characteristics of Pneumococcus in conjunctiva among children in Nha Trang, Vietnam.
Methods:

The study was conducted in 6 communes of Nha Trang between October and November 2016. We targeted to recruit 60 (4-11 months old), 60 (14-23 months old) children in each commune. Conjunctival swabs, nasopharyngeal swabs, and demographic data were collected. *S. pneumoniae* presence was screened by lytA realtime PCR and serotyping was done by microarray method. Characteristics of the children with *S. pneumoniae* in conjunctiva were analyzed by logistic regression.

Results:

A total of 699 children were enrolled of which 80 (11.4%) had Pneumococci in conjunctiva. Older age group, lower birth weight, respiratory-illness hospitalization history, cough, running nose, eye symptom in last two weeks, nursery attendance and nasopharyngeal Pneumococcus carriage were associated with Pneumococcus positive conjunctiva by univariate analysis. Lower birth weight (adjusted odds ratio [aOR] 0.9991, 95% confidence interval [95%CI] 0.9985-0.9997), nursery attendance (aOR 2.53, 95%CI 1.37-4.66), and nasopharyngeal Pneumococcus carriage (aOR 10.86, 95%CI 5.84-20.17) had positive association with Pneumococcus positive conjunctiva by multivariable logistic regression.

Conclusion

Pneumococcus in conjunctiva was detected in 11.4% of Vietnamese children aged less than 24 months in pre-PCV era. Lower birth weight, having ever been to nursery, and Pneumococcus carriage in nasopharynx were independently associated with conjunctival carriage.

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ISPPD-0363
STATISTICAL MODELS FOR INVESTIGATING THE IMPACT OF THE PNEUMOCOCCAL CONJUGATE VACCINE ON SUSPECTED MENINGITIS AMONG CHILDREN IN WEST AND CENTRAL AFRICA


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2Medical Research Council Unit - The Gambia, Vaccine and Immunity, Banjul, The Gambia
3WHO Regional Office for Africa, WHO Regional Office for Africa, Brazzaville, Congo

Background and Aims:

We explored statistical models to determine the impact of the pneumococcal conjugate vaccine (PCV) on suspected meningitis and mortality. Data from World Health Organisation (WHO) supported sentinel-based surveillance of meningitis in nine West and Central African countries collected between 2010 and 2016 were used.

Methods:

We used time-series plots to indicate when disease trends were altered in each country following PCV implementation. We evaluated several time points from intervention up to 18 months after intervention fitting interrupted time-series models with periodic functions (sine and cosine) to account for seasonality.

Results:
PCV was introduced in the countries between 2009 and 2015. Despite substantial heterogeneity, overall meningitis admission trends showed declining pattern except in Nigeria. The highest and lowest trend estimates (95%CI) 12 months after intervention were -2.4(-3.5,-1.2) and -0.01(-0.1,0.1) for Benin and Gambia respectively. The observed declines were not significant for all time points across the different countries. Nigeria had phased introduction of PCV and was also the last country to introduce PCV in the surveillance programme. The Fourier transforms fitted well for most countries (Figure 1). Similar declines were observed for mortality among children with suspected meningitis.

**Conclusion**

The introduction of PCV across West and Central African countries has led to declines suspected cases and mortality among children less than five years. Vigilant monitoring of invasive bacterial disease is needed to ensure that the gains made are sustained.

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**ISPPD-0195**

**IS TIME-SERIES TREND MODELING THE RIGHT APPROACH TO ESTIMATE THE EXPECTED PUBLIC HEALTH IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINES?**

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²GSK, Vaccines, Wavre, Belgium

**Background and Aims:**

With the advent of extensive epidemiological surveillance databases, time-series models (TSMs) are increasingly being used to assess the impact of vaccine introductions like Pneumococcal Conjugate Vaccines (PCVs) in various countries. The objective of this analysis was to assess the robustness of TSMs in estimating the impact of higher-valent PCVs.

**Methods:**

We calculated the incidence of Invasive Pneumococcal Disease (IPD) cases in children <5 and adults ≥65 years of age using surveillance data from England and Wales, Finland and Australia following the introduction of higher-valent PCVs. If only annual rates were available, a simple curve-fitting approach was used. If rates were available on a quarterly basis, a damped multiplicative Holt-Winters’ method was used. Incidence for the two age groups was projected 10 years forward from the last available data point.

**Results:**

The future estimates for IPD incidence based on historical data were observed to be highly dependent on the underlying model used. Non-vaccine type IPD incidence in older adults was estimated to increase irrespective of vaccine or TSM used, while a much smaller increase in children <5 years of age was observed for Finland and Australia compared to England and Wales.

**Conclusion**

While TSMs may be used to predict the short-term incidence of IPD, the underlying model chosen greatly impacts the results. Given the complex nature of pneumococcal disease, its transmission, and confounding factors affecting them, public health assessments using TSMs of surveillance data, or other models, have to be interpreted with caution.
**Funding:** GlaxoSmithKline Biologicals SA.

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**ISPPD-0278**

**CLONAL DIVERSITY, SEROTYPES AND ANTIMICROBIAL RESISTANCE INFERENCE OF S. PNEUMONIAE CAUSING INVASIVE DISEASE IN INDIAN CHILDREN BETWEEN 2009-2017**

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¹KIMS hospital and research center, Microbiology, Bangalore, India

**Background and Aims:**

Although *Streptococcus pneumoniae* is a leading cause of childhood pneumonia in India, very few studies have explored pneumococcal epidemiology using multilocus sequence typing (MLST). We aimed to study the population structure characteristics of pediatric invasive pneumococci by MLST, its serotype and antimicrobial resistance pattern and relate to serotypes included in the current pneumococcal conjugate vaccine (PCV13) used in National immunization programme.

**Methods:**

125 IPD isolates from several hospitals in the country collected during 2009-17 were analyzed. Serotypes were determined by PCRSeqTyping and/or Quellung reaction. Multilocus sequence types were identified analyzing seven housekeeping genes (aroE, gdh, gki, recP, spi, xpt, ddl). Sequence Types were analyzed for clonality with eBURST algorithm. Antibiotic susceptible profile was generated by broth microdilution method.

**Results:**

MLST analysis identified 59 known and 29 novel STs. eBURST analysis grouped the isolates into 5 clonal complexes and 67 singletons. The most frequent clonal types found were ST473 (n=6), ST289 (n=6) and ST320 (n=5). 18 (14%) isolates were related to seven of the 43 PMEN clones. The most common serotypes were serotype 19F (n=15), 1(n = 11) and 19A(n = 10). Antibiotic resistance for Erythromycin, Levofloxacin, Tetracycline and Cotrimoxazole was 31, 8, 40 and 60% respectively. Penicillin non-susceptible pneumococci accounted for 12% of isolates. 29% of the isolates had multidrug resistance. PCV13 covered 65% of the serotypes.

**Conclusion**

A high level of serotype and genetic diversity was observed in pediatric IPD strains. This study underscores the importance of a detailed population study to determine circulating pneumococcal serotypes and to monitor vaccine impact.

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**ISPPD-0297**

**NATIONAL SURVEILLANCE ON SEROTYPES AND ANTIMICROBIAL RESISTANCE IN S. PNEUMONIAE CAUSING IPD AMONG ADULTS IN ARGENTINA, 2013-2016.**

D. Napoli¹, P. Gagetti¹, C. Sorhouet¹, S. Fossati¹, M. Moscoloni¹, O. Veliz¹, A. Argentina Spn Working Group², R. Mabel¹, A. Corso¹

¹INEI-ANLIS Dr. Carlos G. Malbrán, Bacteriology, Buenos Aires City, Argentina
²Surveillance Network, Bacteriology, Argentina, Argentina

**Background and Aims:**

A high level of serotype and genetic diversity was observed in pediatric IPD strains. This study underscores the importance of a detailed population study to determine circulating pneumococcal serotypes and to monitor vaccine impact.
**S. pneumoniae** (SPN) is a major cause of severe invasive disease being associated with mortality and morbidity worldwide. The Laboratory National Surveillance Program for adults was initiated in Argentina in 2013. Aim: to study the serotype distribution and antibiotic resistance in SPN causing IPD in >18y.o during 2013-2016.

**Methods:**

641 SPN from sterile fluids were collected from 56 hospitals (16 provinces and Buenos Aires City). Strains received at the National Reference Laboratory were serotyped by Quellung and MICs were performed by agar dilution method (CLSI).

**Results:**

The 43.8% of the isolates belong to >65y.o. and 57.7% were male. Diagnosis: pneumonia (70.5%), meningitis (11.9%), sepsis (11.5%), others (6.1%).

The 11 most prevalent serotypes were 3 (8.9%), 1 (8.4%), 8 (8.4%), 12F (8.3%), 7F (8%), 24F/A/B (4.4%), 19A (4.1%), 22F (3.6%), 11A (3.1%), 9V (2.7%), 14 (2.5%) and others (37.7%). Serotype distribution was similar among groups of 18-64y.o and >65y.o, except for serotype 1 (p<0.05). No significant differences among serotypes were detected throughout the study period.

PCV13/PPSV23 serotypes represented 44.8%/74.4% (without differences among 18-64 y.o and ≥65y.o).

Overall, 19.9% of isolates were penicillin non-susceptible according meningitis breakpoint (MIC ≥ 0.12 mg/L), 17.2% MIC = 0.12-1 mg/L and 2.4% MIC=2 mg/L; only 0.3% of them were non-susceptible by non-meningitis breakpoint (MIC≥4 mg/L). Most penicillin non-susceptible isolates were serotypes 19A (16.7%), 24F,A,B (14.3%), 14 and 16F (8.7%). Non-susceptibility rates were: 1.6% / 0.2% for meningitis/non-meningitis cefotaxime break-points, 2.4% meropenem, 11.8% erythromycin, 16.3% tetracycline and 30.4% trimethoprim-sulfamethoxazole. All strains were susceptible to amoxicillin, rifampin, levofloxacin, chloramphenicol, vancomycin and ceftaroline.

**Conclusion**

During the four years of study and among the groups of age included, there was no significant difference in the serotype distribution and susceptibility profile.

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**ISPPD-0629**

**ETIOLOGY, ANTIMICROBIAL SUSCEPTIBILITY AND THE ROLE OF STREPTOCOCCUS PNEUMONIAE AS A MAJOR CAUSE OF ACUTE OTITIS MEDIA WITH RUPTURED TYMPANIC MEMBRANE IN ETHIOPIAN CHILDREN**

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¹Armauer Hansen Research Institute, Bacteriology, Addis Ababa, Ethiopia
²Addis Ababa University, Microbiology-Immunology and Parasitology, Addis Ababa, Ethiopia
³Addis Ababa University, Pediatrics and Child Health, Addis Ababa, Ethiopia
⁴Yekatit 12 Medical College, Pediatrics and Child Health, Addis Ababa, Ethiopia
⁵ALERT Center, Pediatrics and Child Health, Addis Ababa, Ethiopia
⁶Armauer Hansen Research Institute, Biostatistics and Data Management, Addis Ababa, Ethiopia
Background and Aims:

Acute otitis media (AOM) is one of the most common illnesses in infants and children. It is mainly caused by Streptococcus pneumoniae, non-typeable Haemophilus influenzae and Moraxella catarrhalis. In 5-30% of children with AOM, tympanic membrane perforation occurs. Pneumococcal Conjugate Vaccines (PCV) 10 has been introduced in Ethiopia in September 2011. The aim of the study was to identify the etiological agents, evaluate the role of S. pneumoniae as a cause of AOM and determine antimicrobial susceptibility pattern of pneumococcal isolates in children with AOM in Ethiopia.

Methods:

A prospective observational study was performed in two hospitals and one pediatric specialty center in Addis Ababa, Ethiopia from September 2016 to September 2017. All consecutive children between the ages of 0-15 yrs. diagnosed with AOM with tympanic perforation by pediatricians were enrolled. Middle ear discharges were collected with sterile swabs, cultured and antibiotic susceptibility testing performed. Serotyping is being performed by PCR and sequencing.

Results:

There were 55 children with AOM (mean age of 2.9 yrs ± 3.14), 33 (60%) males and 22 (40%) females. S. pneumoniae was the leading cause of AOM responsible for 15 (27.27%) of the cases followed by Staphylococcus aureus (14.5%) and H. influenzae (9%). Five (33.3%) of the S.pneumoniae isolates were resistant to erythromycin, 9 (60%) to tetracycline and 12 (80%) to trimethoprim-sulfamethoxazole and none to chloramphenicol.

Conclusion

S. pneumoniae is the leading and dominant cause of AOM in Ethiopia, 6 years after the introduction of PCV 10 and has a high level of resistance to commonly prescribed antibiotics.

ISPPD-0163
TRENDS IN INVASIVE PNEUMOCOCCAL DISEASE (IPD) CAUSED BY PCV13 AND PPV23-UNIQUE VACCINE SEROTYPES IN OLDER ADULTS (≥65 YEARS OF AGE) IN CANADA

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1Pfizer Canada Inc, Vaccine, Kirkland, Canada

Background and Aims:

The pneumococcal polysaccharide vaccine (PPV23) and a herd effect from the pediatric pneumococcal conjugate vaccine (PCV) program are expected to affect the incidence of IPD in adults. The objective of this study is to assess the vaccine-serotype specific trends of IPD in older adults in Canada since the introduction of pediatric PCV13 program.

Methods:

Serotype specific IPD incidences in Canada were assessed from publicly available surveillance data, provincial reports and publications.
Results:

National report showed that while there was still high burden of PCV13-IPD in 2015 with >20% of all IPD cases from serotypes 19A, 3 and 7F combined; PCV13 cases have declined in older adults since the introduction of pediatric PCV13 program in 2010/2011. On the contrary, no apparent changes were seen with overall PPV23-IPD largely because PCV13 reductions were offset by the increase in PPV23-unique serotypes (Figure 1A) (1). Similar trends were observed in the two most populous provinces Ontario(2) and Quebec (Figure 1B) (3). Interestingly, Manitoba also reported increase of PPV23-unique IPD (Figure 1C) (4) despite 70% uptake of PPV23 in older adults (5).

Conclusion

While the incidence of PCV13 vaccine-types has decreased in older adults, the incidence of PPV23-unique types has increased, despite a publicly funded program, resulting in small net benefit overall. PPV23 epidemiological data should be interpreted by taking into considerations the herd effect from PCV13 pediatric program.

1. NML2015
2. CMAJ2016;4(3)
3. INSPQ2015
4. Hum Vaccin Immunother 2017;13(8)
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A COMPARISON OF METHODS FOR EVALUATING THE IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINES

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Background and Aims:

The World Health Organization has recommended worldwide introduction of pneumococcal conjugate vaccines (PCV) into immunisation programs to prevent childhood pneumonia. Observational post-licensure studies have shown reductions in hospitalised all-cause childhood pneumonia following PCV introduction. However, estimates of vaccine impact vary widely across studies due to factors including case definitions, hospital admission criteria, baseline disease incidence and PCV coverage. Importantly, the methods used to assess vaccine impact vary across studies. The aim of this study was to compare statistical methods for evaluating PCV impact on hospitalised pneumonia in Fiji.

Methods:

This study used administrative hospitalisation data from 2007-2015 from Fiji, which introduced PCV10 in 2012. The outcome variable was hospitalisation for all-cause pneumonia in children <2years, as determined by primary discharge diagnoses using ICD-
Results:

Pre-post comparisons indicated a 28% relative reduction (95% CI: 23% - 32%) in incidence rates, or a 40% reduction (34%-44%) if the year of vaccine introduction was excluded. ITS analyses showed a 0.5% (0.3%-0.6%) relative rate reduction if PCV introduction was expressed as a level change, or an annual decrease of 20% (15%-20%) if a change in slope was assumed. These analyses illustrated the sensitivity of results to the analysis method, definitions of pre-and post-PCV periods, and the measures of vaccine impact used.

Conclusion

To enable comparison across studies and to inform policy-makers considering PCV introduction, clearer guidelines are needed for the analysis and reporting of vaccine impact.

ISPPD-0169
NASOPHARYNGEAL CARRIAGE AND SEROTYPE DISTRIBUTION IN CHILDREN UNDER TWO YEARS OF AGE IN A RURAL COMMUNITY IN PAKISTAN AFTER INTRODUCTION OF 10 VALENT PNEUMOCOCCAL VACCINE
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Background and Aims:

*Streptococcus pneumoniae* (SP) is carried in the nasopharynx (NP) of healthy children. PCV10 was introduced in Pakistan’s Expanded Program of Immunization in April 2013 using a 3+0 schedule at 6, 10 and 14 weeks of age. We describe here, overall and vaccine type (VT) carriage rates in immunized and unimmunized children <2 years from a rural community in Sindh, Pakistan with a previously reported carriage rate of 32% prior to vaccine introduction.

Methods:

Children < 2 years of age were enrolled during Oct 2014 through Jan 2016. NP specimens were collected and pneumococcal serotypes were identified using real-time sequential multiplex PCR assay. A child was defined as immunized if she/he had received all three doses of PCV10.

Results:

1550 children were enrolled; SP carriage was identified in 77% and 18.9 % of children with SP carried VT. Most common VT serotypes were 6B and 23F. There was a 43% decrease in comparison with the pre-vaccine period. 48% percent were fully immunized. VT carriage rate in immunized children was significantly lower than in those unimmunized (15.6% vs. 21.8 %, p-value < 0.001).

Conclusion
PCV10 introduction was associated with decreased VT carriage in immunized individuals, and there was a trend in the unimmunized, although a clear indirect effect on NP carriage may require higher vaccine coverage rates.

ISPPD-0346
CARRIAGE, DISEASE AND REPLACEMENT AMONG UNDER 5 YEAR OLDS: IMPOSING STRUCTURE THROUGH MODELLING
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Background and Aims:

Among pneumococcal conjugate vaccinated (PCV) children, vaccine serotype (VT) invasive pneumococcal disease decreases due to direct vaccine effects on both VT-carriage and progression from VT-carriage to disease (IPD). Indirect effects decrease VT-carriage and disease also among the unvaccinated and, due to serotype replacement, increase non-VT-IPD and non-VT-carriage.

To assess and understand the overall impact of vaccination, disentangling these simultaneous and interrelated effects is important. However, standard statistical methods often fail to do so. Here, we propose a mathematical model for pediatric surveillance IPD data aiming to separate the various effects of interest.

Methods:

The model describes expected IPD incidences, stratified by age, calendar time since onset of PCV, serotype (VT/non-VT) and vaccination status (vaccinated/no), assuming that post-vaccination VT-carriage decreases in calendar time at a different rate for vaccinated and unvaccinated children and is replaced by non-VT-carriage.

Pre-vaccination data on carriage and IPD is used to determine age-specific VT and non-VT case-to-carrier ratios. For the vaccinated, the estimation of model parameters (time-dependent total impact on VT-carriage, efficacy against VT-disease progression) is based on observed post-vaccination IPD cases from nationwide registry data on vaccination and IPD stratified correspondingly.

Results:

Applied to the Finnish post-PCV10 (2011-2015) data, the model supports a 97% total impact against VT-IPD, modest total impact on VT-carriage (30% in 2011 and 40% in 2015) and serotype replacement confined to 18+ month-olds.

Conclusion

We propose a convenient mathematical model for serotype replacement to estimate, utilising comprehensive pediatric post-vaccination IPD surveillance data, the time-dependent total impact on pneumococcal carriage and disease.

ISPPD-0490
THE IMPACT OF PNEUMOCOCCAL DISEASE ON HEALTH-RELATED QUALITY OF LIFE: A SYSTEMATIC REVIEW
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Background and Aims:
In many countries, cost-utility analyses are used to justify funding decisions regarding interventions targeting pneumococcal disease. The source of the utility values assigned to health states varies widely across these analyses. To address this, the purpose of this study was to systematically review studies examining the impact of pneumococcal disease on health-related quality of life.

Methods:
We performed systematic literature searches in MEDLINE, EMBASE, EconLit and the Tufts Cost-Effectiveness Registry for studies examining the health-related quality of life among patients with one of 4 syndromes caused by S.pneumoniae: pneumonia, otitis media, sepsis/bacteremia & meningitis. We also searched the grey literature, published cost-effectiveness analyses of pneumococcal vaccines and conducted reference list searches. Two reviewers independently screened articles, abstracted data and assessed methodological quality.

Results:
We screened 10,023 articles and included 42 primary studies, with study samples ranging from 9 to 625 patients. Sepsis/bacteremia (range: 0.18-0.93) and meningitis (range: 0.18-0.77) were associated with the lowest health-related quality of life in terms of elicited utility values, followed by pneumonia (range: 0.15-0.83) and acute otitis media (range: 0.63-0.99). The utilities from each study varied markedly by treatment setting, disease severity, instrument used and type of respondent.

Conclusion
This review highlights the range of utility estimates available for health states associated with pneumococcal disease. By synthesizing and describing the available data, this review can serve to inform future economic evaluations and estimates of disease burden.

ISPPD-0494
THE COST-EFFECTIVENESS OF A PNEUMOCOCCAL CONJUGATE VACCINE (PCV13) PROGRAM FOR OLDER ADULTS (65+) IN ONTARIO, CANADA IN THE CONTEXT OF INFANT IMMUNIZATION
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Background and Aims:

Despite being approved by Health Canada and recommended by the National Advisory Committee on Immunization (NACI), PCV13 is currently not funded for immunocompetent adults in Canada. The purpose of this study was to assess the cost-effectiveness of publicly funding PCV13 for older adults in Ontario, Canada, as well as for specific subpopulations of this cohort.

Methods:

We performed a cost-utility analysis using a microsimulation model to examine the impact of funding PCV13 in addition to the current standard of care, the 23-valent pneumococcal polysaccharide vaccine (PPV23). Quality-adjusted life years (QALYs) and costs in Canadian dollars (CAD) were calculated over a lifetime horizon from the healthcare payer perspective. Data on serotype prevalence, transition probabilities, costs, and utilities were obtained from local laboratory data, population-based health administrative databases and a systematic search of the literature.

Results:

In the base case analysis, the addition of PCV13 to the current standard of care (PPV23) resulted in an ICER of greater than $50,000/QALY for those vaccinated at age 65. The analysis was highly sensitive to the proportion of all-cause pneumonia attributable to S.pneumoniae, PCV13 effectiveness against pneumonia, and the forecasted changes in serotype distributions. The success of infant immunization has reduced the prevalence of PCV13 serotypes among the older adult population via herd immunity, and when this decline was forecasted further into the future, the ICER increased correspondingly.

Conclusion

PCV13 may be cost-effective for immunocompetent older adults in certain forecasted scenarios. However, this cost-effectiveness is likely to decrease over time as PCV13 strains become less prevalent.
Background and Aims:

Otitis media is inflammation of the middle ear and occurs commonly in infants and young children, representing one of the most common reasons for physician visits and antibiotic prescriptions in this age group. The purpose of this study was to assess the epidemiology and economic burden of otitis media in Ontario, Canada.

Methods:

We conducted a retrospective population-based cohort study of residents <6 years of age in Ontario, Canada using health administrative data. We identified subjects with incident episodes of otitis media between 2012 and 2014. The beginning of each episode was based on the first inpatient (ICD-10-CA codes: H65-H67) or outpatient claim (OHIP codes: 381,382) for otitis media. Exposed subjects were matched with unexposed subjects from the general population using hard- and propensity score-matching. Attributable costs represented the mean difference in costs between the exposed subjects and their matched pairs.

Results:

From 2012-2014, the average incidence of otitis media episodes was 362 per 1000 person-years. The majority of infected subjects received care exclusively in the outpatient setting (97.3%), with most episodes involving a single visit physician visit. Among the patients with at least one episode, approximately 11% met the criteria for recurrent otitis media. Cumulatively, these episodes translated to an annual healthcare cost burden of approximately $50 million in the year after diagnosis.

Conclusion

Otitis media remains a common illness among infants and young children, imposing a notable economic burden on the healthcare sector. This represents the first Ontario study to estimate individual-level costs of otitis media using administrative data.
Methods:

We conducted a community-based birth cohort study of acute respiratory infection (ARI) in infants from birth to 12 months in an urban and rural setting in Yogyakarta province, Indonesia. We recruited pregnant women in the third trimester and followed-up infants fortnightly from birth until 12 months to identify and record all ARI episodes. Pneumonia episodes were classified according to the WHO criteria.

Results:

From December 2015 to December 2017, we enrolled 422 newborns and identified 1,601 ARI episodes with a total of 412 child years of observation (CYO). The incidence rate of ARI was 3.89 (95% CI 3.70–4.08) episodes per CYO. Of those episodes, 96 and 7 episodes were classified as pneumonia and severe pneumonia respectively; 9% of all pneumonia episodes were hospitalized and no reported death due to pneumonia. The incidence rate of pneumonia was 0.25 (95% CI 0.21–0.30) episode per CYO, highest in infants <2 months - 0.57 (95% CI 0.26–1.27). Univariate analysis identified the risk factors for pneumonia (OR; 95% CI) were: male sex (2.00; 1.33–3.00), paternal smoking (1.52; 1.02–2.27) and overcrowding (1.76; 1.08–2.87).

Conclusion

The incidence of pneumonia in this cohort of Indonesian infants was high, particularly in infants < 2 months of age, and were similar to current global estimates for low and middle-income settings.

ISPPD-0439
HEALTH AND ECONOMIC IMPACT OF PCV15 SEROTYPES IN ADULTS 65 YEARS AND OLDER ACROSS 5 EUROPEAN COUNTRIES
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Background and Aims:

Pneumococcal disease continues to cause significant morbidity and mortality in older adults. A 15-valent pneumococcal conjugate vaccine (PCV) is under development. The vaccine contains the 13 serotypes included in PCV13 and 2 unique serotypes, 22F and 33F. This analysis aims to quantify the burden of pneumococcal disease attributable to PCV15 serotypes in 5 European countries.

Methods:

A published Markov model was adapted to the UK, Germany, France, Italy and Spain. Five health states were considered: no pneumococcal disease, invasive pneumococcal pneumonia (IPD), non-bacteraemic pneumococcal pneumonia (NBPP), post-meningitis sequelae, and death. From a health system perspective, the analysis tracked unvaccinated adults aged 65 years or older in each country from 2017 until death. Model parameters were retrieved through systematic and targeted literature reviews. Pneumococcal disease rates were adjusted for herd effects from infant PCV13 programs. The incidence of 22F and 33F was assumed to remain stable. Costs were discounted at 3%.
Results:

An estimated 468,000 cases and 62,000 deaths from invasive and non-invasive pneumococcal disease were attributable to PCV15 serotypes in older adults across 5 European countries. Total healthcare costs attributable to PCV15 serotypes were estimated to be nearly €1.2 billion in these five countries. 22% of these cases and costs were attributable to serotypes 22F and 33F.

Conclusion

PCV15 serotypes, including the two additional types not in PCV13, contribute to the health and economic burden of pneumococcal disease among older adults in Europe.

ISPPD-0053
THE COST-EFFECTIVENESS OF VACCINATING ADULTS AT INCREASED RISK OF PNEUMOCOCCAL DISEASE WITH THE 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN THE NETHERLANDS
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Background and Aims:

In 2015 we showed that pneumococcal conjugate vaccination (PCV13) of Dutch adults could be highly cost-effective. Since, data have evolved around sero-epidemiology, greater QALY losses associated with community acquired pneumonia (CAP), mortality following CAP, vaccine-uptake, population demographics, and health-care costs. Our objective was to reconsider cost-effectiveness of vaccinating adults with PCV13 in the context of these new data.

Methods:

A previously published and independently validated (by The Dutch National Health-Care Institute) age-and risk-group specific Markov-type model was updated to include the most recent data. Incremental cost-effectiveness ratios (ICER) of PCV13-vaccination of all adults at increased risk of pneumococcal disease (i.e. adults with underlying disease and those ≥50 years) was evaluated.

Results:

Vaccination of all adults at increased risk of pneumococcal disease was considered highly cost-effective (<€20,000/QALY). Differences in ICERs between age-and risk-groups were observed (Table). Specifically, vaccinating only those with immunocompromising conditions was cost-saving, vaccinating immunocompetent patients with chronic medical conditions was highly cost-effective, while vaccinating those with low-risk was moderately cost-effective (<€80,000/QALY). An age-based programme would be most cost-effective for those aged 65-74 years (€11,292/QALY), followed by a programme for 50-64 (€18,988/QALY) and 75-84 year olds.
Conclusion

Considering these new data, vaccinating adults with PCV13 in the Netherlands remained highly cost-effective. Targeting specific groups such as those with underlying diseases or specific age groups could result in even higher value for money.

**ISPPD-0438**

**STREPTOCOCCUS PNEUMONIAE ASYMPTOMATIC CARRIAGE CAN LAST SEVERAL MONTHS IN THE HEALTHY IMMUNOCOMPETENT ADULT HOST**

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**Background and Aims:**

Limited information on adult pneumococcal colonization is available and even less from longitudinal studies. We studied the dynamics of *S. pneumoniae* colonization in the upper respiratory tract of immunocompetent adults (smokers and non-smokers), using real time PCR.

**Methods:**

In 2015 and 2016, 87 adults aged 25-50 years old, living in Portugal, were followed for 6 months. Nasopharyngeal, oropharyngeal and saliva samples were obtained monthly from each participant. Individuals found to be pneumococcal carriers were sampled weekly until two consecutive negative samples were obtained. Pneumococcal carriage was identified by culture and by real-time PCR, targeting *lytA* and *piaB* genes. Serotyping was performed by real-time PCR and/or multiplex PCR.
Results:

Twenty-five adults (28.7%) carried pneumococci at least once; six were colonized for several months with a single serotype (7F, 8, 19A, 37 and NT). Adults with regular contact with young children were significantly more prone to be carriers than those with no contact [54.2% (13/24) vs 19.0% (12/63); p=0.001]. Smokers were more likely to be pneumococcal carriers than non-smokers although this was not statistically significant [32.5% (13/40) vs 25.5% (12/47); p=0.474]. Real-time PCR increased carriage detection from 14.8% to 17.1% in nasopharyngeal samples, from 2.3% to 20.6% in oropharyngeal samples, and from 0% to 11.2% in saliva samples.

Conclusion

Pneumococcal carriage in healthy adults is significant, particularly among those with regular contact with children. Our results challenge the paradigm of pneumococcal colonization dynamics among adults as they suggest that duration of carriage can be long, lasting several months.

Background and Aims:

A 5-10% case-fatality rate following pediatric pneumococcal meningitis with 25-35% of survivors suffering from long-term sequelae has been described, however other invasive pneumococcal disease (IPD) outcomes are less well documented. We determined risk factors associated with death and intensive care unit (ICU) admission in children with IPD over 26 years (1991-2015).

Methods:

Active, population-based surveillance was conducted by IMPACT, covering ~90% of the pediatric tertiary care beds in Canada. IPD cases included inpatients and outpatients aged 0-16 years with positive blood, CSF and/or sterile site culture and/or PCR for *Streptococcus pneumoniae*, with/without other manifestations of pneumococcal disease. Clinical details were collected from hospital records. Risk factors for death and ICU admission were analyzed by univariate and multivariable analyses.

Results:
6,060 children were hospitalized with IPD between 1991 and 2015. The majority were aged <2 years (n=3,287, 54%). The most common manifestations were bacteremia (n=5,403, 89%), pneumonia (n=1,707, 28%), meningitis (n=991, 16%) and otitis media (OM) (n=953, 16%). Overall, 1,064 children (18%) were admitted to ICU. There were 182 deaths (3.0%). 87/991 (9.6%) with meningitis died. Median hospital length of stay was 7 days and median ICU admission was 3 days. ICU admission was independently associated (p<0.05) with meningitis (odds ratio[OR]=13.9), pneumonia (OR=2.5), bacteremia (OR=0.62), OM (OR=0.61), year of admission, hospital and age. Mortality was independently associated (p<0.001) with meningitis (OR=5.1) and OM (OR=0.26).

Conclusion

This large study over a long duration demonstrates the significant burden of IPD, identifying risk and protective factors for bad outcomes, highlighting the poor prognosis of pneumococcal meningitis.

ISPPD-0102
BURDEN OF COMMUNITY-ACQUIRED PNEUMONIA IN PATIENTS WITH CANCER

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Background and Aims:

Data on the burden of community-acquired pneumonia (CAP) in cancer patients is scarce. We aimed to study the incidence rate of CAP and related mortality in patients with five cancer subtypes.

Methods:

We used health claims data from the InGef database to conduct cohort studies in patients with a new diagnosis of lung, hematological, breast, gastro-intestinal tract and renal/urinary-tract cancer and a comparator cohort without cancer between 2011 and 2015. CAP cases were identified in both the hospital and ambulatory care setting. Crude and age- and sex-standardized incidence rates (sIR) of CAP and the mortality after CAP were calculated.

Results:

The study population comprised 89,007 patients with cancer. There was wide variation in CAP morbidity and related mortality by cancer subtype (Table 1). The sIR was 21-fold higher in patients with lung cancer compared to the comparator cohort. For other cancer subtypes, the sIR was increased 4.3 fold to 1.7 fold. CAP did not have a strong impact on the one year mortality in lung cancer, but was a strong predictor of death in other cancer types, especially in hematological, gastro-intestinal tract and renal/urinary tract cancer.
The incidence rate of CAP and related mortality is high in German patients with cancer with strong variations by cancer subtype. These data underline the importance of preventive measures including vaccination against pneumococci and influenza in this high-risk group.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Lung</th>
<th>Hematological</th>
<th>Breast</th>
<th>Gastrointestinal tract</th>
<th>Renal/Urinary tract</th>
<th>Comparator cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude incidence rate of CAP per 100,000 person-yrs</td>
<td>14467.4</td>
<td>2976.7</td>
<td>931.0</td>
<td>1576.1</td>
<td>1807.6</td>
<td>451.8; 408.5 for women only (breast cancer)</td>
</tr>
<tr>
<td>sIR of CAP per 100,000 person-yrs</td>
<td>9525.0</td>
<td>1934.9</td>
<td>689.8</td>
<td>821.2</td>
<td>848.9</td>
<td>-</td>
</tr>
<tr>
<td>Proportion of CAP cases hospitalized (%)</td>
<td>66.3</td>
<td>74.8</td>
<td>63.1</td>
<td>77.8</td>
<td>76.5</td>
<td>51.4</td>
</tr>
<tr>
<td>30-day mortality (%)</td>
<td>20.0</td>
<td>16.9</td>
<td>7.2</td>
<td>18.5</td>
<td>18.1</td>
<td>-</td>
</tr>
<tr>
<td>One year mortality (%)</td>
<td>63.5</td>
<td>42.1</td>
<td>19.8</td>
<td>47.0</td>
<td>49.6</td>
<td>-</td>
</tr>
<tr>
<td>30-day hospital readmission (%)</td>
<td>29.5</td>
<td>28.1</td>
<td>18.9</td>
<td>26.1</td>
<td>21.3</td>
<td>-</td>
</tr>
</tbody>
</table>

Conclusion

The incidence rate of CAP and related mortality is high in German patients with cancer with strong variations by cancer subtype. These data underline the importance of preventive measures including vaccination against pneumococci and influenza in this high-risk group.

ISPPD-0185
DIFFERENCES ON CLINICAL COURSE OF CHILDREN HOSPITALIZED FOR COMMUNITY ACQUIRED PNEUMONIA (CAP) WITH OR WITHOUT STREPTOCOCCUS PNEUMONIAE (SP) INFECTION
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Background and Aims:

This study was designed to assess differences of hospitalized children with CAP with or without documented SP infection.

Methods:
This was a retrospectively study that collected information from children, 29 days to < 15 years of age, hospitalized with CAP at Soochow University Affiliated Children’s Hospital between 2010 - 2014. Children who were residents of downtown Suzhou, with discharge diagnose codes (ICD-10) including J09 to J18 and J20 to J22 were included. Medical charts, chest X-ray and laboratory reports were reviewed for included children.

Results:

A total of 31,302 CAP cases were included and in 21,509 (68.7%) children cultures were obtained and 3,276 (15.2%) were positive for SP. Among children ≤5 years old, SP positive rate increased with age (≤6m: 7.5%; ≤12m: 17.9%; ≤24m: 19.3%; ≤5y: 22.0%), while a slight decrease in children >5 years (13.2%). The following were more common in children with positive SP cultures compared with negative ones: fever (64.5% vs 51.2%), cough (98.2% vs 97.0%), wheeze (43.0% vs 38.5%), abnormal CRP level (≥8mg/L) (37.7% vs 25.3%) and used of antiviral therapy (69.8% vs 66.4%) and glucocorticoids (88.0% vs 85.3%) (P<0.001 for all). No statistically significant difference between SP positive and negative children was observed in gender, abnormal CXR findings, antibiotics therapeutics, length of hospitalization stay and prognosis (P>0.05).

Conclusion

SP infection leads to more severe clinical symptoms and needs to be treated more carefully in children with CAP.

ISPPD-0206
EFFECT OF SAMPLE SIZE ON THE ABILITY TO ESTIMATE THE IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINES USING TIME SERIES DATA
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Background and Aims:

Quantifying the population-level impact of pneumococcal conjugate vaccines (PCVs) against pneumonia is challenging because factors other than vaccination can influence incidence. We recently found that when using large national-level databases, information on control diseases can be used to distinguish changes in pneumonia hospitalizations caused by PCVs from changes caused by other factors (synthetic control (SC) analysis). Because vaccine impact studies are often conducted using datasets from smaller populations, we evaluated whether these control diseases could effectively adjust for unrelated trends when only a small number of events per time unit is available.

Methods:

We estimated the impact of PCV10 on pneumonia hospitalizations among cases <12 months and 80+ years of age during 2004–2014 at the regional and state level in Brazil. A simulation study was also performed, using the national-level time series to generate time series drawn from smaller populations.
Results:

Control diseases were able to adjust for underlying trends in larger states and regions but not in smaller states. The simulation study confirmed that the estimated impact was more likely to be biased when data become sparse. This was particularly an issue when a strong secular trend was present. Pre-smoothing the control time series to capture underlying shared trends improved the ability of the control to adjust for these underlying trends.

Conclusion

The SC approach is a promising tool for accurately estimating vaccine impact, but further modification is needed when only sparse data are available for control diseases.

ISPPD-0133
THE LONG-TERM IMPACT OF ROUTINE PCV13 VACCINATION ON INVASIVE PNEUMOCOCCAL DISEASE IN ENGLAND AND WALES: A MODELLING STUDY
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Background and Aims:

The introduction of childhood pneumococcal conjugate vaccines (PCVs) has changed the epidemiological patterns for pneumococcal carriage and disease worldwide. Since 2014/15, invasive pneumococcal disease (IPD) due to non-vaccine serotypes has significantly increased in England and Wales and there is a concern that this could offset the overall impact of the vaccine.

Methods:

We developed an individual-based model of pneumococcal carriage and disease transmission. We fitted the model to age and serotype-specific IPD data observed in England and Wales between 2000 and 2016. The model was then used to predict the long-term impact of PCV13 use.

Results:

In 2020/21, the incidence of IPD (per 100 000 population) due to the additional six serotypes in PCV13 was estimated to be 1.91 (95% confidence interval (CI) 1.14 – 2.67) in children <2 years and 3.59 (95% CI 2.74 – 4.44) in adults ≥65 years old. The incidence rate ratios for overall disease in the epidemiological year 2020/21 when compared to pre-PCV years (2000-2006) were estimated to be 0.24 (95% CI 0.19 – 0.30), 0.21 (95% CI 0.16 – 0.26), 0.37 (95% CI 0.29 – 0.45), 0.55 (95% CI 0.43 – 0.66), 0.67 (95% CI 0.52 – 0.83) and 0.63 (95% CI 0.46-0.80) in children aged <2 years, 2-4 years, 5-14 years, and adults aged 15-44 years, 45-64 years and ≥65 years, respectively.

Conclusion
Model predictions suggest that PCV13 will still offer a long-term reduction in overall disease in the population, despite the persistence of residual disease due to PCV13 serotypes and significant serotype replacement currently observed.

ISPPD-0562
PNEUMOCOCCAL VACCINATION IN ICELAND: DELAYED FIRST PRESENTATION OF AOM
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Background and Aims:

One of the most important risk factors for recurrent otitis media is age at first episode of acute otitis media (AOM) and delaying the first episode has been shown to decrease the risk for recurrent disease. Vaccination with the 10-valent pneumococcal vaccine (PHiD-CV) was initiated in Iceland in 2011, with immediate high uptake. The aim was to evaluate if the time from birth to first diagnosis of acute otitis media (AOM) changed after initiation of the vaccination.

Methods:

All children in Iceland born 2005-2014, were followed on an individual level basis from birth to first diagnosis of AOM or third birthday, whichever came first. Birth cohorts were grouped as vaccine non-eligible (VNEC, 2005-2010) or vaccine eligible (VEC, 2011-2014). Median age at first visit for AOM for both genders and groups was calculated using the Kaplan-Meier estimator.

Results:

Included were 49,293 children, of which 59.6% were diagnosed with AOM, 60% of children in VNEC and 56% in VEC. The Kaplan-Meier estimate of the median age at first AOM visit differed by 122 days between the groups, with median ages being: 686 days (95%CI:672-703) for children in VNEC and 808 (95%CI:784-837) for children in VEC. Girls consistently showed a later presentation compared to boys in all birth-cohorts.

Conclusion

The age at first presentation of AOM has increased in Iceland since the initiation of the vaccination. This is noteworthy as risk for recurrent disease decreases substantially as children are older at first presentation of AOM.

ISPPD-0589
PNEUMOCOCCAL VACCINATION IN ICELAND: HERD EFFECT ON OTITIS MEDIA IN CHILDREN <4 MONTHS OF AGE
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²University of Iceland, Department of Mathematics, Reykjavik, Iceland
Background and Aims:

The ten-valent pneumococcal conjugate vaccine (PHiD-CV) was introduced in the paediatric schedule in Iceland in 2011, with vaccinations given at 3, 5 and 12 months of age. The aim of this study was to estimate the herd effect on acute otitis media (AOM) in children too young to have received the direct protection.

Methods:

The study is a whole-population, individual level cohort study, all children born in Iceland from 2005-2015 were followed from birth to 4 months of age. All physician visits due to AOM were extracted from a database including all primary health clinics in Iceland. Repeated visits within 30 days were excluded. Birth cohorts were grouped as vaccine non-eligible (VNEC, 2005-2010) or vaccine eligible (VEC, 2011-2015). Crude incidence rates were compared between VNEC and VEC and incidence rate ratio (IRR) calculated.

Results:

Included were 53,150 children, with 17,945 person-years of follow-up time and 635 visits due to AOM. The incidence rate was reduced from 4.68 to 2.85 episodes per 100 person years (IRR: 0.61, 95%CI:0.52-0.70) in VNEC and VEC, respectively.

Conclusion

After the initiation of the pneumococcal vaccination, a significant reduction in primary care visits due to AOM was found in children less than 4 months of age, children too young to have received primary vaccination doses. Although children are first vaccinated at 3 months, it is unlikely to convey substantial protection against AOM before four months of age. This is the first report of herd effect in children <4 months of age.
visits with-in 30 days were excluded. Birth cohorts were grouped as vaccine non-eligible (VNEC, 2005-2010) or vaccine eligible (VEC, 2011-2015). A cox-regression model for repeated events was used to model the data on individual level, accounting for censoring. VE was calculated as (Hazard ratio–1)x100%.

Results:

53,150 children, with 140,912 person-years of follow-up time and 58,794 AOM episodes were included. Both incidence rate and mean number of visits differed significantly between VNEC and VEC, 43 vs 38 per 100 person-years and 1.61 vs 1.37 per child, respectively. Cumulative incidence was lower and fewer children had >5 episodes in VEC than VNEC. The VE against all-cause AOM was 22% (95%CI 12-31%). When stratified by number of previous episodes, the hazard of the first two episodes of AOM were reduced (HRs:0.84 (95%CI:0.82-0.86) and 0.95 (95%CI:0.93-0.98)). For children that were diagnosed more than twice with AOM, the HR for additional episodes did not differ between the groups.

Conclusion

The vaccine effectiveness against all-cause AOM was high and mainly conveyed through prevention of the first two episodes of AOM. The non-restricted definition of AOM used makes the results important.
Results:

Of 9,398 carriage isolates from the pre-PCV10 period, 1,184 (12%), 848 (9%), 1 (0.01%) and 0 were of serotypes 6A, 6B, 6C and 6D, respectively; of 1,052 carriage isolates from the post-PCV10 period the numbers were 74 (7%), 24 (2%), 2 (0.19%) and 0, respectively. Following PCV10 introduction, the relative prevalence of 6A and 6B reduced by 44% and 75%, respectively; the incidence rate ratio for IPD caused by 6A and 6B following PCV10 introduction was 0.36 (95%CI 0.16-0.83) and 0.22 (95%CI 0.08-0.63), respectively. No invasive isolates of 6C/6D were found.

Conclusion

Serotypes 6C/6D do not contribute to disease in Kilifi. Following PCV10 introduction, 6A/6B are transmitted less frequently; 6A IPD has been reduced, 6B IPD has been considerably reduced.

Background and Aims:

Public health authorities in multiple countries have invasive pneumococcal disease (IPD) surveillance systems to monitor changes in disease epidemiology and quantify the public health impact of vaccines. However, assessments of surveillance data lack standardization across countries and vary in how data are reported, targeted age groups, and pneumococcal serotype grouping. This makes cross-country comparisons time consuming and inefficient.

Methods:

We created a web-based application called the IPD Surveillance Repository and Visualization Tool, a user friendly multi-country surveillance data repository to quickly analyze and visualize available disease data. The core of the application creates a standardized database that is flexible enough to store data from an unlimited number of countries, even if reporting methods differed. In addition, a visualization tool works via a suite of analytical routines that visualize and export requested data via a dashboard.

Results:

Currently, the application includes surveillance data from 13 countries. Analysis can be done by country or across countries, type of PCV used in national immunization programs, age group, individual serotype or serotype group, and surveillance year. Outputs include number of cases, incidence rates, or serotype distribution, trends of individual or grouped serotypes. Examples are shown in the figures below.

Conclusion
This application could serve as a model for the standardized storage, reporting, and analytics of within- and cross-country comparisons of IPD epidemiology.

Visualization Tool Illustrations

Example 1. Country comparison allows users to study how incidence rates have changed across countries for given age groups or strains.

Example 2. Serotype distribution allows users to understand how the frequency distribution of pneumococcal serotypes within an age group has changed over time across countries.

Example 3. Top strains can be identified for each year in a country based on their relative frequency, and then details about how those strains have changed within and across countries over time can be analyzed.
THE PREVALENCE OF Streptococcus pneumoniae SEROGROUP 6 IN INDONESIAN POPULATION

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Background and Aims:

Streptococcus pneumoniae serogroup 6 is one of the most frequent serogroups causing invasive pneumococcal disease worldwide. Moreover, many previous studies in Indonesia showed that serogroup 6 had the highest rate in the population. However, there is no study in Indonesia that specifically determines the prevalence of each serotype and antibiotic susceptibility of serogroup 6. Meanwhile, this study is necessary to determine vaccine strategy. In this study, we determine the prevalence and antimicrobial resistance pattern of Streptococcus pneumoniae serogroup 6 colonizing nasopharyngeal of Indonesian population.

Methods:

We used 82 archived isolates of S. pneumoniae serogroup 6 that were isolated from nasopharyngeal swab of Indonesian population. Isolates were serotyped by PCR and followed by BsmAI restriction. Disk diffusion was used to determine antibiotic susceptibility of isolates.

Results:

Prevalence of serotype 6A, 6B, 6C, and 6E among all isolates were 45%, 45%, 9%, 1%, respectively. Meanwhile, serotype 6D, 6F, and 6G weren’t found in any isolates. Most of isolates were susceptible to Erythromycin (96%), followed by Clindamycin (94%), Oxacillin (87%), Chloramphenicol (79%) and Trimethoprim-sulfamethoxazole (52%). 6% isolates were also found to be Multi-Drug Resistant Streptococcus pneumoniae (MRSP) and dominated by serotype 6B.

Conclusion

This study discovered that serotype 6A and 6B were the dominant serotype among other serotypes of serogroup 6. Serotype 6E was detected in nasopharyngeal colonization of Indonesian population. Resistance to Trimethoprim-sulfamethoxazole was commonly observed in serogroup 6, with serotype 6B as the major resistant isolates.
Last years significantly increased number of non-PCV vaccine serotypes’ carriers, as well as frequency of invasive pneumococcal disease. In Latvia PCV was initiated in 2010.

Methods:

The study took place in Children’s clinical university hospital from 2015 to 2017. Including criterion was children of any age with bacterial infection. Included patients underwent nasopharyngeal swab collection for *S. pneumoniae* detection, blood analyses, also clinical data were summarized involving vaccination status.

Results:

95 patients were enrolled in the study, 50.5% girls and 49.5% boys. All patients were divided into 2 groups. The first group contained patients with diagnosed pneumonia (N=61, 64.2%), the second one – SIRS positive/sepsis (N=34, 35.8%). 14 patients (14.7%) had positive *S. pneumoniae* nasopharyngeal culture, 64 – negative (67.4%) and in 17(17.9%) patients analysis was not performed due to different causes. No patients with positive swab received antibiotics before the analysis, opposite to 11 *S. pneumoniae* negative children (17.2%) who received antibacterial therapy prior to a swab. We found a strong correlation between pneumonia diagnosis and positive *S. pneumoniae* (p<0.001, Chi-Square test). Results of *S. pneumoniae* culture and vaccination status did not show statistical association (p=0.14, Fisher’s test).

<table>
<thead>
<tr>
<th>Nasopharyngeal swab</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevenar13 (Types 1,14,18C,19A,19F,23F,3,5,6A,6B,7F,9V)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>9(14.5%) Types: 3, 9L/9N, 3, 23F, 4, 4-unknown</td>
<td>5(31.3%) Types: 9L/9N, 6A/6B, 3F/47F, 2-unknown</td>
<td>14(18%)</td>
</tr>
<tr>
<td>Negative</td>
<td>53(85.5%)</td>
<td>11(68.7%)</td>
<td>64(82%)</td>
</tr>
<tr>
<td>Total</td>
<td>62(79.5%)</td>
<td>16(20.5%)</td>
<td>78(100%)</td>
</tr>
</tbody>
</table>

Conclusion

*S. pneumoniae* nasopharyngeal swabs more often were positive in children with pneumonia diagnoses. Results of swabs analyses did not show statistical association with vaccination status. Antibacterial therapy before hospitalization could influence culture results.

ISPPD-0043

SEROTYPE REPLACEMENT AMONG ADULTS OVER 50 YEARS OF AGE IN THE ERA OF 13-PNEUMOCOCCAL CONJUGATE VACCINE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background and Aims:
Over 1.6 million deaths occur worldwide due to *Streptococcus pneumoniae* annually. Children under 2 years and adults over 50 years of age are at the greatest risk. Pneumococcal Conjugate Vaccines (7-valent and 13-valent) are integrated in childhood national immunization programs (NIPs) of most countries in the world.

AIMS:

This systematic review and meta-analysis was aimed at summarizing available data on the serotype replacement in adults over 50 after PCV13 introduction in NIPs.

Methods:

We conducted a systematic literature search up to May 2017 in Cochrane, Embase and Medline. We included all observational studies (OBS) that reported the incidence of pneumococcal serotype burden in adults over 50 before and after the introduction of PCV13 into the childhood NIPS. Incidence rate ratio (IRR) were pooled across studies using random-effects models.

Results:

Data were pooled from 7 OBS studies (N=10,026 cases). In adults aged 50-64 year, the reduction in PCV7type IPD was 48% (95%CI: 21-66%, p-value<0.001) and PCV13type IPD was 38% (95%CI: 19-53%, p-value<0.001) whereas in adults aged 65 year and older, reduction of PCV7type IPD was 54% (95%CI: 44-63%, p-value<0.001) and PCV13type IPD was 39% (95%CI: 30-47%, p-value<0.001). In Contrast, an increase of 17% (95%CI: 4-32%, p-value<0.001) and 13% (95%CI: 4-23%, p-value<0.001) in non-vaccine type IPD among 50-64 and 65 and older was seen after introduction of PCV13.

Conclusion

While there is a significant reduction of pneumococcal disease burden due to PCV7 and PCV13 serotypes among adults over 50 years, a significant increase in non-vaccine serotypes for culture confirmed disease after PCV13 introduction in NIPs.

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ISPPD-0070

**INCREASING ROLE OF SEROTYPE 3 IN INVASIVE PNEUMOCOCCAL DISEASE IN GERMANY, 2000-2016**

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Background and Aims:

Serotype 3, despite inclusion in the latest pneumococcal conjugate vaccine (PCV) persists as a major cause of invasive pneumococcal disease (IPD) in Germany. The infant PCV recommendation was given in 2006 (3+1 schedule) and changed in 2015 (to 2+1). Germany lacks a PCV recommendation for older adults. We sought to describe the expansion of serotype 3 as a cause of IPD.

Methods:

3965 serotype 3 isolates were identified by Neufeld-Quellung reaction at the German National Reference Center for Streptococci from July 1, 2000 to June 30, 2017.
Results:

In children under 3 and adults 65 and over, estimated incidence increased from 0.13 to 0.36, and 0.11 to 1.81 cases per 100,000, respectively. Of 31 serotype 3 IPD cases in children born after the release of PCV13 with a known vaccination status, 23 received at least 1 dose of PCV13, but only 3 children had received the appropriate number of doses in the recommended timeframes.
Conclusion

Serotype 3 IPD cases are on the rise in Germany. It is possible that unvaccinated and under-vaccinated children are acting as a niche for young children, while the lack of a PCV program could be to blame in older adults.

ISPPD-0117
COMPARISON OF PROVINCIAL PNEUMOCOCCAL DISEASE INCIDENCE RATES FROM TWO DIFFERENT REPORTING SYSTEMS IN CANADA
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²OXON, Epidemiology, London, United Kingdom

Background and Aims:

Data on invasive pneumococcal disease (IPD) is publicly available from two reporting systems in Canada. IPD is a Notifiable Disease (ND) (1), and incidence rates (IR) are published in provincial surveillance reports. The Canadian Institute of Health Information (CIHI) Discharge Abstract Database (DAD) collects data on discharges from all Canadian hospitals.

The objective of this analysis was to assess the concordance of IR between the two systems to validate the consistency of the data for accurate analysis and interpretation.

Methods:

The IR of IPD for all ages was extracted from provincial ND reports. Cases of pneumococcal pneumonia, sepsis and meningitis were obtained from CIHI DAD using ICD-10-CA codes J13, A40.3 and G00.1 (2). IR were estimated using population data from Statistics Canada.

Results:

Figures 1-5 show annual IR from ND reports and from CIHI DAD for 5 provinces from 2004/05 to 2009/10. Visual inspection showed that the IR matched between the two systems in some provinces, but non-overlapping confidence intervals were noted in other provinces. In Nova Scotia the ND rate matched CIHI DAD sepsis/rate.
Conclusion

Comparisons of Notifiable Disease reports on IPD with data extracted from CIHI DAD revealed different levels of concordance across provinces. These limitations should be taken into consideration when interpreting retrospective data.

References:


Infant pneumococcal conjugate vaccines (PCVs) have reduced invasive pneumococcal disease (IPD) due to vaccine-specific serotypes. Predicting future pneumococcal epidemiology is challenging given the complex nature of serotype dynamics and vaccine impact. We developed an intuitive approach to modeling IPD through observed PCV impact in various settings.

Methods:

Historical age-group and serotype-specific IPD incidence was obtained from three PCV10 settings (Finland, Netherlands, and Colombia) and four PCV13 settings (United Kingdom, United States, Quebec, and Ontario). Equations were fitted to longitudinal changes in incidence for each age group, serotype, and country/province over time periods when a serotype was covered or not covered by infant vaccination. We forecasted population impact of PCV13 and PCV10 and report results among infants (ages <2 years) and elderly (65+ years) over 5-years post-vaccine introduction in each setting.

Results:

Based on forecasted impact over 5 years post-vaccine introduction, PCV13 was estimated to have greater average overall IPD incidence reduction than PCV10 in infants and the elderly, primarily due to reductions in serotypes 3 and 19A (Table 1). Both vaccines largely eradicated disease from common PCV10 serotypes. Increases in non-vaccine-type disease greatly varied by setting.

Conclusion

Forecasting IPD incidence using real-world impact is an intuitive process that illustrates benefits of PCV13 and PCV10 by identifying age- and serotype-specific trends that inherently capture direct and indirect effects of vaccination.

Table 1: Results Forecasted as Percentage Change in IPD Incidence Over 5 Years

<table>
<thead>
<tr>
<th>Ages  &lt;2 Years</th>
<th>Serotype 3</th>
<th>Serotype 19A</th>
<th>Common (PCV10)</th>
<th>Non-PCV13 Type</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV10 Settings</td>
<td>+43.1% (+22.7%, 68.1%)</td>
<td>+36.9% (-3.5%, +58.6%)</td>
<td>-92.7% (-71.1%, -53.0%)</td>
<td>+12.8% (+7.0%, +22.8%)</td>
<td>-42.9% (-10.7%, -68.2%)</td>
</tr>
<tr>
<td>PCV13 Settings</td>
<td>-54.5% (-38.1%, -73.4%)</td>
<td>-96.4% (-87.2%, -100%)</td>
<td>-97.7% (-95.1%, -100%)</td>
<td>+20.0% (+3.0%, +39.5%)</td>
<td>-67.6% (-38.4%, -84.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ages 65+ Years</th>
<th>Serotype 3</th>
<th>Serotype 19A</th>
<th>Common (PCV10)</th>
<th>Non-PCV13 Type</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV10 Settings</td>
<td>+30.2% (+1.5%, +52.1%)</td>
<td>+57.0% (+29.1%, +72.8%)</td>
<td>-47.2% (-29.6%, -57.7%)</td>
<td>+51.1% (+30.9%, +90.2%)</td>
<td>+1.0% (+20.7%, +15.0%)</td>
</tr>
<tr>
<td>PCV13 Settings</td>
<td>-36.0% (-6.6%, -41.3%)</td>
<td>-66.8% (-35.1%, -100%)</td>
<td>-74.9% (-60.0%, -97.1%)</td>
<td>+17.9% (6.4%, 31.1%)</td>
<td>-30.9% (-18.1%, -44.2%)</td>
</tr>
</tbody>
</table>

Conclusion

Forecasting IPD incidence using real-world impact is an intuitive process that illustrates benefits of PCV13 and PCV10 by identifying age- and serotype-specific trends that inherently capture direct and indirect effects of vaccination.

ISPPD-0422

DYNAMIC TRANSMISSION MODELING OF PNEUMOCOCCAL CONJUGATE VACCINE AND POTENTIAL DOSING REDUCTION IN THE UNITED KINGDOM

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Background and Aims:

7- and 13-valent pneumococcal conjugate vaccines (PCV) have been an effective part of routine immunization using a 2+1 schedule in the United Kingdom (UK) for the previous 11 years. Studies are ongoing to evaluate effects of removing a dose from the primary series. Our objective is to model the health and economic impact of reducing from a 2+1 to a 1+1 PCV13 schedule.

Methods:

A dynamic transmission model was developed using UK serotype-specific invasive pneumococcal disease (IPD) surveillance data from 2001-2016. Pneumonia and otitis media cases were calculated assuming a relative proportion to IPD. Cases and costs (2016 GBP, 3.5% discounted) were calculated over a 5-year period for the entire UK population. Scenario analyses were undertaken to evaluate the impact of parameter uncertainty.

Results:

Compared with maintaining the 2+1 schedule, reducing to 1+1 was predicted to incur 8,561-25,394 additional cases of pneumococcal disease, 249-665 more deaths, and £9.9-£26.8MM additional disease-related medical costs (Table 1) across all age groups over the 5-year period. Serotype 19A IPD was responsible for 77-95% of incremental cases.

Table 1: Estimated Cases of Disease over a 5 year period by Dosing Schedule

<table>
<thead>
<tr>
<th>Schedule</th>
<th>IPD</th>
<th>Pneumonia</th>
<th>AOM</th>
<th>Total</th>
<th>Pneumococcal Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>2+1</td>
<td>23,078</td>
<td>636,260</td>
<td>917,902</td>
<td>1,577,239</td>
<td>85,810</td>
</tr>
<tr>
<td>1+1</td>
<td>23,165 - 23,309</td>
<td>638,250 - 641,624</td>
<td>924,386 - 937,700</td>
<td>1,585,800 - 1,602,634</td>
<td>90,059 - 90,475</td>
</tr>
<tr>
<td>Incremental</td>
<td>87 - 231</td>
<td>1,990 - 5,364</td>
<td>6,484 - 19,798</td>
<td>8,561 - 25,355</td>
<td>249 - 665</td>
</tr>
</tbody>
</table>

Note: Ranges represent a variety of sensitivity analyses varying vaccine effectiveness, adherence, and population dynamics.

Conclusion

Results suggest that removal of an infant priming dose would increase pneumococcal disease cases and medical costs compared with maintaining a 2+1 schedule, with much of this increase from resurgence in 19A. It is important that policymakers consider potential public health impact when considering modifications to vaccination strategies.
Background and Aims:

PCVs have been successfully implemented in 3+1, 2+1, and 3+0 schedules. However, due to limited resources and crowded infant vaccination schedules a number of studies are ongoing to evaluate immunogenicity and effect on nasopharyngeal carriage of 1+1 PCV dosing schedule. Because of uncertainty of real-world impact of 1+1 schedule implementation, we modeled invasive pneumococcal disease (IPD) under 2+1 and 1+1 PCV13 schedules.

Methods:

A dynamic transmission model was built to simulate the effects of a 2+1 or a 1+1 schedule. The model was parameterized using UK serotype-specific invasive pneumococcal disease (IPD) surveillance data and published literature. The model was run prospectively to predict cumulative differential impact of each schedule on IPD incidence. Scenario analyses were undertaken to examine impact of model assumptions and parameter uncertainty around vaccine effectiveness, implementation, and population dynamics.

Results:

Compared with a 2+1 schedule over 5 years, reducing to a 1+1 schedule resulted in 87 to 231 more cases of IPD in the UK corresponding to a 22% – 50% increase in vaccine-type IPD in <2 year-olds. Scenario analyses suggest that effectiveness of a 1+1 schedule to impact nasopharyngeal carriage and maintain the herd effect has the most substantial impact on IPD as well as mucosal disease.

Conclusion

The results demonstrate continued use of a 2+1 schedule would provide a greater public health benefit compared to switching to 1+1. Policy makers should consider the uncertainty of clinical effects of a 1+1 schedule when considering modifications to a successful vaccine program.

ISPPD-0208
OVER-REPRESENTATION OF SEROTYPES CAUSING PNEUMOCOCCAL DISEASE IN ADULTS
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3Johns Hopkins Bloomberg School of Public Health, International Health & Department of Epidemiology, Baltimore, USA
4Tel Aviv University, Sackler Faculty of Medicine, Tel Aviv, Israel
5Johns Hopkins Bloomberg School of Public Health, Center for American Indian Health, Baltimore, USA
6Ben-Gurion University of the Negev, Faculty of Health Sciences, Be’er Sheva, Israel

Background and Aims:

Clear age-related differences exist in the incidence of invasive pneumococcal disease (IPD) caused by individual serotypes. Data on invasiveness and frequency of exposure to different serotypes is of particular importance for disease prevention strategies in adults.
serotypes can be informative for understanding and predicting differences in serotype-specific incidence and serotype replacement between age groups.

Methods:

Using data from Israel and the Navajo Nation, we modelled serotype-specific IPD in different age groups and time periods as a function of the frequency of that serotype in carriage among children for each time period, serotype-specific invasiveness in children, and a term to account for unexplained serotype-specific variation. Serotype-specific disease patterns were also evaluated by stratifying the Israeli IPD data by comorbidity status and age.

Results:

Serotypes 3, 15A, 16F and 19A were among those over-represented in IPD in older adults and in those with comorbidities. This indicates that people in this age-strata are either exposed to these serotypes more frequently than children or are more susceptible to developing disease. Conversely, serotypes 1, 2, 5, 7F and 8 were over-represented in adults compared to children and more over-represented in younger adults than in older adults. The observed age-related frequencies of these serotypes however, was not affected by comorbidity status. Similar age-related patterns were observed in data from both Israel and the Navajo Nation.

Conclusion

Differences in the frequency of serotype-specific disease by age are likely explained by age-related differences in susceptibility to or exposure to specific serotypes. Understanding such differences in susceptibility could help forecast the impact of serotype replacement in the future.

ISPPD-0578
DEVELOPMENT AND RELIABILITY ASSESSMENT OF VACCINE ATTITUDE SCALE (VAS) TO MEASURE VACCINE HESITANCY IN KARACHI, PAKISTAN
M.T. Yousafzai

Background and Aims:

There is no locally developed, reliable vaccine related parental attitude scale to measure the vaccine hesitancy in Pakistan. The aim of this study was to develop a tool and assess its reliability to measure vaccine hesitancy among parents in Pakistan.

Methods:

We reviewed literature, consulted experts to develop vaccine attitude scale (VAS). VAS containing 14 likert items each with 5 responses ranging from strongly agree to strongly disagree was developed (sum of scores ranged 14 to 70). The tool was administered to 901 parents during PCV10 coverage survey in three districts of Sindh. The households were selected using WHO sampling method. We performed factor analysis with Eigen values >0.3 for the factors loading and chronbach’s alpha for reliability assessment.

Results:
The mean±std score on full VAS was 48±3 and cronbach’s alpha was 0.61. Factor analysis identified VAS measure two domains related to the vaccine attitude; 1) 10 items vaccine perceptions/concerns (mean±std score 40±5.5; cronbach’s alpha 0.95) and 2) 4 items vaccine preventable disease salience and community benefit (mean±std score 7±3; cronbach’s alpha 0.97). The odds of children being unvaccinated with PCV10 was 5 times higher among parents who scored 13-20 as compared to less than 13 on the sub-scale related to disease salience and community benefit. The odds of children being unvaccinated was 1.5 times higher among parents scoring 40-50 as compared to less than 40 on sub-scale related to vaccine perception.

Conclusion
The four items scale addressing disease salience and community benefit is sufficiently reliable tool to predict vaccine hesitancy among parents.

ISPPD-0298
PREVALENCE OF ACUTE OTITIS MEDIA IN CHILDREN UNDER 10 YEARS OF AGE IN COLOMBIA 2009-2014
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Background and Aims:
Colombia has a tool created by the health ministry (SISPRO), which consolidates information based on the individual registries of health service delivery. Objective: To determine the prevalence of acute otitis media (AOM) in children under 10 years of age in Cartagena and Colombia, 2009 - 2014. Before and after the introduction of PCV-10 to the immunizations program.

Methods:
ecological study using SISPRO as a source of information, diagnoses of ICD-10 (H651, H659, H660, H664, H669) were identified between 2009 and 2014 and were classified as suppurative and non-suppurative AOM.

Results:
according to SISPRO, in Colombia between 2009 and 2014, 8,376,566 cases of AOM were reported. 38.6% in children under 5 years old and 14.5% between 5 and 9 years old. PCV-10 was included in 2011, that year 465,444 cases of AOM were reported in children under 10 years of age, since then cases increased 38.2%, 22.7%, 69.6%, 12%, in 2012, 2013 and 2014 respectively. From 2011 to 2014, the reported cases of AOM increased by 90.0%. In Cartagena, between 2009 and 2014, 50,354 cases were reported, 23.4% of non-suppurative AOMs were in children under 5 years of age. 21.3% of suppurative AOM cases, occurred in children under 5 years of age. Between 2009 to 2014. Diagnosis of non-suppurative AOM increased 95.5% and of suppurative AOM 83.4% for all age groups in Cartagena, City.

Conclusion
after 4 years of PCV-10 in Colombia, according to the SISPRO data, the prevalence of reported episodes of AOM in children under 10 years has increased.
Sponsor: Colciencias 657-2014
Background and Aims:

Acute otitis media (AOM) is the most common childhood infections with annual costs $US3-5 billion dollars (1). Aim: To estimate the costs associated with AOM in pediatric patients in Cartagena-Colombia.

Methods:

Prospective micro-cost study from 2014 to 2015. Surveys were applied to the parents to determine direct and indirect costs of AOM. PCV-10 was included in the immunization program in November 2010. National Minimum Wage (NMW) was COP$616.000/(US$308) in 2014.

Results:

62 cases of AOM were diagnosed. 61.2% female. Average age 16.0 ± 13.5SD month. 90% were from city. 70.9% of mothers were housewife. Total attributable costs per patient (p/p) was USD$70.19, total for 62 patients USD$4,351.99. Mean of indirect cost p/p US$55.59, average spending on food US$3.67, cleaning products US$3.10, transportation US$9.34, medications US$7.24, laboratory exams US$1.94, parenteral time spent caregiving 3.7 days, money not earned by parents US$ 18.63, pay a caregiver US$2.00. Average of direct cost p/p was US$18.77 but if we included the assessment by pediatrician and otolaryngology, the cultures performed on 28 patients and the tympanocentesis, direct costs will increase US$103.44. Total cost p/p was 22% of the NMW that can be until 51.6% with specialist valuation.

Conclusion

Money not earned by parents per patient represented 6% of the NMW. Estimated costs of AOM in this study are lower than the costs estimated in a review of high-income countries (1) and similar to low-income countries such as Nigeria. Information on total costs (direct and indirect) are necessary for public health decision-making and for full cost-effectiveness assessments.

Sponsor: Colciencias 657-2014
MOLECULAR CHARACTERIZATION OF STREPTOCOCCUS PNEUMONIAE STRAINS ISOLATED FROM INVASIVE DISEASE IN THE PRE- AND POST-PCV10 PERIODS IN BRAZIL, 2005 TO 2015


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Background and Aims:

In Brazil, PCV10 was introduced in the National Immunization Program for children up to 2 years of age in 2010. Institute Adolfo Lutz (IAL) is the national reference laboratory for meningitis and pneumococcal diseases and performs laboratory-based epidemiological surveillance in the country. The aim of this study was to evaluate the genetic diversity among pneumococcal strains isolated in Brazil during 2005-2015.

Methods:

A random sample of 866 isolates was selected from a collection of 9,996 invasive pneumococcal strains, 376 pre-PCV10 (2005-2010) and 490 post-PCV10 (2011-2015) introduction, and characterized by MLST using PCR (n=412) or whole-genome sequencing (n=450) as part of the Global Pneumococcal Sequencing project (www.pneumogen.net).

Results:

A total of 243 sequence types (ST) were identified, organized in 40 clonal complexes (CC). Pre-PCV10 introduction, the most common CC were CC156 (n=65), CC62 (n=44) and CC193 (n=25), mainly associated with serotypes 14 (90.7%), 19A (90.9%) and 18C (92.0%), respectively. Post-PCV10, 19A/CC320 isolates (n=103, 21%) became the most common lineage. The proportion of 14/CC156 and 19A/CC62 isolates decreased from 15.7% to 4.9% (p<0.001) and from 10.6% to 4.9% (p<0.001), respectively. Conversely, the proportion of 19A/CC276 isolates increased significantly after PCV10 introduction (from 1.6% to 4.1%, p=0.016).

Conclusion

These isolates show considerable genetic diversity among pneumococcal strains circulating in Brazil. An expansion of the 19A/CC320 lineage was observed after vaccine introduction, while 19A/CC62 lineage decreased significantly. The 14/CC156 lineage, which was the most predominant pre-PCV10, decreased post-PCV10 as well.
Acknowledgment: MCC Brandileone(304211/2014-1) receives scientific productivity scholarships from CNPq-Brazil.

ISPPD-0204
GLOBAL EMERGENCE AND POPULATION DYNAMICS OF DIVERGENT SEROTYPE 3 CC180 PNEUMOCOCCI

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Background and Aims:

Serotype 3 Streptococcus pneumoniae is globally distributed and remains a significant cause of morbidity and mortality despite inclusion in the 13-valent pneumococcal conjugate vaccine (PCV13). Recent studies suggest serotype 3, which is dominated by the CC180 Netherlands 3–31 (PMEN31) clone, has increased in carriage prevalence since implementation of PCV13 in the US, and invasive disease rates have remained unchanged.

Methods:

To investigate persistence of serotype 3, we analyzed genomic and epidemiological data from 301 serotype 3 CC180 isolates from 24 countries. We also employed phenotypic and functional assays to evaluate various aspects of serotype 3 biology – net capsular surface charge, levels of polysaccharide shedding, and susceptibility to opsonophagocytic killing (OPKA), which are associated with carriage duration, invasiveness, and vaccine escape.

Results:

The recent increase of CC180 is related to a globally emerging clade we term Clade II, estimated to have appeared ~1968 (Figure 1). Compared to the historically prevalent Clade I, Clade II isolates are divergent in protein-antigenic composition, competence, and antibiotic resistance. The higher observed recombination rate of Clade II (r/m = 2.37) is correlated with genomic variations in competence machinery. Results from OPKA suggest serotype 3
isolates resist serotype-specific immunity. Differences in surface charge, shedding, and PCV13 use were not associated with rates of recent emergence.

Conclusion

Among sampled countries, the rise of Clade II is linked to genotypic and phenotypic differences, but not the varied use of PCV13. Our analysis emphasizes the need for routine, representative sampling of isolates from disperse geographic regions.

ISPPD-0598
LONGITUDINAL SURVEILLANCE REVEALS HIGH CLONALITY OF PNEUMOCOCCAL CARRIAGE IN THE FIRST YEAR OF LIFE IN THE GAMBIA
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Background and Aims:

In adults pneumococcal carriage induces an anticapsular antibody response that may protect against subsequent acquisition of the same serotype. It is unclear how this paradigm shifts among young children with developing immunity. We provide genomic insights into longitudinal pneumococcal carriage in the first year of life.

Methods:

Nasopharyngeal swabs were collected from 98 infants biweekly for the first seven months of life and at weeks 35, 43 and 52, across 21 villages in the Western Region of The Gambia. Whole genome sequencing was performed on 1072 pneumococcal isolates from the subjects and their phylogeny visualised using microreact.

Results:

The main serotypes carried longitudinally during the first year of life were 19A (150, 14.0%), 6A (106, 9.9%), 6B/6E (64, 6.0%), 23B (48, 4.5%) and 34 (48, 4.5%). A high level of clonality was associated with carriage whereby subjects were colonised by the same genotype over successive visits. Within a village, children were more likely to be colonised by specific sequence types (STs) in a given serotype. Marabout villages, which people visit for spiritual healing, had the highest diversity. Travelling caused some children to acquire a new ST but they were recolonised by the prevailing village ST upon their return. Isolates belonging to the same ST recovered from a subject at different times differed in the core genome.

Conclusion
Pneumococcal carriage in the first year of life in rural Gambia is clonal and villages are associated with clonal lineages. Our data suggests that infant may not be protected against re-colonisation of the same serotype.

ISPPD-0628
GENETIC DIVERSITY AND DISTRIBUTION OF THE PNEUMOCOCCAL SURFACE LIPOPROTEINS AND IMPLICATIONS ON POTENTIAL PROTEIN-BASED VACCINES
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Background:

With almost 100 serotypes, the currently licensed vaccines are limited in that they are serotype specific leading to serotype replacement by non-vaccine serotypes in disease and the 23-valent polysaccharide vaccine is also not immunogenic in young children. Therefore, conserved pneumococcal proteins represent an alternative vaccine candidates to combat pneumococcal diseases. This study was designed to identify and evaluate surface proteins with positive signatures for lipoproteins for their potential as protein vaccine candidates.

Methods:

1769 pneumococcal isolates recovered from both disease and carriage between 1993 to 2014 were screened. Using reverse Vaccinology, a holistic approach was taken to look at the level of diversity and distribution of core (>90% presence in my dataset) pneumococcal surface lipoproteins. The candidate proteins then underwent immunogenicity prediction using bioinformatic techniques and were ranked based on their potential as vaccine candidates using a scoring algorithm.

Results:

169 hits were initially obtained using established lipoprotein pattern searches. After further testing to eliminate false positives and less conserved hits, a total of 30 candidate proteins were included in the final data set. These include previously evaluated lipoproteins PsaA, AdcA, AdcAll, PiuA, PiaA as well as several new candidates that have not been evaluated in detail thus far, including YesO\(_2\), TauA and PrsA.

Conclusion:

Lipoproteins have been shown to possess important qualities for inclusion in future protein vaccines. This study has both confirmed the potential of previously evaluated proteins and also revealed new potential candidates.

ISPPD-0580
NEW ALLELES AND MULTI-LOCUS SEQUENCE TYPES OF NASOPHARYNGEAL AND INVASIVE ISOLATES OF MULTIDRUG-RESISTANT Streptococcus pneumoniae
Background and Aims:

In Medellín-Colombia, we recently demonstrated a strong association between the multidrug-resistant (MDR) serotype-19A, and the pilus-islet-1 and pilus-islet-2. Interestingly, the emergence of serotype 19A in Colombia has been linked with the spread of ST320, which has been also identified, up to date, as the unique pneumococcal clone that bears both kind of pili. Hence, we aimed to explore the genetic diversity or confirm the clonality of serotype 19A isolates, which were found to be pilus-double positive in Medellín.

Methods:

A study population set of 34 pilus-double positive serotype-19A isolates was evaluated by MLSTs. 24 colonizers from a cross-sectional study among children <5-years, and 10 clinical isolates from IPD-Cases of all ages (Passive Surveillance). Serotype-19A was confirmed by Quellung Reaction and pilus-islet-1/pilus-islet-2, by conventional PCR. The seven housekeeping gene fragments were amplified, purified and sent for sequencing, following the instructions on https://pubmlst.org.

Results:

Interestingly, the MLST results showed that 11/34 pilus-double positive serotype-19A isolates (10 colonizers and 1 IPD isolate) presented one single nucleotide substitution on the ddl gene allele-1 (position 280G), which has been assigned as the new ddl allele-861 (280A) after MLST curation. Consequently, the new ST13455 has been assigned for the MLST profile: aroE-10, gdh-16, gki-19, recP-15, spi-6, xpt-20, ddl-861. Likewise, 2/34 isolates are currently under curation for new alleles and MLST profiles. Finally, 21/34 isolates were confirmed as genetically related to the international MDR clone ST320.

Conclusion

A new ddl allele-861 and a new MLST profile ST13455 was found in Medellín for the emergent, pilus-double positive and multidrug-resistant S.pneumoniae serotype-19A.

ISPPD-0229
STREPTOCOCCUS PNEUMONIAE COLONIZATION IN TWO SOUTH AFRICAN COMMUNITIES WITH HIGH HIV PREVALENCE, 2016-2017
Background and Aims:

Data on Streptococcus pneumoniae colonization in communities with high HIV prevalence following pneumococcal conjugate vaccine (PCV) introduction are limited.

Methods:

During 2016-2017, we conducted a prospective community cohort study in two South African communities – one rural and one peri-urban. Consenting members of randomly selected households were enrolled. Nasopharyngeal swabs were collected twice per week from participants in the year of enrolment, irrespective of signs and symptoms. Specimens were tested for Streptococcus pneumoniae using a real-time PCR targeting the autolysin gene. The risk of colonization with S. pneumoniae was calculated by dividing the number of individuals that tested positive at least once during the study period by the population at risk.

Results:

Overall, 1069 individuals in 208 households were enrolled. Children aged <5 years accounted for 17.0% (182/1069) of participants. Among individuals with known HIV serostatus, the HIV prevalence was 13.3% (133/998). S. pneumoniae was detected in 38.3% (22,915/59,833) of all specimens tested. The risk of colonization was 98.6% (1054/1069). On univariate analysis, this differed by year [2016: 98.0% (509/521) vs. 2017: 99.0% (545/548), p=0.02] but did not differ by age [<5 years: 100.0% (182/182) vs. ≥5 years: 98.3% (872/887), p=0.08], HIV status [99.3% (HIV-infected: 132/133) vs. HIV-uninfected: 98.5% (852/865), p=0.5] or setting [rural: 99.1% (545/550) vs. peri-urban: 98.1% (509/519), p=0.2].

Conclusion
Eight years after PCV introduction, S. pneumoniae colonizes individuals at high levels irrespective of age, HIV-status or setting.

ISPPD-0154
PHYLOGENETIC DIVERSITY OF STREPTOCOCCUS PNEUMONIAE SEROTYPE 3 CAUSING INVASIVE PNEUMOCOCCAL DISEASE IN CANADA
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Background and Aims:
The 13-valent polyvalent conjugate vaccine (PCV13) was introduced in Canada in 2010 and by 2016 invasive disease caused by Streptococcus pneumoniae PCV13 serotypes 6A, 7F and 19A declined by 72.8%, 76.4% and 67.3% respectively, whereas levels of PCV13 serotype 3 have remained relatively unchanged.

Methods:
Core single nucleotide variant phylogenetic analyses were performed on whole genome sequencing (WGS) data generated using the Illumina MiSeq platform on 19 serotype 3 isolates collected across Canada from 2008–2015, and compared to 88 international serotype 3 genomes.

Results:
Isolates included invasive cultures from blood (n=18) and peritoneal fluid (n=1), patient ages ranged from 28–96 years and 47% (n=9) were from females. Two phylogenetic lineages (n=15) were identified among the Canadian MLST ST208 clonal complex isolates (n=19). The largest clade (n=13) consisted of antimicrobial susceptible isolates with the earliest isolate collected in 2008, and isolates of this clade were distributed among the international serotype 3 strains. A smaller more recent clade (n=4) clustered distantly from the international strains, consisted of isolates collected from 2012–2013 in Canada and had resistance to chloramphenicol, clarithromycin, clindamycin and doxycycline with cat, ermB and tetM resistance determinants. Virulence factor analysis indicated a high degree of homogeneity among the strains.

Conclusion
Some Canadian S. pneumoniae serotype 3 isolates have diversified into a relatively recent lineage distinct from the main international ST208 clone. Although the phylogenetic lineages are closely related, WGS discriminated the ST208 clonal complex of S. pneumoniae serotype 3.

ISPPD-0328
PNEUMOCOCCAL REFERENCE MICROBIOLOGY SERVICE PROVISION USING WHOLE GENOME SEQUENCING: JOINING THE REVOLUTION
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Background and Aims:

Whole Genome Sequencing (WGS) is the new gold standard in reference microbiology for identification and characterisation of bacterial isolates. As with all disruptive technologies, implementation of WGS presents new challenges from conception to implementation. Following the recent transition of Public Health England’s national reference laboratory Streptococcus pneumoniae identification and capsular typing reference service from phenotypic methods to WGS, we sought to compare our WGS service with others in Public Health England (PHE) in order to inform future plans and developments.

Methods:

We compared the PHE Streptococcus pneumoniae WGS reference service with those for Salmonella; Mycobacterium tuberculosis and Staphylococcus aureus.

Results:

Similarities across all four services included laboratory workflow processes and confirmation of species identification using WGS prior to further analysis using dedicated automated bioinformatics pipelines. Multilocus sequence typing (MLST) was included in 3 of 4 schemes and antimicrobial resistance genes were also reported in 3 services. Serotyping prediction for Salmonella was derived following determination of multilocus sequence typing (MLST), whereas pneumococcal serotype was determined following mapping to capsular polysaccharide locus sequences. Single nucleotide polymorphism (SNP) analysis was routinely performed for two services. Other specific targets included toxin gene profiling for S. aureus.

Conclusion

Major benefits of WGS include a single laboratory workflow, increased traceability and more quantifiable quality metrics. Additional benefits include derivation of MLST data and ability to mine genomes for other pathogenicity and antibiotic markers. New approaches to linkage of WGS data with epidemiological data are required in order to maximise the benefits WGS provides.

ISPPD-0567
GENETIC DIVERSITY, SEROTYPE PREDICTION AND RESISTOTYPING OF NASOPHARYNGEAL ISOLATES OF S. PNEUMONIAE FROM INDIAN HAJJ PILGRIMS BY WHOLE GENOME SEQUENCING
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288
Background and Aims:

The Islamic Hajj pilgrimage is the largest annual mass gathering in the world. The overcrowding of people promotes the acquisition, spread and transmission of respiratory pathogens, including *Streptococcus pneumoniae*. We used whole genome sequencing to evaluate the genetic diversity, determine serotypes and resistotypes of *S. pneumoniae* isolated from pre and post Indian Hajj pilgrims from 2016.

Methods:

83 NP isolates obtained from pre(36) and post(47) Hajj pilgrim cohorts were sequenced on Illumina Hiseq2500 as a part of Global Pneumococcal sequencing project. The Sanger Institute’s in-house bioinformatics pipeline was used to analyze genomic features.

Results:

Phylogenetic tree analysis revealed high level of heterogeneity among the isolates. PreHajj and postHajj isolates diverged into 12 and 9 clonal lineages respectively. MLST identified 15 known and 16 novel STs in preHajj and 11 known and 30 novel STs in postHajj isolates. None of the STs were common in pre and postHajj cohorts. The common serotypes in PreHajj were 19F(n=7), 22F(n=7) and 3(n=4) and postHajj were 28A(n=7), 31(n=5) and 6A,11A(n=4 each). Genes coding for erythromycin(ermB1,mef1), tetracycline(tetM1) and cotrimoxazole resistance were present in 10,20,19 preHajj and 14,31,27 postHajj isolates respectively. Chloramphenicol resistance gene (cat1,n=9) was found only in postHajj isolates.

Conclusion

Understanding of the genetic changes in the pneumococci during carriage is important to know the dynamics of the pneumococcal population. The study reveals high genetic diversity, changes in clonal types and increased carriage of resistance genes in postHajj *S. pneumoniae* isolates. Longitudinal genomic studies are needed to comprehend the relationship between carriage and disease in pilgrims.

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ISPPD-0318

A NATION DIVIDED: ARE NON-TYPEABLE HAEMOPHILUS INFLUENZAE FROM THE LUNGS AND THE NASOPHARYNX THE SAME?

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Background and Aims:

Molecular characterisation of lower airway non-typeable *Haemophilus influenzae* (NTHi) populations can provide novel data to help inform future vaccine development, guide
antibiotic treatment strategies and stewardship, and determine how NTHi contributes to chronic lung disease. Our aim was to establish whether upper and lower airway NTHi are genetically distinct.

Methods:

Comparative genomics was performed on paired NTHi isolates (n=207) from nasopharyngeal (NP) swabs and bronchoalveolar lavage (BAL) samples from 123 children with protracted bacterial bronchitis or bronchiectasis, plus asymptomatic carriage NTHi isolates (n=75).

Results:

Phylogenomic analysis (core genome) showed no clustering based on sample site (Figure 1). For 65% (42/65) of paired NP and BAL NTHi from the same child, genomes were highly similar, suggesting the strains were introduced recently from the NP to the lung.

![Image](image.png)

Figure 1. Maximum parsimony phylogeny of paired NP and BAL, and asymptomatic NP NTHi

Stratified genome-wide association studies (GWAS) did not identify discrete genetic determinants capable of discriminating the different populations in this dataset. Network analysis will be applied to GWAS outputs to characterise the combination of determinants capable of discriminating strains with pathogenic potential from those that are primarily colonisers; if such niche partitioning exists.

Conclusion

Genomic analysis suggests that the NP is likely the major reservoir for lower airway NTHi. Where NTHi strains unique to the lower airways were identified, further exploration will determine whether these strains are associated with an increased propensity to cause lower
Identifying Non-Random Patterns of Capsule Switching in Pneumococcus

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Background and Aims:
Since the introduction of conjugate vaccines, serotypes not targeted by the vaccine have increased in frequency in carriage and disease. One source of these emergent strains is from serotype switching, where strains producing a vaccine-targeted capsule acquire the ability to produce a non-vaccine type. Our goal was to quantify non-random serotype switching patterns and to determine the potential role of shared biochemical characteristics of the capsule in influencing these patterns.

Methods:
Using the 35,000+ isolates of pneumococcus in the PubMLST database, we performed association rule mining to identify pairs of serotypes that tend to co-occur on the same sequence type (MLST) more often than expected by chance. We also computed Simpson’s Diversity Indices (SDI) for individual serotypes with respect to MLST. A higher value of the SDI is an indirect correlate of serotype switching frequency. Controlling for frequency of colonization, we performed a regression analysis to evaluate the association between polysaccharide components and SDI.

Results:
As expected, we found that serotypes in the same serogroup tended to occur on the same MLST type. We also identified other associations of serotype pairs co-occurring on the same MLST type. These serotypes share antigenic characteristics and have similar structures. Finally, we found that glucuronic acid in the capsule was associated with lower diversity of the serotype, after controlling for carriage frequency, potentially highlighting a restriction in capsule switching ability for serotypes with certain capsular characteristics.

Conclusion
These findings support the hypothesis that non-capsular factors influence serotype switching patterns.

Hotspots of Recombination in Pneumococci Isolated from Nepalese Children Prior to PCV Introduction

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Background and Aims:

Environmental influences such as human immune responses and antibiotic use are thought to elicit selective pressure on the genome of pneumococcus. These selective pressures are evident by the frequency of recombination in affected genes. We aimed to identify the recombination patterns of pneumococci isolated from Nepalese children prior to PCV introduction.

Methods:

DNA from 458 (388 carriage and 70 invasive) pneumococcal isolates from Nepalese children, collected prior to national PCV introduction, underwent whole-genome-sequencing on the Wellcome Trust Sanger Institutes core sequencing pipeline. Population clusters were defined by sequence similarity using hierBAPS. Regions of recombination within clusters were determined using Gubbins with hotspots defined as regions with a recombination frequency above the 95th centile. BLASTn comparison of these regions with Streptococcus pneumoniae ATCC700669 was then used to identify the genes within hotspots.

Results:

281 described genes were found to be present in a hotspot in more than one of the population clusters. The genes which were in hotspots of recombination across the most clusters were pspA, SPN23F03020, SPN23F03030, mraW, ftsL, pbp2x, arcA, and pspC. Interestingly, the two surface proteins pspA and pspC were identified as hotspots in the same group of five population clusters.

Conclusion

Host immunity and antibiotic use may influence genetic plasticity, given the number of population cluster recombination hotspots that contained genes such as pspA, pspC, and pbp2x.

ISPPD-0406
INSIGHTS INTO POTENTIAL PCV EFFECTS ON PNEUMOCOCCAL LINEAGES USING WHOLE GENOME SEQUENCING


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Background and Aims:

Using the Global Pneumococcal Sequencing Project database of pneumococcal whole genome sequences collected prior to any pneumococcal conjugate vaccine (PCV) introduction we aimed to identify how pneumococcal lineages might be affected by PCV introduction.
Methods:

DNA from 7596 pneumococcal isolates, comprising 2512 carriage, 4815 invasive, and 269 isola tes from other sources, underwent whole-genome-sequencing on the Wellcome Trust Sanger Institutes core sequencing pipeline. Lineages were defined by clustering genomes on sequence similarity using hierBAPS. Simpson's index of serotype diversity (a value between 0 and 1) for each lineage was calculated, with higher values indicating greater diversity.

Results:

45 pneumococcal lineages were identified. Two monophyletic lineages which were represented entirely by serotype 1 and serotype 5 isolates respectively (Simpson's index of 0) were observed, which would thus be unlikely to escape negative selection following vaccine introduction. Contrastingly however, three lineages which were comprised of 65/324 (20.1%), 54/157 (34.4%), and 51/183 (27.9%) serotypes included in the PCV13 vaccine, and had Simpson's indices of 0.83, 0.88, and 0.92 respectively, may be more likely to escape selection as a result of PCV introduction.

Conclusion

Using whole-genome sequencing of pneumococci collected prior to PCV introduction, it is apparent that a number of lineages which contain PCV serotypes also contain non-vaccine types and may be more capable of progressively escaping selective pressure of PCV introduction in settings where these strains exist. Further correlation of these data with post-PCV pneumococcal populations may be used to further inform PCV effect on pneumococcal lineages.
Serotype3 IPD cases in children <18 years were identified via surveillance in collaboration with Massachusetts Department of Public Health. We sequenced isolates from fully vaccinated cases (PCV13) and matched unvaccinated controls. Isolates were sequenced using Illumina platform and the data analyzed using core genome MLST approach (cgMLST, 866 loci). The genetic data was correlated with clinical data (year and syndrome of IPD, vaccination status).

Results:

No difference in incidence, time after immunization, or clinical syndrome was observed pre- and post-PCV13. cgMLST analysis was completed for 18 (of 47) isolates (10 from fully vaccinated cases, 5 unvaccinated cases from prePCV13 and 3 postPCV13 era). cgMLST revealed that strains were distributed into two major genetic clusters with >95% similarity and differing between them in at least 280 loci (32%) (Fig 1). There were no significant differences in distribution of isolates when comparing vaccine failures to controls or year of IPD. Pneumonia isolates were more common in cluster 2. Further sequencing is ongoing.

Conclusion

Serotype3 isolates from IPD cases pre- and post-PCV13 show conserved genetic backgrounds. Preliminary analysis suggests serotype3 isolates from pneumonia cases are associated with one specific cluster.
Background and Aims:

Following the introduction of 7-valent pneumococcal conjugate vaccine (PCV7) into the childhood immunization program in Hong Kong in 2009, a local epidemiological study has revealed changes in carriage serotypes in young children. Given this observation, the study aimed to provide a high-resolution picture of the changes in the pre- and post-vaccine era by whole genome sequencing (WGS) pneumococci collected in Hong Kong.

Methods:

A total of 452 isolates collected from 1999-2015 in Hong Kong were selected to represent the pre- (1999-2008) and post-vaccine (2009-2015) implementation eras for both carriage (n=300) and Invasive Pneumococcal Disease (IPD; n=152). WGS was performed by the Sanger Institute as part of the Global Pneumococcal Sequencing (GPS) project; software employed for analyses were Velvet, RAxML, pneumoCaT, Roary, and Gubbins. Sequence clusters (SC) were defined based on maximum-likelihood (ML) phylogeny. Penicillin susceptibilities were determined with E-Test.

Results:

Eleven sequence clusters (SC) were identified amongst the pneumococcal population in Hong Kong. Capsular switching events were detected in eight of the SCs, involving both PCV7 and non-PCV7 serotypes. Four of these capsular switches were penicillin resistant (using the meningitis breakpoint), while the rest the isolates on the same branch of the ML tree were penicillin susceptible.

Conclusion

The observations of capsular switching variants associated with PCV7 serotypes, and those involved in penicillin resistance acquisition, suggested that immune responses from vaccination and natural exposure, and exposure to beta lactam antibiotics were potential driving forces for genetic changes resulting in capsular switching events.

ISPPD-0678

LINKAGE BETWEEN PNEUMOCOCCAL CAPSULE-ASSOCIATED PHENOTYPE AND ENCODING OF PROTEIN ANTIGENS IN THE ACCESSORY GENOME

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³IPSDD-11

Background and Aims:

Serotype-defining polysaccharide capsular antigens determine many aspects of pneumococcal fitness. Additionally, a repertoire of extracellular protein antigens contributes to host-pathogen interactions. Many of these proteins are polymorphic due to homologous recombination, and are maintained in the pneumococcal population at intermediate frequencies. To better understand the biological basis of this antigenic diversity, we tested
whether capsule-associated phenotypes predict encoding of major protein antigen variants (PAVs).

**Methods:**

We examined presence and absence of PAVs in pneumococcal isolates carried by 273 and 265 Navajo children ages 0-5y before and after PCV7 implementation, respectively. We defined capsular phenotype using a principle components decomposition of previously-measured fitness factors—including capsule thickness, surface charge, resistance to neutrophil-mediated killing, and metabolic characteristics—and epidemiological attributes including serotype-specific carriage duration, invasiveness, and case-fatality ratio. We used logistic regression to test whether distinct PAVs were associated with capsular phenotype, controlling for lineage effects.

**Results:**

A principal component closely associated with pneumococcal fitness (PCA1; 40% of variance) predicted encoding of 7 out of 12 PAVs assessed in the pre-PCV7 era \((p<10^{-7})\) but only 2 of 11 in the PCV13 era \((p=0.015)\). Two further principal components also predicted encoding of more protein antigens than expected under a null hypothesis of no association between capsular phenotype and PAVs.

<table>
<thead>
<tr>
<th>PAV</th>
<th>PCA1 Pre-PCV7 era</th>
<th>PCA1 PCV13 era</th>
<th>PCA2 Pre-PCV7 era</th>
<th>PCA2 PCV13 era</th>
<th>PCA3 Pre-PCV7 era</th>
<th>PCA3 PCV13 era</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPC609</strong></td>
<td>0.34 (0.18, 0.66)</td>
<td>1.62 (0.94, 2.81)</td>
<td>0.99 (0.63, 1.12)</td>
<td>1.71 (1.31, 2.21)</td>
<td>0.99 (0.66, 1.49)</td>
<td>0.76 (0.41, 1.43)</td>
</tr>
<tr>
<td><strong>SP2914</strong></td>
<td>1.22 (1.28, 1.73)</td>
<td>- -</td>
<td>1.74 (1.23, 2.45)</td>
<td>0.87 (0.58, 1.31)</td>
<td>0.97 (1.42, 3.20)</td>
<td>0.75 (0.41, 1.44)</td>
</tr>
<tr>
<td><strong>nanA</strong></td>
<td>1.85 (1.13, 3.01)</td>
<td>0.70 (0.42, 1.19)</td>
<td>0.69 (0.43, 0.97)</td>
<td>1.31 (0.82, 2.09)</td>
<td>2.00 (1.28, 3.11)</td>
<td>1.10 (0.66, 1.84)</td>
</tr>
<tr>
<td><strong>phoD</strong></td>
<td>0.28 (0.14, 0.54)</td>
<td>0.54 (0.22, 1.30)</td>
<td>0.29 (0.46, 1.96)</td>
<td>0.71 (0.33, 1.58)</td>
<td>0.40 (0.29, 0.70)</td>
<td>0.61 (0.20, 1.29)</td>
</tr>
<tr>
<td><strong>ply</strong></td>
<td>0.42 (0.17, 1.04)</td>
<td>0.57 (0.26, 1.20)</td>
<td>2.87 (1.11, 7.42)</td>
<td>3.12 (1.34, 7.38)</td>
<td>0.47 (0.20, 1.11)</td>
<td>0.42 (0.20, 1.11)</td>
</tr>
<tr>
<td><strong>pspC-1</strong></td>
<td>0.92 (0.67, 1.27)</td>
<td>0.56 (0.35, 1.34)</td>
<td>0.63 (0.43, 0.92)</td>
<td>0.46 (0.24, 0.87)</td>
<td>1.69 (1.15, 2.48)</td>
<td>0.83 (0.36, 1.97)</td>
</tr>
<tr>
<td><strong>pspC-2</strong></td>
<td>0.53 (0.27, 1.02)</td>
<td>5.83 (1.39, 24.44)</td>
<td>0.87 (0.48, 1.59)</td>
<td>0.12 (0.04, 0.35)</td>
<td>1.15 (0.70, 1.86)</td>
<td>5.04 (2.13, 11.95)</td>
</tr>
<tr>
<td><strong>atxA</strong></td>
<td>3.43 (1.96, 6.02)</td>
<td>1.39 (0.01, 2.40)</td>
<td>0.74 (0.05, 1.19)</td>
<td>2.23 (1.17, 4.32)</td>
<td>1.97 (1.25, 3.08)</td>
<td>0.78 (0.45, 1.38)</td>
</tr>
<tr>
<td><strong>strF</strong></td>
<td>1.65 (0.99, 2.42)</td>
<td>0.79 (0.45, 1.43)</td>
<td>0.32 (0.16, 0.79)</td>
<td>0.61 (0.31, 1.21)</td>
<td>2.07 (1.39, 3.08)</td>
<td>0.61 (0.26, 1.33)</td>
</tr>
<tr>
<td><strong>psaA</strong></td>
<td>1.78 (1.22, 2.53)</td>
<td>1.07 (0.66, 1.73)</td>
<td>1.29 (0.60, 1.83)</td>
<td>1.79 (1.14, 2.83)</td>
<td>0.98 (0.69, 1.40)</td>
<td>0.41 (0.22, 0.74)</td>
</tr>
<tr>
<td><strong>zmpA</strong></td>
<td>0.07 (0.02, 0.29)</td>
<td>8.06 (2.22, 33.39)</td>
<td>1.40 (0.81, 2.15)</td>
<td>0.91 (0.50, 1.66)</td>
<td>0.50 (0.31, 0.80)</td>
<td>1.10 (0.56, 2.04)</td>
</tr>
<tr>
<td><em><em>rmpC</em>”</em>*</td>
<td>0.44 (0.27, 0.73)</td>
<td>1.29 (0.64, 2.60)</td>
<td>0.52 (0.28, 0.97)</td>
<td>0.46 (0.20, 1.08)</td>
<td>1.63 (0.91, 2.92)</td>
<td>4.38 (1.49, 12.76)</td>
</tr>
</tbody>
</table>

*Meta-\(p\) values quantify the probability of detecting the observed number of statistically-significant findings at a 5% type-2 error threshold under a null hypothesis of no association.

*Our analysis of rmpC address the presence or absence of the plus-encoding antigen rather than distinguishing between variants.
Conclusion

We identify linkage between capsule-associated pneumococcal phenotype and PAVs. Understanding the biological function and immunogenicity of PAVs can guide interpretation of these findings in the context of evolutionary selection.

ISPPD-0556
GENETIC SIMILARITY OF EMERGING ST6011 SEROTYPE 3 AND ST6011 SEROTYPE 15A STREPTOCOCCUS PNEUMONIAE IN HONG KONG
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Background and Aims:

Serogroup 15 and serotype 3 pneumococci were noted to be emerging in the PCV13 period in Hong Kong. This study was carried out to identify the possible events leading to the emergence of these strains.

Methods:

Whole genome sequencing was performed on 16 ST6011 serotype 15A, 32 ST6011 serotype 3, one ST180 and one ST6012 serotype 3 isolates. These genomes were used to identify the nearest neighbor for reference mapping. S. pneumoniae G54 was chosen by this process and all sequenced genomes were mapped by the REALPHY software.

Results:

Alignment of the ST6011 serotype 3, ST6011 serotype 15A and ST 6011 serotype 3 isolates indicated that these isolates fall within three distinct clusters (Figure 1). From the tree, ST180 serotype 3 and serotype ST 6011 serotype 15A and ST 6011 serotype 3 were estimated to have a divergence date of >80 years ago. However the ST 6011 serotype 15A and ST 6011 serotype 3 isolates also demonstrated divergence~ 80 years ago. In contrast, strains for each group of the ST180 serotype 3 or ST 6011 serotype 15A or ST 6011 serotype 3 have a recent divergence date of ~5 years ago.

Conclusion

A possible clonal expansion, than a capsular switch even would have led to the emergence of the ST6011 serotype 3 and ST6011 serotype 15A isolates.

ISPPD-0326
A MULTIDRUG RESISTANT PNEUMOCOCCAL CC230 SUB-LINEAGE HARBOURING A MOSAIC TET(S/M) GENE ENCODING TETRACYCLINE RESISTANCE IN SOUTH AFRICA
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Background and Aims:

A mosaic tet(S/M) gene encoding tetracycline resistance has been found in a wide range of Streptococcus spp., but has been rarely reported in pneumococci. We assessed a global collection of pneumococcal genomes to identify tet(S/M) and characterise their geographical distribution and genetic background.

Methods:

We detected tet(S/M) and other resistance determinants in the Global Pneumococcal Sequencing project curated database (n=12,254, http://www.pneumogen.net/gps/) using ARIBA. Around 38% of the genomes in this database were from South Africa. Antibiotic susceptibility was predicted based on genotypes. Phylogenetic analysis was performed using GUBBINS.

Results:

The tet(S/M) gene was identified in 130 isolates from South Africa (n=123), Malawi (n=4), and one each from Brazil, Mozambique, and the USA. The majority of these were invasive isolates (n=106). All tet(S/M)-positive isolates belonged to clonal complex (CC)230, except for one that belonged to CC320. A CC230 SNP tree (figure 1) showed that all tet(S/M)-positive isolates formed a sub-lineage with nonsusceptibility to penicillin, erythromycin, tetracycline and cotrimoxazole. This sub-lineage was primarily associated with vaccine serotype 14 (98%, 127/129). The tet(S/M) gene was located in a conserved Tn916S transposon that inserted within a Tn5253-like ICE element that co-carried ermB.
Conclusion

There was a low prevalence of \textit{tet}(S/M) within the GPS dataset, and the conserved genomic location of \textit{tet}(S/M) and closely related genetic background suggested a clonal spread of a \textit{tet}(S/M)-positive CC230-sublineage within South Africa.

\textbf{ISPPD-0200}

\textbf{NON-CODING RNA AS MODULATOR OF STREPTOCOCCUS PNEUMONIAE VIRULENCE}

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\textsuperscript{1}\textit{Far Eastern Federal University, Natural Science School, Vladivostok, Russia}

\textbf{Background and Aims:}

Small noncoding RNAs (sRNAs) play important roles in gene regulation in both prokaryotes and eukaryotes. As the dynamics of functioning of CiaRH (the two-component regulatory system which is responsible for β-lactam resistance, maintenance of cell integrity, competence and virulence) of Streptococcus pneumoniae is poorly studied, the aim of our study was to define role of potential of small RNA in CiaRH mechanism and overall in pathogenesis of pneumococcal infection.
Methods:

We isolated RNA from Streptococcus pneumoniae TIGR4 strain, then transcriptional start points were determined by 5′-RACE as described previously using the same RNA adapter and gene-specific primers, in vitro CiaR binding, and in vivo analysis of CiaR-mediated regulation.

Results:

promoters were identified to be directly controlled by the response regulator CiaR. The genes that are transcribed from these promoters included ciaRH, loci that are predicted to be involved in the modification of teichoic acids (lic), in sugar metabolism (mal, man), stress response (htrA), chromosome segregation (parB), protease maturation (ppmA) and unknown functions. Ten of the regulon are activated by CiaR, and one was found to be controlled negatively. Five strongest promoters of the CiaR regulon drive expression of small RNAs. These small RNAs, designated csRNAs for cia-dependent small RNAs, are non-coding, between 60 and 71 nt in size, and show a high degree of similarity to each other.

Conclusion

many of the identified sRNAs have important niche-specific role in virulence what constitute the most comprehensive analysis of pneumococcal sRNAs and provide the first evidence of the extensive roles of sRNAs in pneumococcal pathogenesis.

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ISPPD-0768

PRESENCE OF NON-PNEUMOCOCCAL STREPTOCOCCI CONTAINING PNEUMOCOCCAL GENE HOMOLOGUES MAY CAUSE FALSE POSITIVE RESULTS IN DETECTION BY QPCR IN SALIVA SAMPLES IN YOUNG CHILDREN

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2University of London, Institute for Infection and Immunity- St. George’s, London, United Kingdom
3London Bioscience Innovation Centre, BUGS Bioscience, London, United Kingdom
4Centro Hospitalar e Universitario de Coimbra, Hospital Pediatrico, Coimbra, Portugal

Background and Aims:

Pneumococci(Sc) are detected by PCR in a high proportion of saliva samples from healthy children. We analysed paired nasal swab and saliva samples from children, in which both samples were lytA qPCR positive(Ct≤35), by molecular microarray serotyping.

Methods:

The products of standard culture on selective agar plates from 49 sample pairs, obtained from healthy children aged 6 months to 5 years attending pre-school nursery in Coimbra, Portugal, were subjected to molecular serotyping analysis by microarray as previously described.

Results:

Among 49 nasal swab samples, 45 had evidence of Sp by microarray, 4 only related non-Sp and one no evidence of Sp or related species. In 28 there was evidence of single Sp
serotypes and in 9 of multiple serotypes. By contrast only 3/49 saliva samples had evidence of Sp by microarray, in each case matching the Sp detected in nasal sample from the same child but in all 3 at low abundance within a complex mix of other species.

**Conclusion**

These results suggest that the common finding of qPCR results suggestive of the presence of Sp in saliva samples in young children may, in reality, reflect presence of genetically related streptococci from the oral flora, usually in complex mixtures. While our findings do not definitively rule out the presence of small numbers of viable pneumococci whose presence is masked by rich oral microbial flora, nevertheless, they suggest that transmission of Sp via saliva may be less important than via nasal secretions in this age group.

Work supported by an investigator-led project grant from Pfizer.

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**ISPPD-0274**

WHOLE GENOME SEQUENCING OF STREPTOCOCCUS PNEUMONIAE SEROGROUP 19 ISOLATES BEFORE THE INTRODUCTION OF VACCINE IN THE NATIONAL IMMUNIZATION PROGRAMME OF INDIA (NIP)

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²The Wellcome Trust Sanger Institute, Infection Genomics, Hinxton, United Kingdom
³Emory University, Hubert Department of Global Health, Atlanta, USA
⁴Centers for Disease Control and Prevention, Respiratory Diseases Branch, Atlanta, USA

**Background and Aims:**

Infection caused by *Streptococcus pneumoniae, a highly recombinogenic bacterium*, is a major cause of morbidity and mortality worldwide. Introduction of PCV13 in NIP (May 2017) is bound to have impact on the epidemiology of disease in India. Serogroup-19 is among the most prevalent *Streptococcus pneumoniae* serotypes in India. We performed Phylogenetic analysis of serogroup-19 strains to understand the larger impact

**Methods:**

39IPD and 33Nasopharyngeal carriage isolates of *S. pneumoniae* serotype 19F (n=25IPD;18NP), 19A (n=14IPD;12NP) and 19B (n=3NP) collected across the country between 2009–2017 were sequenced using Illumina HiSeq 2500 system, as part of the Global Pneumococcal Sequencing project. Population structure, STs and presence of antibiotic resistance conferring genes were analyzed. The phylogenetic tree was built with FastTree after mapping to ATCC700669. Resistance genotyping was performed using a CDC pneumococcal typing protocol

**Results:**

Population structure analysis of serogroup 19 showed high level heterogeneity. 19F, 19A and 19B serotypes showed 17, 13 and 2 diverged specific clonal lineages respectively. MLST resolved the 72 isolates into 18 known and 11 novel STs. ST236 (PMEN14, n=9,12.5%) and ST271 (n=9,12.5%) were the most prevalent clones, followed by ST320 (n=6,8.3%). High resistance to tetracycline (54%), erythromycin (44.4%) and cotrimoxazole (55.5%) was observed. Multi-drug resistance was present in 26(36%) isolates. 30.5%(n=22) of isolates were penicillin nonsusceptible with majority of them belonging to 19F serotype(n=14)
Conclusion

Whole genome sequencing of serogroup 19 identified a genetically diverse collection with novel clones and lineages associated with antimicrobial non-susceptibility. The study has implication to understand the potential long-term public health impact and cost-effectiveness of conjugate vaccine.

Background and Aims:

Pneumococcal infections cause a high death toll in India. The recently rolled out (May, 2017) PCV in the national infant immunization schedule is expected to reduce disease burden. To assess the impact of the vaccine on pneumococcal population, characterization of pneumococcal isolates sampled prior to vaccination is required. Here we present a population genomic study of the S. pneumoniae strains collected across India before vaccine introduction.

Methods:

204 Invasive pneumococcal disease and 182 Nasopharyngeal carriage isolates of S. pneumoniae strains collected across India from 2009-2017 were sequenced, as part of the Global Pneumococcal Sequencing project. The Sanger Institute’s in-house bioinformatics pipeline was used to determine population genetic structure, phylogenomics, serotype prevalence and resistotypes.

Results:

Population genetic structure analysis reveals high level of heterogeneity and 22 genetically distinct sequence clusters. In the pre-vaccine era, serotype 19F (11.1%) was the most common serotype, followed by 19A (6.75%), 6A (5.9%), 6B (5.4%), 14 (4.9%) and 1 (4.4%). Invasive and carriage isolates of children 65% and 55%, respectively, were of serotypes included in PCV13. MLST data divided the population into 130 known and 97 novel STs. 46 isolates belonging to 11(1,2,3,14,15,19,25,26,27,32 and 38) PMEN clones were detected. Overall, 39.2% (n=151) carried at least one resistance determinant, including 72 (18.7%) isolates demonstrating multi drug resistance.

Conclusion

High throughput genome sequencing in this study elucidates STs, genome evolution, and population level characterization, which is of relevance to disease control. It provides a comprehensive baseline for use in measuring impact of PCV13 on circulating pneumococci in India during the era of pneumococcal vaccine introduction with increasing coverage over time.
ISPPD-0701
CONCORDANCE BETWEEN CONVENTIONAL AND WHOLE-GENOME SEQUENCING GUIDED SEROTYPING OF INVASIVE PNEUMOCOCCAL DISEASE ISOLATES IN NSW, AUSTRALIA
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³The University of Sydney, Marie Bashir Institute for Infectious Diseases and Biosecurity, Sydney, Australia
⁴Westmead Hospital, Institute of Clinical Pathology and Medical Research, Westmead, Australia

Background and Aims:

Streptococcus pneumoniae can cause a range of invasive and non-invasive diseases and is a leading cause of morbidity and mortality in young children and the elderly. Routine use of pneumococcal vaccination has significantly reduced the burden of invasive pneumococcal disease (IPD) in Australia and elsewhere. However, continued surveillance of IPD is required to monitor serotype replacement and emergence of antibiotic resistance. While the Quellung reaction remains the gold standard for serotyping of pneumococci isolates, molecular methods based on microarrays, polymerase chain reaction (PCR) and whole genome sequencing (WGS) improve the resolution of laboratory surveillance.

Methods:

We used the WGS based serotyping bioinformatics tool, PneumoCaT (Pneumococcal Capsular Typing) in order to compare the molecular serotype with capsular antigenic type detected by Quellung and also to investigate the diversity of capsular gene. This comparison was performed on 107 IPD isolates, which represented all IPD cases from <5 year old children referred to NSW PRL in 2015 and 2016.

Results:

Concordance between molecular and phenotypic serotyping was noted in 87% (93/107) of isolates. Of the discordant serotyping results 8 of 14 isolates had PneumoCaT serotypes attributed to a different serogroup compare to Quellung, and 4 of the 14 differed in serotype but belong to the same serogroup. Homology of sequotyping primers is also being investigated.

Conclusion

Our findings illustrate the added value of S. pneumoniae genome sequencing in the characterisation and high-resolution laboratory surveillance of IPD.

ISPPD-0226
MOLECULAR EPIDEMIOLOGY OF 14 NEWLY-DISCOVERED PUTATIVE BACTERIOCINS IN STREPTOCOCCUS PNEUMONIAE
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²Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

Background and Aims:

Streptococcus pneumoniae can cause a range of invasive and non-invasive diseases and is a leading cause of morbidity and mortality in young children and the elderly. Routine use of pneumococcal vaccination has significantly reduced the burden of invasive pneumococcal disease (IPD) in Australia and elsewhere. However, continued surveillance of IPD is required to monitor serotype replacement and emergence of antibiotic resistance. While the Quellung reaction remains the gold standard for serotyping of pneumococci isolates, molecular methods based on microarrays, polymerase chain reaction (PCR) and whole genome sequencing (WGS) improve the resolution of laboratory surveillance.

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Concordance between molecular and phenotypic serotyping was noted in 87% (93/107) of isolates. Of the discordant serotyping results 8 of 14 isolates had PneumoCaT serotypes attributed to a different serogroup compare to Quellung, and 4 of the 14 differed in serotype but belong to the same serogroup. Homology of sequotyping primers is also being investigated.

Conclusion

Our findings illustrate the added value of S. pneumoniae genome sequencing in the characterisation and high-resolution laboratory surveillance of IPD.
Background and Aims:

Competition among bacterial members of the nasopharynx is believed to be mediated by bacteriocins: antimicrobial toxins produced by bacterial species to inhibit the growth of other closely-related bacteria. Their ability to kill bacteria makes bacteriocins attractive candidates for the development of novel antimicrobials. We recently identified 14 newly-discovered putative bacteriocins, tripling the number of known bacteriocins among pneumococci. We aimed to further assess these bacteriocins in the context of the pneumococcal population structure.

Methods:

Using a large global and historical dataset of 571 pneumococci isolated from 1916-2009, we determined the prevalence, molecular epidemiology and co-occurrence patterns of the pneumococcal bacteriocins.

Results:

The number of different bacteriocins within each genome varied from 6 to 11 among pneumococci and certain combinations of bacteriocins were more frequently represented in the dataset. All bacteriocins detected more than once in the dataset were identified among pneumococci isolated over several decades and from a variety of different countries. We observed that many pneumococcal genomes harbour partial bacteriocin clusters that lack the toxin gene, while still retaining the immunity and/or the transporter genes. Whole-genome-based population analyses identified three genomic regions that are putative hotspots for the integration of bacteriocin clusters in the pneumococcal chromosome. Our data suggest a switching mechanism, whereby different bacteriocin clusters can replace one another via genetic recombination.

Bacteriocin clusters identified among a dataset of 571 pneumococci recovered since 1914 from patients of all ages residing in 39 different countries.

<table>
<thead>
<tr>
<th>Bacteriocin</th>
<th>Genome(s)</th>
<th>Year(s) of Isolation</th>
<th>Countries (n)</th>
<th>CC(n)</th>
<th>Serotypes (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete</td>
<td>Partial</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus A</td>
<td>374 (65.5%)</td>
<td>31 (5.4%)</td>
<td>405 (70.9%)</td>
<td>1916-2009</td>
<td>36</td>
</tr>
<tr>
<td>Streptococcus B</td>
<td>415 (72.7%)</td>
<td>156 (27.3%)</td>
<td>571 (100%)</td>
<td>1916-2009</td>
<td>39</td>
</tr>
<tr>
<td>Streptococcus C</td>
<td>571 (100%)</td>
<td>0 (0.0%)</td>
<td>571 (100%)</td>
<td>1916-2009</td>
<td>39</td>
</tr>
<tr>
<td>Streptococcus D</td>
<td>6 (1.1%)</td>
<td>0 (0.0%)</td>
<td>6 (1.1%)</td>
<td>1968-2005</td>
<td>5</td>
</tr>
<tr>
<td>Streptococcus E</td>
<td>74 (13.0%)</td>
<td>49 (86.9%)</td>
<td>570 (99.8%)</td>
<td>1916-2009</td>
<td>39</td>
</tr>
<tr>
<td>Streptolactocin A²</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>2 (0.4%)</td>
<td>1972-2006</td>
<td>2</td>
</tr>
<tr>
<td>Streptolactocin B²</td>
<td>45 (7.9%)</td>
<td>48 (8.4%)</td>
<td>93 (16.3%)</td>
<td>1930-2006</td>
<td>16</td>
</tr>
<tr>
<td>Streptolactocin C²</td>
<td>73 (12.8%)</td>
<td>23 (37.4%)</td>
<td>286 (50.1%)</td>
<td>1937-2009</td>
<td>27</td>
</tr>
<tr>
<td>Streptolactocin D²</td>
<td>49 (8.6%)</td>
<td>0 (0.0%)</td>
<td>49 (8.6%)</td>
<td>1938-2006</td>
<td>13</td>
</tr>
<tr>
<td>Streptolactocin E²</td>
<td>3 (0.5%)</td>
<td>161 (28.2%)</td>
<td>164 (28.7%)</td>
<td>1937-2009</td>
<td>25</td>
</tr>
<tr>
<td>Streptolactocin F²</td>
<td>23 (4.0%)</td>
<td>0 (0.0%)</td>
<td>23 (4.0%)</td>
<td>1937-2006</td>
<td>7</td>
</tr>
<tr>
<td>Streptolactocin G²</td>
<td>186 (32.6%)</td>
<td>13 (2.3%)</td>
<td>199 (34.9%)</td>
<td>1936-2009</td>
<td>25</td>
</tr>
<tr>
<td>Streptolactocin H²</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
<td>1996-2008</td>
<td>1</td>
</tr>
<tr>
<td>Streptolactocin I²</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
<td>2005</td>
<td>1</td>
</tr>
<tr>
<td>Streptolactocin J²</td>
<td>140 (24.5%)</td>
<td>237 (41.5%)</td>
<td>377 (66.0%)</td>
<td>1916-2009</td>
<td>33</td>
</tr>
<tr>
<td>Streptolactocin K²</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
<td>2005</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus c²</td>
<td>205 (35.9%)</td>
<td>4 (0.7%)</td>
<td>209 (36.6%)</td>
<td>1937-2009</td>
<td>20</td>
</tr>
<tr>
<td>Streptolactocin ℓ²</td>
<td>20 (3.5%)</td>
<td>0 (0.0%)</td>
<td>20 (3.5%)</td>
<td>1959-1966</td>
<td>8</td>
</tr>
<tr>
<td>Streptolactocin ℶ²</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
<td>2005</td>
<td>1</td>
</tr>
<tr>
<td>cll²</td>
<td>551 (96.5%)</td>
<td>14 (2.5%)</td>
<td>565 (97.5%)</td>
<td>1916-2009</td>
<td>39</td>
</tr>
<tr>
<td>bll²</td>
<td>N/A</td>
<td>N/A</td>
<td>571 (100%)</td>
<td>1916-2009</td>
<td>39</td>
</tr>
</tbody>
</table>

a, CC, clonal complex. Singletons (single genotypes with no closely related variants) were excluded from the count.

Synonym(s) for the previously identified bacteriocins are as follow: b, pneumolactocidin and salivaricin; c, IzAN1 and ICFsp23SP6581 lamibiotic; d, SP3e-BS72 lamibiotic; e, phi lamibiotic; f, pneumocyslicin; g, chAB; h, spl and plc.
Conclusion

We revealed that not only do pneumococci possess a substantially greater and more varied array of bacteriocins than previously recognised, the bacteriocins, often in a particular combination, are associated with specific genetic lineages.

ISPPD-0493
GENOMICS GUIDED DETECTION OF CHROMOSOMAL AND PLASMID MEDIATED ANTIBIOTIC RESISTANCE OF STREPTOCOCCUS PNEUMONIAE
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Background and Aims:

*Streptococcus pneumoniae* can acquire genetic material through horizontal gene transfer from other respiratory flora enabling this bacterium to rapidly develop antibiotic resistance. Rates of antibiotic resistant pneumococci are difficult to determine and they depend on numerous factors including selective pressure from antibiotic overuse. In Australia, an estimated 10 -12% of invasive pneumococcal disease (IPD) isolates of *S. pneumoniae* have reduced susceptibility to penicillin, however, *in vitro* susceptibilities are only available for 70% of isolates. Whole genome sequencing (WGS) provides high resolution monitoring of population changes and can accurately and rapidly predict pneumococcal serotype. The aim of this study was to validate prediction of penicillin resistance using WGS datasets, demonstrating the utility and benefit of WGS over traditional phenotypic surveillance.

Methods:

We validated our approach on 158 sequenced IPD isolates (representatives of 20 serotypes), where minimum inhibitor concentration data for penicillin was available. Illumina reads were *de novo* assembled and penicillin binding protein sequences (Pbp1a, Pbp2a, Pbp2b and Pbp2x) were selected and concatenated. Phylogeny was constructed and compared to phenotypic susceptibility and resistance results obtained from Etest using CLSI breakpoints.

Results:

Phenotypic and genotypic methods showed concordance for 94% (148/158) of isolates. The method is currently being expanded to evaluate plasmid mediated resistance to tetracycline and additional genomic markers of penicillin resistance, such as *folA*.

Conclusion

These findings demonstrate the added value of pneumococcal WGS in inferring *in vitro* resistance to penicillin as part of public health laboratory surveillance of IPD.
Background and Aims:

Pneumococcal carriage is a recognised precursor for invasive disease. Serotype 6A/6B is commonly carried in The Gambia especially in infants. We studied the genotypic diversity of serotype 6A/6B carriage in infants who were vaccinated or not vaccinated with pneumococcal conjugate vaccine in the Western region of The Gambia.

Methods:

A longitudinal study recruited 102 new-borns and followed them bi-weekly for the first six months and then monthly, for a year. Altogether, 1,595 nasopharyngeal swabs were collected from vaccinated and unvaccinated participants. *Streptococcus pneumoniae* was isolated from 1,258(78.9%) participants and serotyping done by latex agglutination. Overall, 185(14.7%) serotype 6A/6B isolates from 54(52.9%) participants were differentiated by serotype-6 specific PCR and antimicrobial susceptibility determined by Kirby-Bauer method and E-test. The whole genome phylogeny of 158 isolates was analysed with microreact.

Results:

The whole genome phylogeny shows close relationship between serotype 6A and 6B. Although most participants (45, 44.1%) were persistently colonized by one serotype, 9 (8.8%) participants exchanged between serotype 6A and 6B. Carriage was found to be clonal within individuals and at community level. In some instances, genotype replacement was observed. Among 34(49.3%) vaccinated participants, 17(24.6%) and 5(7.2%) were colonised by 6A and both serotypes, respectively. Amongst unvaccinated participants, 6(18.2%), 3(9.1%), and 4(12.1%) were colonised by 6A, 6B, and both serotypes, respectively. The E-test shows 74.1% and 82.1% resistance to tetracycline and trimethoprim/sulfamethoxazole, respectively.

Conclusion

Carriage of 6A/6B in the first year of life was highly dynamic and involves cloud-diversity within hosts. High-levels of resistance to tetracycline and trimethoprim/sulfamethoxazole are cause for concern.
Background and Aims:

Accurate serotyping of *Streptococcus pneumoniae* isolates is needed for monitoring trends in invasive pneumococcal disease (IPD) incidence and for evaluating national vaccination programs. Whole genome sequencing (WGS) data has proved a valuable resource for extraction of pneumococcal serotypes with opportunity for further in-depth analysis. We evaluated an automated WGS-based serotyping bioinformatics tool, Pneumococcal Capsule Typing (PneumoCaT)\(^1\), with previously characterized IPD isolates in Finland.

Methods:

In Finland, clinical microbiology laboratories submit IPD isolates to the National Reference Laboratory (NRL) for species confirmation and serotyping; isolates were serotyped using counterimmunoelectrophoresis, latex agglutination and Quellung test (2002–2009) or sequential multiplex PCRs supplemented with Quellung (2010–2016). The PneumoCaT analysis was performed on WGS data generated using Illumina platform and the results were compared with serotyping data obtained with phenotypic and/or PCR-based methods.

Results:

During 2002–2016, altogether 11706 IPD isolates were submitted to the NRL. Of the total 55 different serotypes, serotypes 14 (14%), 3 (11%), 4 (9%), 19A (7%), 23F (7%), and 22F (7%) were most common, accounting for 55% of isolates. Nineteen serotypes were isolated less than ten times. 322 isolates were selected for PneumoCaT analysis. These covered all 55 serotypes and included all serotypes in PCV10/13 and PPV23 vaccines. As an additional test set, 70 isolates from a previous quality assessment among European reference laboratories\(^2\), covering five additional serotypes, were sequenced.

Conclusion

The results of PneumoCaT analysis will be presented at the meeting.

References:


Background and Aims:

The pneumococcus produces a polysaccharide capsule, encoded by the cps locus, that provides protection against phagocytosis and determines serotype; nearly 100 serotypes have been identified with new serotypes still being discovered. The Global Pneumococcal Sequencing (GPS) project was set up to establish a large genomic database of pneumococci from around the world to examine the effect of global vaccine introduction. The aims of this study were to: investigate the cps loci of ~18,000 GPS genomes, characterise the diversity of the 66 serotypes included, and identify putative novel cps loci for further study.

Methods:

Serotypes were assigned using SeroBA and sequence reads were mapped back to cps locus references using BWA to create alignments which were used to construct phylogenies using FastTreeMP. Samples with divergent cps loci were investigated further.

Results:

There was considerable diversity observed in the cps loci of the 66 serotypes examined (Figure 1) with some serotypes being highly conserved (serotype 1) and others very diverse (serotype 6A). Closer examination of each serotype identified seven putative novel cps loci: 9X, 11X, 16X, 18X, 29X, 33X and 36X.
Conclusion

The large number and global distribution of GPS genomes provided an unprecedented opportunity for identifying novel cps loci. Differing amounts of diversity were observed among the cps loci and seven putative novel cps loci were identified. Examples of each will be sent for structural and immunologic analysis.

GLOBAL PNEUMONIA CONTROL AND VULNERABLE POPULATIONS

ISPPD-0471
CHILDHOOD PNEUMONIA IN THE EASTERN HIGHLANDS PROVINCE OF PAPUA NEW GUINEA: CLINICAL PREDICTORS OF SEVERE DISEASE
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2Papua New Guinea Institute of Medical Research, Infection and Immunity Unit, Goroka, Papua New Guinea
3Eastern Highlands Provincial Hospital, Paediatrics, Goroka, Papua New Guinea
4Princess Margaret Hospital for Children, Department of Infectious Diseases and PathWest Department of Microbiology, Perth, Australia
5The University of Western Australia, School of Paediatrics and Child Health, Perth, Australia

Background and Aims:

Pneumonia is the leading cause of death in young children globally, and is particularly prevalent in the highlands of Papua New Guinea. We investigated clinical predictors of severe pneumonia to prioritise which children require urgent in-patient management in this resource-limited setting.

Methods:

From a prospective case-control study enrolling children < 5 years of age presenting to healthcare facilities in Goroka Town, Eastern Highlands Province, clinical history and physical examination findings from 971 patients with clinically-defined moderate or severe pneumonia were analysed. Binary logistic regression modelling was used to identify predictive factors for death and severe illness.

Results:

Overall, 475 patients were admitted to hospital and 496 were managed in the community. Prevalence of hypoxaemia (SpO2 < 90%) on admission was 28.8%, and central cyanosis (OR 9.38; 95% CI 5.63-15.64), reduced breath sounds on auscultation (OR 2.58; 95% CI 1.68-3.96) and apnoea witnessed during examination (OR 2.28; 95% CI 1.41-3.70) independently predicted hypoxaemia. Difficulty feeding/drinking (OR 2.78; 95% CI 1.30-6.51) and nasal flaring or grunting (OR 2.91; 95% CI 1.30-6.51) independently predicted bacteraemia, of which there were 35 confirmed cases. The in-hospital case fatality was 2.3%, and drowsiness (OR 5.64; 95% CI 1.21-26.29) and dehydration (OR 42.94; 95% CI 5.17-356.58) independently predicted death.
Conclusion

Children presenting with pneumonia and difficulty drinking/feeding, drowsiness or dehydration require immediate referral to hospital. Ongoing training of healthcare workers is essential to ensure they recognise the signs of severe disease, provide timely and appropriate management and refer to hospital when necessary.

Background and Aims:

Nearly one million children die of pneumonia annually in resource-limited countries. In the Dominican Republic's main pediatric hospital, 45% of pneumonia admissions are complicated by effusion. In 2013, DR introduced PCV13 using a 2+1 schedule. We evaluated PCV13 impact on pneumococcal pneumonia with pleural effusion (Pneumococcal-PPE).

Methods:

Enhanced hospital surveillance data from July 2014–June 2016 (post-PCV13) were compared to pre-PCV13 surveillance (94 cases from July 2009–June 2011). A PPE case was defined as radiologic evidence of pneumonia with effusion in a child aged <15 years with fever (>38.5˚C). Pneumococcus was detected by culture and lytA qPCR on pleural fluid and underwent serotyping. National PCV13 coverage data for 2014–2016 was obtained from the health ministry.

Results:

Data were abstracted on 218 (87.9%) of 248 post-PCV13 PPE cases; median age was 3 years. National PCV13 coverage for first, second and third doses was 93%, 68%, and 28%, respectively. Pneumococcus was detected in a similar proportion of PPE cases pre- and post-PCV (56.4% vs. 52.4%, P=.51). The proportion of Pneumococcal-PPE caused by PCV13-serotypes remained stable among children age-eligible to have received ≥1 dose of PCV13 (86% vs. 88%, P=1.0). Compared to pre-PCV, serotype14 accounted for a decreased (13% vs 28%, P=.03) and serotype1 for an increased (37% vs 23%, P=.09) proportion of Pneumococcal-PPE cases post-PCV; this did not appear related to an outbreak.

Conclusion

No clear evidence of PCV13 impact was detected, possibly related to low PCV13 third dose coverage. Increasing vaccination coverage might impact disease rates.
RESPIRATORY INFECTIONS IN LOW- AND MIDDLE-INCOME COUNTRIES: A SYSTEMATIC REVIEW
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²University of Melbourne, Department of Paediatrics, Melbourne, Australia

Background and Aims:
Hospitalised pneumonia incidence varies considerably between sites due to many factors including variations in exposure to disease risk factors and host susceptibility, in addition to variations in admission criteria and access to care. World Health Organization has developed guidelines to standardise clinical care and admission criteria for pneumonia based on severity. However, their implementation and adherence are variable. As pneumococcal vaccine impact evaluations often measure the incidence of hospitalised pneumonia before/after the introduction of vaccine, we undertook a systematic review to identity the risk factors for hospitalisation in under-five children with acute lower respiratory infections (ALRI) in low- and middle-income countries.

Methods:
Keyword searches for published articles were conducted in Medline (Ovid), Embase (Ovid) and PubMed databases in March 2017. Two reviewers screened results using Covidence and performed full-text screening using eligibility criteria. Relevant data were extracted from eligible studies, and quality was assessed using the Newcastle-Ottawa scale. Risk factors were documented.

Results:
There were 3,894 articles screened, and 12 observational studies met the eligibility criteria. Consistent risk factors for admission were signs of severity (chest-indrawing, hypoxaemia and tachypnoea). Commonly assessed but inconsistent risk factors were malnutrition, lack of breastfeeding, low socioeconomic status, younger age, presence of RSV and household cigarette smoke exposure. Considerable heterogeneity was found in exposure/outcome definitions, statistical analyses used, quality of studies, and comparisons used to ascertain categorical exposure-outcome associations.

Conclusion
Clinical predictors for ALRI-hospitalisation vary considerably between settings and these findings help explain variability in PCV impact evaluation results.

ISPPD-0380
TITLE: POTENTIAL CHALLENGES IN COLLECTING PNEUMONIA-RELATED COSTS FROM DIFFERENT HEALTH FACILITY LEVELS IN UGANDA
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¹Makerere University School of Public Health, Health Policy Planning and Management, Kampala, Uganda
²Johns Hopkins School of Public Health, International Vaccine Access Center, Maryland, USA

Background and Aims:
Background: Guidelines to conduct cost of illness studies are not well established. This limitation is compounded by difficulties in collecting costs from different facility levels. We documented key challenges in collecting pneumonia-specific resource use, cost and expenditure data among children attending public, private (profit, non-profit) healthcare facilities, and pharmacies.

Methods:

Methods: This is part of a larger cross-sectional study conducted in four regions of Uganda i.e. Northern, Western, Eastern and Central to estimate the cost of treating pneumonia for one year. Resource use, cost and expenditure data for this study are collected through facility records review from 48 facilities and face-to-face interviews with caretakers of 720 children under 5 years with pneumonia. A follow-up telephone survey is conducted 7-14 days after initial survey to collect additional out-of-pocket healthcare payments.

Results:

Results: We found several practical challenges that impact our ability to collect resource use, cost and expenditure data. Data collection through facility records review has gaps due to missing records; pneumonia cases are not always identified due to nonstandard case definitions; difficulties obtaining facility expenditure data due to facility managers’ unwillingness to release data and inconsistency and wide variation of documentation practices across facilities; challenges collecting out-of-pocket expenditure data due to recall bias, loss to follow-up and caretaker illiteracy.

Conclusion

Conclusions: Collecting resource use, cost and expenditure data is an empirical process. With a judicious mix of practical approaches, it’s possible to assemble a credible set of data for use in cost of illness of pneumonia in Uganda.

ISPPD-0018
BURDEN OF CHILDHOOD PNEUMONIA IN A TERTIARY CARE HOSPITAL OF A DEVELOPING COUNTRY LIKE INDIA
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Background and Aims:

Acute lower respiratory infection (ALRTI) is the leading cause of morbidity and mortality in children in developing countries.

Methods:

A hospital based study was undertaken to determine burden of severe lower respiratory tract infection (LRTI) in children admitted in a tertiary care hospital. Case definition of severe ALRTI as given by World Health Organization (WHO) was used to define severe pneumonia.

Results:

Of the total 2728 children admitted in the hospital, 337 cases (12.3%) were of respiratory infections, among which 141 (41.8 %) cases were of pneumonia, 74 (22 %) bronchiolitis,
and 12 (3.5 %) empyema. Pneumonia was the second most common vaccine preventable disease needing hospitalization, the first being acute diarrheal disorder (217 cases) and third being typhoid fever (136 cases). Most common age group for cases of pneumonia was between 1 month - 1 years, 79 cases (56 %) followed by 1 -5 years 47 cases (33 % ). Cases of pneumonia were seen round the year with marginal surge seen in the months of August, September and October.

**Conclusion**

Vaccine preventable diseases like pneumonia are still the common cause for hospitalization in developing country like India. Improving the universal pneumococcal vaccination in children in India can go a long way in reducing the morbidity and mortality of children due to pneumonia.

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**ISPPD-0388**

**JAMAICAN CHILDREN ARE STILL UNVACCINATED AGAINST STREPTOCOCCUS PNEUMONIAE A PREVALENCE STUDY: SEROTYPE DISTRIBUTION AND ANTIMICROBIAL SUSCEPTIBILITY IN 2013 - 2015**

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²University of The West Indies Mona, Microbiology, Kingston, Jamaica
³University of The West Indies- Mona, Center for Sickle Cell Disease, Kingston, Jamaica
⁴University Hospital of Cleveland, Microbiology, Cleveland, USA

**Background and Aims:**

Understanding pneumococcal serotype prevalence and antimicrobial susceptibility in Caribbean territories is important to guide treatment and assess vaccine coverage. In Jamaica pneumococcal immunization is provided free of cost to the immune-compromised as standard of care. This study identifies the *Streptococcus pneumoniae* serotypes that are more commonly carried by children.

**Methods:**

Jamaican children (0-6yrs) from 6 of the major parishes in Jamaica were screened for nasopharyngeal carriage of *S. pneumoniae* in 2013 and 2014-2015. Patients with sickle cell disease that were seen in the clinic during the study period were also enrolled. Serotypes of *S. pneumoniae* isolates were determined by the capsular swelling method. Antimicrobial drug susceptibilities were determined by CLSI broth microdilution

**Results:**

A total of 740 children were screened in 2013 and 768 in 2015; 509(33.8%) were carriers. The predominant serotypes were vaccine types accounting for 80% of all isolates. High rates of susceptibility to all antimicrobial agents tested were observed, all strains susceptible to levofloxacin, while ceftriaxone, penicillin (≤2 μg/mL breakpoint) and amoxicillin were the most active β-lactam agents. The overall rates of resistance were azithromycin(58%), cefuroxime(31%), cefdinir(30%) and trimethoprim-sulfamethoxazole(36%) serotypes 19F and 23F were highly resistant to cefuroxime, cefdinir and trimethoprim-sulphamethoxazole with resistant rates >50%.

**Conclusion**
This study is the first of its kind to be conducted in Jamaica. Pneumococcal carriage among children in Jamaican is high and vaccine serotypes predominate in the children who have not been vaccinated. Noteworthy, vaccine uptake among some groups have been effective. Resistance to macrolides, oral cephalosporins and SXT was found.

ISPPD-0608
THE BURDEN OF PNEUMOCOCCAL DISEASE IN SOUTHEAST ASIAN ADULTS
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3Chang Gung Memorial Hospital, Department of Pediatrics, Taiwan, China
4MAHSA University, Senior Consultant Chest Physician, Bandar Saujana Putra, Malaysia

Background and Aims:

Streptococcus pneumoniae is the most common cause of community-acquired pneumonia (CAP) meningitis, and bacteremia in adults, and contributes to significant morbidity and mortality. Limited data are available on epidemiology and burden of pneumococcal disease among adults in Southeast Asia.

Methods:

We performed a literature search to define the burden of pneumococcal disease in Southeast Asian adults between 2000 and 2017. Endpoints investigated included S. pneumoniae incidence, hospitalization, pneumonia incidence, and mortality related to S. pneumoniae.

Results:

Incidence of IPD among adults > 65 years varied from 4.9-9.96 per 100,000 in Taiwan, 7.7 per 100,000 in Hong Kong, 26 per 100,000 in Thailand. Pneumococcal pneumonia incidence varied, from 35 per 100,000 in Thailand to 778 per 100,000 in Malaysia with rates of hospitalization as high as 204 per 100,000 in Malaysia.

S. pneumoniae represents up to 35.8% of CAP in India, 23.8 % in Taiwan, 23.1% in Thailand, 12.5% in Singapore and 5.5% in Malaysia. S. pneumonia was also among the most prevalent etiology of CAP-hospitalized patients with the highest prevalence in Thailand, Taiwan and India (22-27%).

Mortality caused by CAP was high in Malaysia, Hong Kong, Thailand, India, Taiwan and Singapore (10.5%, 12.3 %, 14.5 %,> 50 %, 22.9 %, 61 % respectively), while mortality rates of pneumococcal meningitis reached 50 % in Taiwan

Conclusion

S. pneumonia is the most prevalent etiology of CAP and contributes significantly to morbidity and mortality in most countries in Southeast region with higher mortality rates in invasive pneumococcal disease.

ISPPD-0744
CHILDHOOD PNEUMONIA IN LUBUMBASHI / DRCongo: A STUDY OF 85 CASES
M. Dr. MUDEKEREZA FURAHA1
Background and Aims:

INTRODUCTION: Pneumonia is one of the leading causes of death for children under five years of age. In Lubumbashi- DRC, in 2015, they were the third leading cause of death for children under five. The objective of this work was to study its epidemiological and clinical characteristics in Lubumbashi.

GOAL: This work was to study the epidemiological and clinical characteristics in Lubumbashi.

Methods:

METHOD: This is a retrospective descriptive survey conducted on hospitalized children's files from July 1, 2015 to June 30, 2016, in the pediatric ward of the University Clinic in Lubumbashi. The data was analyzed with the software epi info 3.5.4.

Results:

Seven hundred and eighty-one children were hospitalized, during this period, 85 cases of pneumonia were recorded, or 10.9%. The sex ratio was M / F 2. The average age was 2 years and 9 months. Children aged 0-2 years accounted for 62.5% of the workforce. The average time to consult after the onset of symptoms was 12.4 days. 52.8% of patients received home treatment before admission, including 47.4% of antibiotics. Immunization status was correct for vaccinations in 15.3% of cases. The fever accounted for 94.4% of the reasons for consultation and cough 87.5%. Tuberculosis was the cause of pneumonia in 7 children (9.7%).

Conclusion

With a frequency of 10.9% of hospitalization cases, pneumonia is a real public health problem. A reliable diagnostic method of tuberculosis is necessary in the absence of the tuberculin test. The introduction of new antigens into the program, such as the pneumococcal vaccine is necessary.
CLH, HEU, HUC got one dose of PCV-13, while parents were not vaccinated. Nasopharyngeal swabs were collected at six different times from parents and children and subjected to culture and quantitative multiplex realtime PCR.

Results:

Pneumococcal carriage was found at three time points in the HEU and CLH compared to once in the HUC. In parents of the HEU child, pneumococcal carriage was found at four time points. Pneumococcal carriage was not found in parents from either the CLH or HUC at any point. The highest density of pneumococcal carriage (in copies/ml) was found in the HEU child $1.1 \times 10^{10}$ compared to $3.77 \times 10^{8}$ in the CLH and $2.90 \times 10^{5}$ in the HUC. Parents of the HEU child also had high density of pneumococcal carriage, $1.43 \times 10^{10}$. Following one dose of PCV-13 pneumococcal carriage was still found in the HEU and his parents, not in the other families.

Conclusion

HEU children may be at increased risk for higher rates of household carriage of pneumococcus and need to be included in vaccination programs.

ISPPD-0454
OXYGEN SATURATION AS A PREDICTOR FOR TREATMENT FAILURE IN FAST BREATHING PEDIATRIC PNEUMONIA

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Background and Aims:

Pneumonia is the leading infectious cause of death among children under five worldwide, and it is important to understand the risk factors for its progression. During a randomized trial comparing effectiveness of placebo to 3-day amoxicillin treatment for fast breathing pneumonia, we collected vital signs from a subset of enrolled children over 24 hours of hospitalization and assessed their relationship with treatment failure (TF) and clinical relapse (CR).

Methods:

Children age 2-59 months with WHO-defined fast breathing pneumonia were enrolled. The study protocol required a 1-3 day hospitalization for children <6 months of age, children with moderate malnutrition, and children with fever but without malaria. Vital signs including oxygen saturation, respiratory rate and temperature were routinely measured. TF was assessed on or before day 4, and CR was assessed on days 5-14.

Results:
We enrolled 1126 children. Of these children, 450 had a protocol-required hospitalization with vital sign information available. Among children with oxygen saturation ≤93% at any point during the first 24 hours of study hospitalization, 29.4% (10/34) met treatment failure criteria on or before day 4, compared with 10.6% (44/416) of those who never had oxygen saturation ≤93% (p=0.001). This difference remained significant when stratified between the amoxicillin and placebo arms. There was no significant difference in CR between these groups.

Conclusion

Oxygen saturation ≤93% may be an important predictor of pneumonia progression. The use of pulse oximetry should be incorporated into treatment decisions and clinical management of children with pneumonia.

Background and Aims:

Pneumonia is the commonest cause of post-neonatal under-5 mortality worldwide, with pneumococci being the leading childhood bacterial cause. Lao People’s Democratic Republic (Laos) was the first low-income SE Asian country to introduce the 13-valent pneumococcal conjugate vaccine (PCV13) in 2013. This study describes and compares hospitalised childhood pneumonia in Vientiane, Laos pre- and post-PCV13 introduction.

Methods:

A retrospective review of hospitalisations and medical records of 2-59mo admitted to major government-managed Vientiane hospitals from 2011-2013 (pre-PCV13) and 2014-2016 (post-PCV13) was conducted. Hospital admissions were used to calculate annual hospitalised pneumonia incidence, from a population catchment of 68,712 <5yo. Severity, clinical features and outcomes were described from medical records. Pneumonia was defined per WHO Pocketbook of Hospital Care for Children (2nd ed).

Results:

The pre-PCV13 annual hospitalised pneumonia incidence was estimated to be 1530 per 100,000 (95% CI 1477-1584) 2-59mo, 55% were severe, and comprised 20.3% of all-cause hospitalisations. Hypoxia or cyanosis were present in 15.7% of cases, and 23.6% of those <12mo. Supplemental oxygen and intensive care were required for 17.1% and 14.6%,
respectively. Inpatient case-fatality was low (0.3%), but 4.8% were discharged unwell. Simulation analyses based on pre-PCV13 data suggest we have 63% power to detect a 20% decline in 3 years using an interrupted time series analysis.

Post-PCV13 results expected prior to ISPPD.Conclusion

The high pre-PCV13 childhood pneumonia burden demonstrated supports the decision to introduce PCV13 into the Lao national immunisation schedule, and encourages regional sustainable use and high coverage of PCV13.

This study is funded by Gavi, the Vaccine Alliance.

### ISPPD-0339

**DIFFERENCES IN PNEUMOCOCCAL CARRIAGE AND SEROTYPE DISTRIBUTION BETWEEN CHILDREN WITH AND WITHOUT PNEUMONIA IN MOZAMBIQUE, 2014–2016**

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**Background and Aims:**

Pneumococcal nasopharyngeal (NP) colonization studies are traditionally performed among healthy children in the community; however, vaccine-type (VT) colonization prevalence may differ between these children and those with pneumonia. We assessed whether children with pneumonia carried VT-pneumococcus more often than children without pneumonia.

**Methods:**

From 2014–2016, we recruited children born after December 10, 2012 who were hospitalized with X-ray confirmed pneumonia based on World Health Organization guidelines. Children without pneumonia were recruited from the same communities. For each child, we collected clinical data and an NP swab. Pneumococcus was detected by culture for children without pneumonia and by culture and lytA qPCR for children with pneumonia. Serotyping was performed on pneumococcal isolates and lytA-positive specimens. We defined VT as serotypes in the 10-valent conjugate vaccine. Multivariable analyses evaluated the association of pneumonia with VT-pneumococcal colonization.

**Results:**

Of 778 children with and 927 without pneumonia included, 97.4% and 27% were exposed to antibiotics before swab collection, respectively. Based on culture, pneumococcal colonization was 45.1% for children with and 84.5% for children without pneumonia (P<0.001); VT-pneumococcal colonization was 18.6% for children with and 23.4% for children without pneumonia (P=0.02). The addition of PCR for children with pneumonia increased overall and VT-pneumococcal colonization to 79.2% and 31.1%, respectively. On multivariate analysis, pneumonia was associated with VT-pneumococcal colonization (aOR: 1.4, 95%CI 1.10-1.78).

**Conclusion**
Children with pneumonia were more likely to have VT-colonization. Including children with pneumococcal clinical syndromes and using PCR on NP samples should be considered in future colonization studies.

ISPPD-0202
MOLECULAR EPIDEMIOLOGY OF PNEUMOCOCCAL INFECTIONS IN AGED PATIENTS AT THE FAR EAST OF RUSSIA
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Background and Aims:

Pneumococcal infections remain major public health problem worldwide for aged population. Especially it is important for the aged patients, though the lack of information on this subject doesn’t allow to make preventive measures. Aims: was to perform multilocus sequence typing (MLST) in strains of S.pneumoniae gained in patients elder of 60 years at the territory of Primorsky region as the most southern part of the Russian Far East. The strains were taken since Jan 2014 till Dec 2015.

Methods:

MLST was conducted with housekeeping genes on standard method on recommendations of MC Enright (1998) et al.

Results:

there were taken 50 isolates ( group 1, from patients with community-acquired pneumonia), 30 isolates ( group 2, from patients with invasive pneumococcal infections such as bacteriemia and menigitidis). Isolates form 1st group included 24 serotypes ( 26 of non-typable) and 22 sequence types ( ST) according to MLST of which 7 were novel, 8 were of Taiwanese clones (TW-28,19,26) of 19F serotype, 3 were of R6, EU38, SP95. In group 2 of 20 strains there was revealed 8 serotypes ( 12 of non-typable) and 6 ST of Taiwanese clones. The strains from the 1st group were non-susceptible to macrolides in 62% (17 strains). The pattern of antimicrobial agents resistance from the strains of 2nd group was 35% to erythromycin, 15% to tetracycline, 5% to fluoroquinolones.

Conclusion

multilocus sequence typing allows us to suggest the epidemiological significance of Taiwanese isolates of S.pneumoniae in our region.

ISPPD-0450
CLINICAL PREDICTORS OF HYPOXEMIA AMONG MALAWIAN CHILDREN WITH WORLD HEALTH ORGANIZATION (WHO)-DEFINED INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESSES (IMCI) PNEUMONIA AT OUTPATIENT HEALTH CENTERS
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Background and Aims:

Although hypoxemia is associated with mortality among <5 year olds with IMCI pneumonia in low-resource settings, outpatient guidelines weakly endorse pulse oximetry and exclude respiratory danger signs in referral criteria. To assess the performance of IMCI referral criteria in identifying hypoxemia, we evaluated clinical prediction of hypoxemia among outpatient Malawian children with IMCI pneumonia.

Methods:

During a vaccine effectiveness study we standardized healthcare workers at 18 health centers in central Malawi to IMCI, non-IMCI respiratory danger signs (chest indrawing, grunting, very fast breathing, head nodding/tracheal tugging, nasal flaring), and oxyhemoglobin saturation (SpO2) measurements on children <5 years old with a Lifebox® pulse oximeter. We routinely collected data from January 2012-June 2014. We conducted bivariate logistic regression for moderate (SpO2 90-92%) and severe hypoxemia (SpO2<90%). Multivariable model selection was based on c-statistic and Bayesian information criterion (BIC).

Results:

IMCI referral criteria and non-IMCI respiratory danger signs had increased odds ratios for moderate or severe SpO2, versus normal SpO2, in bivariate analysis of 6,312 Malawian children with IMCI pneumonia. The multivariable model with the highest c-statistic for moderate (0.70) or severe hypoxemia (0.83), and most favorable BIC, included IMCI referral criteria and non-IMCI respiratory danger signs. The model with the lowest c-statistic and least favorable BIC included IMCI referral criteria alone (c-statistic: 0.55, SpO2 90-92%; c-statistic: 0.59, SpO2 <90%).

Conclusion

Non-IMCI respiratory danger signs are strongly associated with hypoxemia and merit inclusion in IMCI pneumonia referral criteria for children at outpatient clinics. However, clinical signs alone are insufficient for identifying hypoxemia during routine outpatient care.

ISPPD-0478
PREDICTORS OF WORLD HEALTH ORGANIZATION (WHO) RADIOGRAPHIC ALVEOLAR CONSOLIDATION AMONG 3-35 MONTHS OLD CHILDREN WITH WHO-DEFINED INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESSES (IMCI) PNEUMONIA IN BANGLADESH


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Background and Aims:
Chest radiography is generally considered the reference standard for child pneumonia diagnosis. Due to a lack of radiographic facilities in low-resource settings, especially in rural areas, clinicians use clinical signs to diagnose pneumonia. For this analysis we aimed to determine clinical predictors of WHO radiographic alveolar consolidation among 3-35 months old children in rural Bangladesh.

Methods:

From September 2015 to September 2017 children 3-35 months old with WHO IMCI pneumonia were prospectively recruited by study physicians at three rural outpatient clinics in Sylhet, Bangladesh to participate in a pneumococcal vaccine effectiveness study. Participants had chest imaging by computed radiography and oxyhemoglobin saturation (SpO2) measurement by Masimo Rad-5® pulse oximeters. A panel of physicians standardized to WHO radiographic interpretation methodology diagnosed radiographic alveolar consolidation. Characteristics in bivariate regression with a p-value <0.2 were retained in multivariable models.

Results:

Chest radiographs were obtained in a total of 9,472 children with IMCI pneumonia. In multivariable regression, predictors of radiographic alveolar consolidation, compared to no alveolar consolidation, were female gender (adjusted odds ratio (aOR) 1.3, 95%CI, 1.1, 1.4), history of cough (aOR 1.2, 95%CI, 1.0, 1.5), fast breathing (aOR 1.3, 95%CI 1.1, 1.5), very fast breathing (aOR 1.7, 95%CI 1.3, 2.2), chest indrawing (aOR 1.3, 95%CI 1.2, 1.4), SpO2 90-92% (OR 1.3, 95%CI 1.0, 1.7) and SpO2 <90% (OR 2.2, 95%CI 1.6, 3.1).

Conclusion

Although very fast breathing and a SpO2 <90% are not currently included in the diagnostic criteria for IMCI pneumonia they are strongly associated with WHO radiographic alveolar consolidation among children in rural Bangladesh.

ISPPD-0484

PULSE OXIMETRY AS A COMMUNITY-LEVEL CHILD PNEUMONIA DIAGNOSTIC TOOL: ESTABLISHING POPULATION REFERENCE VALUES AT SEA LEVEL AMONGST HEALTHY RURAL BANGLADESHI CHILDREN 3-35 MONTHS OLD
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Background and Aims:

Child pneumonia diagnostics appropriate for community health workers (CHWs) are needed in low-resource settings. Pulse oximetry non-invasively measures oxyhemoglobin saturation (SpO2) and may be suitable for CHWs, but there are no SpO2 reference values for children at sea level in rural Bangladesh.

Methods:
From September 2015 we trained and supervised 22 CHWs in two subdistricts of Sylhet, Bangladesh to use Masimo Rad-5® pulse oximeters with LNCS® Y-I wrap sensors to measure the SpO2 of ill children during weekly household surveillance. From June-August 2017 CHWs measured the SpO2 of healthy children aged 3-35 months without an acute illness. We evaluated the SpO2 distribution from healthy children and analyzed whether any differences in central tendency measurements of SpO2 were associated with the child’s age or behavioral state.

Results:

CHWs measured a SpO2 from 2,088 healthy children with a mean age of 18.8 months (SD, 9.8 months). Children cried or moved during 4.4% (93/2,088) of measurements, and 99.4% (2,076/2,088) of measurements met quality criteria. SpO2 measurements were not normally distributed and were instead negatively skewed (median, 97%, IQR 96%, 99%). Although there was no difference in the median SpO2 between crying or moving children and calm children (p=0.90), children aged 3-11 months had a lower median (97%, IQR, 96%, 99%) and 2.5th centile SpO2 (91%) than children 12-35 months old (median 98%, IQR, 96%, 99%, 2.5th centile, 92%, p=0.05).

Conclusion

CHWs can effectively measure SpO2 among rural Bangladeshi children. The child’s age should be accounted for when establishing SpO2 thresholds for pneumonia diagnosis at sea level.

ISPPD-0488
OPPORTUNITIES AND BARRIERS IN PULSE OXIMETRY USE FOR CHILDREN WITH PNEUMONIA IN LOW-RESOURCE SETTINGS (LRS): A QUALITATIVE EVALUATION FROM MALAWI AND BANGLADESH
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Background and Aims:

Little is known about pulse oximetry implementation challenges during pediatric pneumonia management in LRS and what device modifications may address these challenges. To better understand this we conducted focus group discussions (FGDs) with healthcare workers (HCWs) from Malawi and Bangladesh as part of a human centered design process to develop a reusable, low-cost, universal pediatric oximeter probe for LRS.

Methods:
HCWs from Malawi and Bangladesh who had received training in pulse oximetry and had been using oximeters during pediatric care, including community healthcare workers, non-physician clinicians, and hospital-based nurses and physicians, were purposively sampled for FGDs. We used thematic analysis with a framework approach to evaluate FGD responses.

**Results:**

We conducted six FGDs with 49 participants and identified five themes: trust, value, user-related experience, sustainability, and design. HCWs discussed the confidence gained through using oximeters, resulting in improved caregiver trust and value of the device; although there were conflicts between the weight given to clinical judgement versus oximeter results. HCWs reported an ease of oximeter use, but identified movement and physically smaller children as measurement challenges. Challenges in sustainability from battery durability and replacement parts were reported, although many HCWs had used the devices longer than four years suggesting robustness. Desirable features included back-up power banks and integrated respiratory rate and thermometer capability.

**Conclusion**

HCWs valued pulse oximetry as a pediatric spot-check device in LRS. Areas highlighted as challenges, and therefore re-design opportunities, included battery charging and durability, and probe fit and motion tolerance among pediatric populations.

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**ISPPD-0112**

**IMPACT OF COMORBID CONDITIONS ON IMMUNOGENICITY OF A NEW FORMULATION OF 15-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN ADULTS 50 YEARS OF AGE AND OLDER—AS PER NADIA WILL BE COMBINED WITH ANOTHER ABSTRACT**

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**Background and Aims:**

Chronic obstructive pulmonary disease (COPD), chronic heart disease (CHD), and diabetes mellitus (DM) are associated with increased risk for pneumococcal disease. Impact of co-morbid conditions on the safety and immunogenicity of 2 different formulations (A and B) of PCV-15 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F*, 23F, 33F*) were evaluated in immunocompetent pneumococcal vaccine-naïve adults ≥50 years (PN006) and adults ≥65 years previously vaccinated with PPV23 (PN007).

**Methods:**

Adults (230/arm in PN006 and 125/arm in PN007) received a single dose of either PCV15 or PCV13. Serotype-specific Immunoglobulin G (IgG) geometric mean concentrations (GMCs) and opsonophagocytic activity (OPA) geometric mean titers (GMTs) were measured immediately prior and 30 days postvaccination.
Subjects were categorized based on the presence of one or more of the following co-morbid conditions: COPD, CHD, and DM.

NCT 02547679

Results:

More subjects enrolled in PN007 (≥65 years) had heart conditions compared to other pre-existing medical conditions. Overall, serotype-specific IgG GMCs and OPA GMTs were generally comparable between individuals with or without these co-morbid conditions. In addition, for each co-morbid condition, serotype-specific IgG GMCs and OPA GMTs were comparable between recipients of PCV-15 and PCV-13 for the shared serotypes. Results for subjects enrolled in PN006 are currently analyzed and will be provided.

Conclusion

Serotype-specific immune responses to serotypes included in PCV 15 were generally comparable between immunocompetent subjects with or without medical conditions associated with increased risk for pneumococcal disease.

[*Non-shared serotypes with PCV13].

ISPPD-0121

IMPACT OF TIMING OF PRIOR PPV23 VACCINATION AND AGE ON IMMUNE RESPONSES FOLLOWING VACCINATION WITH 15-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV-15)

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Background and Aims:

Safety and immunogenicity of a new formulation of PCV-15 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F*, 23F, 33F*) was evaluated in adults ≥65 years of age previously vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPV23).

Methods:

A single dose of either PCV-15 or PCV-13 was administered to healthy adults (125/arm) who received PPV23

≥1 year prior to study entry. Randomization was stratified by age (65 to 74 years, ≥75 years) and time since PPV23 (1 to 3 years, >3 years). Serotype-specific IgG geometric mean concentrations (GMCs) and opsonophagocytic activity (OPA) geometric mean titers (GMTs) measured immediately prior and 30 days postvaccination.

NCT02573181

Results:
Taken individually, subjects 65 to 74 years generally had higher IgG GMCs and OPA GMTs than those ≥75 years, and longer time interval since PPV23 was also associated with higher antibody responses.

Analysis based on combined stratification factors showed that older age combined with longer interval since PPV23 were associated with higher immune responses than older age and shorter interval since PPV23. No significant impact of time interval was observed in younger age stratum. Furthermore, older adults with longer interval since PPV23 had numerically higher fold-rises in IgG and OPA and higher percentage of subjects with ≥4-fold rise in IgG GMCs and OPA GMTs.

**Conclusion**

PCV-15 is immunogenic in adults ≥65 years of age who received PPV23 vaccination at least 1 year prior to PCV-15. Age and time since PPV23 vaccination may impact immune responses.

*Non-shared serotypes with PCV-13*
Safety profiles were comparable across vaccination groups. At PD3, serotype-specific IgG GMCs and OPA geometric mean titers (GMTs) induced by PCV-15 were generally comparable to PCV-13 for most shared serotypes. PCV-15 induced higher IgG and OPA responses to serotypes 22F and 33F than PCV-13. Overall, serotype-specific antibody levels decreased at pre-dose4 and significantly increased at PD4. No significant differences were observed with increase in PnPs and MAPA.

**Conclusion**

New PCV-15 formulation is safe and induces IgG and OPA responses to all 15 serotypes in the vaccine. In comparison to earlier formulation, new formulation shows improvement in IgG GMCs and OPA GMTs for most serotypes when compared to PCV-13.

*Non-shared serotypes with PCV-13

**ISPPD-0625**

**IMPACT OF PNEUMOCOCCAL CONJUGATED VACCINE ON HOSPITALIZATIONS FOR PNEUMONIA IN A REFERRAL HOSPITAL SETTING IN CAMEROON**

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**Background and Aims:**

Pneumonia represents a large disease burden, with pneumococcal pneumonia being responsible for 35-50% of all cause pneumonia. PCV13 was introduced in July 2011 and 5 years after, we sought to know the effect of this vaccine on hospitalizations for pneumonia.

**Methods:**

Log book review for diagnosis on discharge in under five children, was done from 2007 to 2016 in 7 hospitalization units. Only the intensive care unit had consistent data. Total number of hospitalizations was noted. Control conditions were malaria and sickle cell disease. Pre PCV13 era was 2007 - 2010, while the post PCV13 era was 2012 - 2016.

**Results:**

In under five children, there was a 27.6% decline in annual number of pneumonia admissions; and a 36.7% decline in hospitalizations due to pneumonia.

In infants 0 to 11 months, there was a 52% decline in annual numbers of pneumonia admissions; and a 15% decline in hospitalizations due to pneumonia.

**Conclusion**

After PCV13 introduction, a marked decline in pneumonia hospitalizations was demonstrated among under five children.
ISPPD-0639
NASOPHARYNGEAL CARRIAGE OF STREPTOCOCCUS PNEUMONIAE IN CHILDREN UNDER FIVE YEARS IN THE NATIONAL REFERRAL HOSPITAL IN UGANDA POST PCV10
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Background and Aims:

Streptococcus pneumoniae is a severe invasive bacterial infection leading to morbidity and mortality among children. This study investigated the magnitude of nasopharyngeal carriage of S. pneumoniae and its associated factors among children under five admitted in national referral hospital Uganda between January 2014 to December 2015

Methods:

Under-fives attending child clinics in Uganda enrolled and investigated for nasopharyngeal carriage of SP. Data was collected using standardized collection tool. Nasopharyngeal swabs were taken and processed as per standard lab procedures. SP isolated were identified using conventional methods. Antimicrobial susceptibility testing was performed using the disc diffusion method

Results:

350 children were enrolled of which 172 (19.1%) were males; 309 (88.3%) were females. 253 (72.3%) had received at least one dose of PCV10. 83 (23.7%) had used antibiotic at median duration of 5 days in the past 14 days. 43 (12.3%) carried SP in their nasopharynx. Children with chronic diseases and those at school were 3.4 and 4.4 times more at risk to be carriers of SP compared to their counterparts (OR, 3.4 (1.0-11.6) 95%, p=0.05) and OR, 4.4 (1.2-15.7) 95% (p=0.023) respectively. The resistance levels of SP to penicillin, cotrimoxazole and erythromycin were 40%, 88.2% and 41.7%, respectively. All the SP isolates were found to be 100% sensitive to ciprofloxacin.

Conclusion

High nasopharyngeal carriage of penicillin resistant SP is observed in Uganda despite a good coverage of pneumococcal vaccination. The carriage is significantly associated with schooling and presence of chronic diseases. Continuous surveillance of penicillin resistant strains coupled with serotyping of the isolates is highly recommended to determine the influence of the pneumococcal vaccination.

ISPPD-0684
IMPACT OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV13) ON INVASIVE PNEUMOCOCCAL DISEASE (IPD) AMONG PEOPLE LIVING WITH HIV IN THE UNITED STATES, 2008–2014
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Background and Aims:

HIV infection increases the risk for IPD. In the U.S., PCV13 was introduced for children in 2010 and for adults with HIV in 2012. We evaluated impact of these policies on IPD incidence among adults ≥19 years with and without HIV.

Methods:

We identified IPD cases through Active Bacterial Core surveillance. Sterile site isolates were serotyped using Quellung or PCR. HIV status was ascertained through medical chart review. We estimated IPD incidence (cases per 100,000 population) using national case-based HIV surveillance and U.S. Census data. We estimated percent changes in IPD incidence comparing pre-PCV13 (2008–2009) and post-PCV13 (2013–2014) periods.

Results:

From 2008–2014, we identified 19,733 IPD cases; 1,662 were in adults with HIV. Overall and PCV13-type incidence declined among adults with and without HIV (Table), driven by reductions in types 19A and 7F. Non-vaccine serotype IPD declined significantly among adults with HIV, but not among adults without HIV. The majority (97.2%) of cases with HIV were among adults 19–64 years; similar trends were observed in this age group as seen in all aged adults. Overall IPD and PCV13-type incidence was 18-fold higher among adults with versus without HIV in 2013–2014.

Table. Invasive pneumococcal disease incidence (cases per 100,000) among adults ≥19 years old living with and without HIV, 2008–2014

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<tr>
<th>Group</th>
<th>Incidence rate (95%CI), 2008–2009</th>
<th>Incidence rate (95%CI), 2013–2014</th>
<th>% (95%CI) change from 2008–2009 to 2013–2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with HIV</td>
<td>299.3 (274.8, 325.3)</td>
<td>193.0 (174.8, 212.5)</td>
<td>-35.5 (-43.2, -26.8)</td>
</tr>
<tr>
<td>PCV13 plus 6C</td>
<td>139.3 (122.8, 157.5)</td>
<td>54.7 (45.2, 65.5)</td>
<td>-60.3 (-68.5, -51.2)</td>
</tr>
<tr>
<td>Unique PPV serotypes²</td>
<td>69.9 (58.4, 83.1)</td>
<td>67.7 (57.2, 79.7)</td>
<td>-3.1 (-23.6, 22.8)</td>
</tr>
<tr>
<td>Non-vaccine serotypes</td>
<td>90.0 (76.8, 104.8)</td>
<td>70.6 (59.8, 82.8)</td>
<td>-16.4 (-37.1, -2.3)</td>
</tr>
<tr>
<td>Adults without HIV</td>
<td>15.2 (14.8, 15.6)</td>
<td>11.0 (10.7, 11.4)</td>
<td>-27.5 (-30.2, -24.6)</td>
</tr>
<tr>
<td>PCV13 plus 6C</td>
<td>8.3 (8.0, 8.6)</td>
<td>3.1 (3.0, 3.3)</td>
<td>-62.5 (-64.8, -60.0)</td>
</tr>
<tr>
<td>Unique PPV serotypes²</td>
<td>3.9 (3.7, 4.1)</td>
<td>4.7 (4.5, 4.9)</td>
<td>21.1 (13.3, 29.5)</td>
</tr>
<tr>
<td>Non-vaccine serotypes</td>
<td>3.0 (2.9, 3.2)</td>
<td>3.2 (3.1, 3.4)</td>
<td>6.7 (-1.3, 15.4)</td>
</tr>
</tbody>
</table>

¹ 1, 3, 4, 5, 6A, 6B, 7F, 7V, 9V, 14, 18C, 19A, 19F, 23F, plus 6C
² 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F

Conclusion
Reductions in IPD incidence among adults with and without HIV occurred following PCV13 introduction. IPD rates remain much higher among adults with versus without HIV. We found no evidence of serotype replacement.

ISPPD-0508
STREPTOCOCCUS PNEUMONIAE SEROTYPE-2 IS HERE TO STAY
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³Johns Hopkins University, International Health, Baltimore, USA
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Background and Aims:
Invasive pneumococcal disease (IPD), caused by Streptococcus pneumoniae (Spn), is a primary cause of morbidity and mortality in Bangladesh. We have conducted surveillance to monitor pneumococcal serotype distribution since 1994. In the early 2000s, we observed an upsurge of serotype-2, non-vaccine serotype, initially thought to be an outbreak and expected to disappear with time. Here, we report current trends of serotype-2.

Methods:
In our semi-national IPD surveillance, we collect blood and/or CSF samples from suspect meningitis and sepsis cases in children <5 years. Spn is detected using culture, immunochromatic tests and/or PCR and serotyped using quellung and/or PCR. We assessed geographical location and outcome of cases and antibiotic susceptibility of isolates.

Results:
From 1996 through September 2017, we recorded 151 serotype-2 cases. Beginning in 2004, serotype-2 was the predominant cause of IPD. All cases were meningitis, 64% were in children aged 0-3 months and 11% patients died. All isolates (n=72) were susceptible to erythromycin, chloramphenicol, penicillin and ceftriaxone; 30% were non-susceptible to cotrimoxazole. Patients arrived from different locations with no signs of outbreaks in a specific area/population.

Conclusion
Continuous surveillance demonstrates that upsurge and persistence of serotype-2 is not the result of any intervention, rather a secular change. Given how early in life the cases occur and none of the PCVs provide protection against serotype-2, we need to consider novel prevention measures. Our findings highlight the importance of continuous monitoring of serotype trends for interpretation of emergence of serotypes as secular or replacement phenomenon, and guide future vaccine formulations and intervention strategies.

ISPPD-0549
ESTIMATING THE COST OF HOSPITALIZED PNEUMONIA, MENINGITIS, AND SEPSIS AMONG CHILDREN IN NEPAL: PNEUMOCOCCAL IMPACT ECONOMIC STUDY (PIES)
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²John Hopkins Bloomberg School of Public Health, Department of International Health,
Background and Aims:

Limited information on cost of pneumococcal disease is available for Nepal. We estimated the cost of hospitalized pneumonia, meningitis, sepsis and lab-confirmed pneumococcal disease.

Methods:

We collected resource utilization and out-of-pocket expenditures from children 1-59 months with hospitalized pneumonia, meningitis, sepsis, and lab-confirmed pneumococcal disease in 5 Nepal hospitals. Data was collected from medical records and caregiver interviews to estimate costs from the societal perspective. Syndrome-specific average costs were multiplied by hospitalized syndrome-specific pneumococcal incidence from secondary sources. Determinants of cost were assessed using generalized linear models. Costs are presented in 2016 USD.

Results:

Data was collected from 1,250 cases; 11% were lab-confirmed bacterial, and 45% were suspected bacterial. Hospitalization ranged from 5 days (pneumonia, sepsis) to 10 days (meningitis). Average cost per episode of pneumonia, meningitis and sepsis was $160 (SD $151), $370 (SD $226) and $266 (SD $289), respectively. Direct medical, non-medical, and indirect costs represented 45%, 24%, and 32% of the average cost, respectively. Lost productivity was greatest among unpaid work. Cost varied between hospitals due to differences in treatment patterns and transportation costs. Length of illness, severity, and hospital type were the most significant determinants of increased cost. For every 100,000 children 1-59 months, hospitalized pneumococcal disease was estimated to cost $73,567–$167,228.

Conclusion

Hospitalized pneumonia, meningitis, and sepsis represent a significant economic burden on society. Along with medical costs, productivity loss was an important driver of overall costs. Cost burden evidence is critical to informing policy decisions and securing financial support for PCV vaccination.

ISPPD-0240
HOSPITALIZATIONS FOR PNEUMONIA IN YOUNGER ADULTS WITH CHRONIC LUNG DISEASE OR DIABETES IN THE UNITED STATES

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Background and Aims:

Young adults with chronic lung disease (CLD) or diabetes, both prevalent medical conditions, are at increased risk of developing pneumonia. Currently, however, these adults are not recommended to receive pneumococcal conjugate vaccination (PCV) in the United States. We described all-cause pneumonia hospitalization rates in US adults aged 18-64 years with CLD and/or diabetes.
Methods:

We obtained nationally-representative estimates for pneumonia hospitalizations (any discharge diagnosis for ICD9 codes: 480.xx–486.xx; 487.0) from the 2014 National Impatient Sample (Healthcare Cost and Utilization Project). Population size was based on the US Census. We estimated prevalence of CLD and diabetes using the Behavioral Risk Factor Surveillance System. We calculated incidence rates of hospitalization.

Results:

In 2014, there were 2.4 million (M) pneumonia hospitalizations in adults, of which 901,470 (38%) were in adults aged 18-64. Individuals with CLD and/or diabetes accounted for 54% of hospitalizations in that age group, and 20.5% of all adult pneumonia hospitalizations.

Prevalence of CLD, diabetes, and CLD and/or diabetes in the US population aged 18-64 was 12%, 8%, and 18%, respectively. Annual incidence of pneumonia hospitalization in adults aged 18-64 was 1,393 for CLD and 1,660 for diabetes per 100,000 persons.

Conclusion

One-out-of-five pneumonia hospitalizations in US adults occurred among individuals aged 18-64 with CLD or diabetes. Currently, however, PCV is not routinely recommended in this population of younger, at-risk adults.

<table>
<thead>
<tr>
<th></th>
<th>US Population</th>
<th>Pneumonia Hospitalizations</th>
<th>Incidence Rates per 100,000 pop.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>199.1 M</td>
<td>901,470</td>
<td>452.8</td>
</tr>
<tr>
<td>Chronic Lung Disease (CLD)</td>
<td>12.2%</td>
<td>338,255</td>
<td>1393.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.7%</td>
<td>253,025</td>
<td>1660.2</td>
</tr>
<tr>
<td>CLD and/or Diabetes</td>
<td>18.1%</td>
<td>486,820</td>
<td>1350.3</td>
</tr>
<tr>
<td>Neither CLD nor Diabetes</td>
<td>81.9%</td>
<td>414,650</td>
<td>254.3</td>
</tr>
</tbody>
</table>

ISPPD-0345
HOSPITAL BASED SURVEILLANCE FOR PAEDIATRIC BACTERIAL MENINGITIS IN TOGO FROM 2010 TO 2016

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2WHO collaborating Centre for New Vaccines Surveillance, Medical Research Council Unit The Gambia at London School of Hygiene and Tropical Medicine, London, United Kingdom
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4WHO Regional Office for Africa WHO/AFRO, New Vaccines Surveillance, Brazzaville, Congo

Background and Aims:

Invasive bacterial disease causes severe morbidity, including meningitis which can be lethal and is preventable by immunization. As a member of the World Health Organisation co-ordinated Invasive Bacterial Vaccine Preventable Diseases surveillance network, Togo
carries out surveillance targeting *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis*, collected from the cerebrospinal fluid of children <5 years old.

**Methods:**

Lumbar punctures were performed on children with suspected meningitis admitted to the Sylvanus Olympio Teaching Hospital in Lome. Phenotypic detection of *S. pneumoniae*, *N. meningitidis* and *H. influenzae* was confirmed via microbiological and latex agglutination techniques. Samples were shipped to the WHO Collaborating Centre, the Medical Research Council Unit, The Gambia, for polymerase chain reaction amplification to corroborate results.

**Results:**

During the surveillance period 3644 children had suspected meningitis and 6.7% of confirmed cases were PBM. *S. pneumoniae* was responsible for the highest proportion of infections (67.6%), followed by *H. influenzae* (31.1%) and *N. meningitidis* (1.3%). The number of meningitis cases caused by pneumococcal conjugate vaccine serotypes decreased over the surveillance period and few cases caused by non-vaccine serotypes were observed. The number of pre- and post-vaccine cases in children <1 years old caused by PCV serotypes was significantly decreased when compared to cases seen in children aged 2-4 years.

**Conclusion**

Continued surveillance is vital for estimating prevalence of PBM, determining vaccine impact, and anticipating epidemics in Togo. Our surveillance shows PCV13 vaccine is effective at preventing invasive bacterial disease among children <5 years of age in the Maritime region and requires expansion to northern regions that have recently had a *N. meningitidis* outbreak.

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**ISPPD-0099**

**EFFECT OF BIOMASS SMOKE: AN INDOOR AIR POLLUTANT ON WOMEN’S RESPIRATORY HEALTH IN EASTERN TERAI REGION OF NEPAL**

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**Background and Aims:**

People in developing countries especially in the rural areas are commonly exposed to high levels of Indoor Air Pollution. Women are spending 3-7 hours daily using biomass in their kitchen. Such air pollution has been reported to be associated with an increased risk of COPD, respiratory symptoms, and impaired lung function. This study aimed to find out the prevalence of biomass use in the study area and the respiratory health problems associated with it in women.

**Methods:**

A descriptive cross-sectional study of women aged 18 years and above in a rural population (n = 415) of Sunsari district, exposed to biomass smoke. A semi-structured questionnaire was used along with an observation checklist. Chest symptomatic were find out and advised proper treatment.
Results:

The prevalence of biomass smoke exposure was 98.8%. The mean age of the study population was 30.50 with SD ±9.86, with a literacy rate of 32.5%. Majority (94.9%) of women were married with 56.9% of them being Muslim and 43.1% Hindu.

Illiterate and people below poverty line were more like to use biomass fuels. The most common respiratory problems were cough (14.7%) followed by phlegm (9.9%) wheeze (6.27%), and (2.65%) had breathlessness. Out of total 15 (3.61%) were smokers.

Respiratory problems were significantly higher in people using leaves/straws as biomass fuel (p=0.034).

Conclusion

The study suggests those who use leaves/straws as kitchen fuel are more likely to develop respiratory problems. There is need of public health measure for prevention & vaccine (PCV) of respiratory disease.

HOST AND ENVIRONMENT

ISPPD-0072

NASOPHARYNGEAL CARRIAGE OF STREPTOCOCCUS PNEUMONIAE, HAEMOPHILUS INFLUENZAE AND STAPHYLOCOCCUS AUREUS IN OUTPATIENT ELDERLY RESIDING IN THE MUNICIPALITY OF SÃO PAULO, BRAZIL

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²Adolfo Lutz Institute, Strategic Laboratory, São Paulo, Brazil
³Adolfo Lutz Institute, Molecular Biology Laboratory- Center of Immunology, São Paulo, Brazil
⁴Hospital of Clinics of the University of São Paulo Medical School, Geriatrics Division, São Paulo, Brazil
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Background and Aims:

S. pneumoniae (Spn), H. influenzae (Hi) and S. aureus (Sau) colonize human nasopharynx and may cause respiratory mucosal and invasive diseases. Scarce information is available on colonization by these bacteria in the elderly population. We investigated the prevalence of Spn, Hi and Sau on the nasopharynx (NP) among elderly.

Methods:

A cross-sectional study was conducted between April and August 2017 in individuals aged ≥60y who attended the referral geriatric ambulatory of Hospital of Clinics, São Paulo. NP
specimens were inoculated into STGG medium and plated for culture after broth enrichment. Methicillin-resistant Sau (MRSA) was detected by mecA gene detection.

**Results:**

Among 810 individuals attending the geriatric ambulatory, 776 were included. Exclusion criteria were: antibiotic use during the preceding week (n=25), refusal to sample collection (n=3), received 13-valent pneumococcal conjugate vaccine (n=2) and cognitive impairment (n=4). Median age of participants was 82y old (range 60-102). A total of 33(4.2%) individuals cohabited with children aged 4y old, and 203(26.1%) reported previous 23-valent pneumococcal polysaccharide vaccine. Prevalence of Spn, Hi and Sau was 1.4%(n=11), 1.5%(n=12) and 15.8%(n=123), respectively. Co-colonization was detected in few samples (Spn/Hi/Sau, n=1; Spn/Hi, n=2; Hi/Sau, n=2; Spn/Sau, n=5). Spn serotypes were: 6C, 15B, 20, 23A, 35B (n=1 each), 9N, 28A, 34 (n=2 each); all Hi were NTHi. MRSA was detected in 14.6%(n=18) of Sau isolates.

**Conclusion**

Lower level of household contact with children in addition to other factors, could explain the low rates of Spn and Hi colonization, in contrast with the high risk for Sau/MRSA colonization.

MCC Brandileone(304211/2014-1), AL Andrade(313286/2014-0) receive scientific-productivity-scholarships from CNPq-Brazil

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**ISPPD-0506**

**IMPROVED NUTRITIONAL STATUS INCREASES PNEUMOCOCCAL CLEARANCE IN HIV INFECTED CHILDREN**

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**Background and Aims:**

Growth failure is a sign of HIV disease progression. HIV-infected children are at increased risk of invasive pneumococcal disease. We looked at the impact of nutritional status on pneumococcal clearance children with and without HIV from two rural districts of West Bengal, India.

**Methods:**

We conducted a prospective cohort study on the impact of pneumonia preventing vaccines in HIV infected children from 2012 to 2014. Nasopharyngeal swabs were collected from 125 children with HIV (CLH) (median age 7) and 47 without HIV (HUC) (median age 3) at different time points pre and post Hib immunization and pneumococcal conjugate vaccines. Median weight-for-age (WAZ), height-for-age (HAZ) z scores were calculated according to WHO child growth standards at six time points over the course of 24 months. Wasting and stunting were defined as below−2 standard deviation. Decrease in pneumococcal colonization was compared with respect to increase in WAZ- HAZ scores over time

**Results:**

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335
CLH had wasting (median WAZ-2.46) and stunting (median HAZ -2.06) at baseline compared to HUC (WAZ -1.72; HAZ-1.34). ART status of CLH increased from 40% at baseline, to 58% over the course of the study. Median nadir CD4 count prior to ART was 287. CLH had increased rate of pneumococcal clearance when there was simultaneous increase in WAZ-HAZ scores over time (OR 1.544; CI 0.48-4.8) as compared to HUC (OR 0.38; CI 0.06-2.39; p=0.316).

Conclusion

Pneumococcal clearance increases with improvement in nutritional status in HIV infected children.

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ISPPD-0313

EFFECT OF HOUSEHOLD DENSITY ON NASOPHARYNGEAL PNEUMOCOCCAL CARRIAGE PREVALENCE IN NEPALI CHILDREN

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2Patan Academy of Health Sciences, Microbiology Laboratory, Lalitpur, Nepal
3University Of Oxford, Oxford Vaccine Group -Department of Pediatrics, Oxford, United Kingdom
4Johns Hopkins Bloomberg School of Public Health, International Vaccine Access Center- Department of International Health, Baltimore- Maryland, USA
5Johns Hopkins Bloomberg School of Public Health, International Vaccine Access Center- Department of International Health, Baltimore- Maryland, USA
6NIHR Oxford Biomedical Research Centre, NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom
7University of Otago, Department of Pathology, Christchurch, New Zealand

Background and Aims:

Household crowding may be an important factor determining nasopharyngeal (NP) carriage prevalence of Streptococcus pneumoniae (Pneumococcus). We investigated this relationship in Nepali children using samples collected before and after PCV10 introduction.

Methods:

4755 healthy children <2 years were enrolled from an urban setting in Kathmandu and a rural setting in Okhaldhunga. NP swabs were cultured and serotyped using standard methods. Household size was recorded for each participant.

Results:

In Kathmandu, 1749 and 1492 were enrolled before (2014-2015) and after (2016-2017) PCV10 introduction, respectively. In Okhaldhunga, 600 and 914 children were enrolled before (February 2015) and after (February 2017) PCV10 introduction, respectively.

Before PCV10 introduction, pneumococcal NP carriage prevalences in children from urban households (including the swabbed child) with 2-3, 4-5, 6-7, and >7 members were 64% (330/516), 65% (498/769), 68% (196/289) and 62% (108/175), respectively (p=0.564). Carriage prevalences in children from rural households with 2-3, 4-5, 6-7, and >7 members were 81% (92/113), 83% (247/296), 86% (113/132) and 81% (48/59), respectively (p=0.811).
After PCV10 introduction, urban carriage prevalences in children from households with 2-3, 4-5, 6-7, and >7 members were 66% (270/412), 62% (401/646), 60% (158/265), and 69% (117/169), respectively (p=0.145). Rural carriage prevalences for children from households with 2-3, 4-5, 6-7, and >7 members were 79% (148/188), 85% (348/412), 86% (176/205) and 88% (96/109), respectively (p=0.120).

Conclusion

Initial analyses suggest that household density in these population samples do not appear to be associated with NP pneumococcal carriage prevalence before or after PCV10 introduction. Further analyses are needed to explore this relationship.

ISPPD-0124
PREDICTORS OF PNEUMOCOCCAL NASOPHARYNGEAL CARRIAGE IN 5-8 WEEK OLD HEALTHY INFANTS IN FIJI

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⁵Fiji National University, Department of Public Health and Primary Care, Suva, Fiji
⁶The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Department of Microbiology and Immunology, Parkville, Australia
⁷University of Melbourne, Department of Paediatrics, Parkville, Australia
⁸London School of Hygiene and Tropical Medicine, Infectious Diseases Epidemiology, London, United Kingdom

Background and Aims:

Of all the cases of pneumococcal meningitis in children <5 years old, about 40% of cases occur in infants <6 months old. Early acquisition of pneumococcal carriage, a prerequisite for disease, is common in resource-poor settings. This study describes the risk factors of pneumococcal nasopharyngeal (NP) carriage in very young Fijian infants and explores the association between vaginal delivery and early carriage.

Methods:

Purposive quota sampling was used to undertake four annual cross-sectional carriage surveys in 5-8 weeks old Fijian infants in 2012-2015. Potential risk factors were collected by questionnaire. NP swabs were collected and processed using standard methods.

Results:

There were 2006 infants in the study. Infants born by vaginal delivery were at greater risk of being colonised compared with infants born by caesarean delivery (aOR 1.48; 95%CI 1.04-2.11; p=0.029). This risk was similar to living with two or more children under 5 (aOR 1.54; 95%CI 1.23-1.94; p<0.001). Other independent risk factors for carriage included: being indigenous Fijian (aOR 3.45; 95%CI 2.68-4.43; p<0.001), having symptoms of upper respiratory tract infection (aOR1.41; 95%CI 1.05-1.90; p=0.024), and living below the poverty line (aOR 1.31; 95%CI 1.05-1.65; p=0.017).
Conclusion

Early pneumococcal acquisition is associated with vaginal delivery. Although causality cannot be ascribed, vertical transmission, the effect of mode of delivery on the infant microbiome, and maternal antibiotic administration during a caesarean section, may all play a role in early carriage. Ethnicity is the strongest predictor of early carriage.

ISPPD-0738
UNDERLYING CO-MORBIDITIES FOR COMMUNITY-ACQUIRED PNEUMONIA AMONG CHILDREN ENROLLED IN THE INNOVATIVE TREATMENTS IN PNEUMONIA (ITIP) CLINICAL TRIALS IN LILONGWE, MALAWI

E. Nkwopara¹, R. Schmicker², T. Mvalo³, J. Lenahan¹, C. Ndamala³, M. Phiri³, E. McCollum⁴, A. Phiri⁵, N. Lufesi⁶, S. May², A. Ginsburg¹

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²University of Washington, Department of Biostatistics, Seattle, USA
³University of North Carolina Project, Lilongwe Medical Relief Fund Trust, Lilongwe, Malawi
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⁵University of Malawi- College of Medicine, Department of Pediatrics and Child Health, Blantyre, Malawi
⁶Malawi Ministry of Health, Acute Respiratory Infection & Emergency Triage Assessment and Treatment, Lilongwe, Malawi

Background and Aims:

Pneumonia is the leading infectious killer of children under five, with the highest burden of childhood pneumonia-related deaths occurring in Africa. Identifying underlying co-morbidities is essential to understanding mortality from childhood pneumonia.

Methods:

We are conducting two clinical trials in Malawi assessing the optimal duration of treatment with amoxicillin dispersible tablets for fast breathing (ITIP1) and chest indrawing (ITIP2) childhood pneumonia. Children 2-59 months with cough and/or difficult breathing are screened for enrollment in ITIP1 if they have fast breathing for age, or for ITIP2 if they have chest indrawing. We reviewed baseline characteristics, physical examinations, laboratory results, and caregiver assessments collected at screening and enrollment.

Results:

From June 2016 through May 2017, 1115 and 1091 children were enrolled in ITIP1 and ITIP2, respectively. Children enrolled in ITIP2 were younger than children enrolled in ITIP1, with 36% in the youngest age group (2-6 months) in ITIP2 vs. 19% in ITIP1 (p<0.001). Moderate malnutrition was higher in ITIP2 compared with ITIP1, based on mid-upper arm circumference of 11.5-13.5cm and/or height/weight z-score of -2 to -3 (24.7% vs. 7.5%, p <0.001). Diarrhea occurred more frequently in ITIP2 than ITIP1 (13.9% vs. 9.3%, p <0.01). Conversely, more children in ITIP1 tested positive for malaria compared with ITIP2 (12.4% vs. 9.1%, p = 0.01).

Conclusion

Moderate malnutrition and diarrhea occurred more frequently in ITIP2 (chest indrawing) children compared to ITIP1 (fast breathing) children while malaria was more frequent in ITIP1.
Background and Aims:

Pneumonia is the major cause of under-5 mortality globally and hypoxemia is one of the indicators of severe pneumonia that corresponds with increased mortality. This study aimed to describe the risk factors associated with hypoxemia in children hospitalized with pneumonia.

Methods:

We prospectively evaluated children aged 2 – 59 months admitted for pneumonia in two districts hospitals in Yogyakarta, Indonesia. This study is a part of the Indonesian Pneumonia and vitamin D study. The diagnosis and severity of pneumonia was determined by doctors based on WHO classification of child-pneumonia. Demographic and clinical data were collected during admission. Oxygen saturation (Sp0₂) was measured on admission, with Sp0₂ level < 90 % was defined as hypoxemic.

Results:

From February 2016 – July 2017, 133 were recruited to the study. Of these, 29% had WHO-defined severe pneumonia. The median Sp0₂ was 94% (IQR: 92 – 97%) with 14% of children hypoxemic. Children with younger gestational age (OR: 1.45, 95% CI:1.11 – 1.89), under-weight on admission (OR:5.03, 95% CI: 1.83 -13.78); and had signs of respiratory distress (OR: 6.52, 95% CI:1.46 – 29.21) were significantly more likely to be hypoxemic even after adjustment for age, gender, socio-economic status, smoking exposure and overcrowded.

Conclusion

More than 1 out of 10 children admitted with pneumonia were hypoxemic, with younger gestational age, poor nutritional status on hospital admission and signs of respiratory distress as significant risk factors. Knowledge of risks factors for hypoxemia may improve management of community acquired pneumonia in resource-limited settings where pulse oximeters are not widely available.
CARRIAGE OF PNEUMOCOCCUS IN HEALTHY CHILDREN
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Background and Aims:

We assessed the association between preterm/term gestation, low/normal birth weight, and nasopharyngeal carriage of Streptococcus pneumoniae (pneumococcus) in rural and urban populations in Nepal.

Methods:

Nasopharyngeal (NP) swabs were collected from healthy children aged 6 to <24 months in Kathmandu (urban) in 2014-2015 and in Okhaldhunga (rural) in February 2015 as part of a study to assess NP carriage of pneumococcus prior to PCV10 introduction. Parental report of gestational age (GA) and birth weight (BW) were recorded. Children were categorized as preterm (<37 weeks GA) or term (≥37 weeks GA), and as low birth weight (LBW) if <2.5kg or normal birth weight (NBW) if ≥2.5kg.

Results:

1749 urban and 600 rural children were enrolled. In the urban setting, pneumococcal carriage prevalence in term children was 66% (1034/1579), while the preterm carriage prevalence was 60% (66/110; p=0.200). In the rural setting, the term carriage prevalence was 84% (495/592) and preterm carriage prevalence was 63% (5/8; p=0.110).

Analyzing birth weight, the carriage prevalence in urban LBW children was 65% (121/187), and in urban NBW children was 65% (937/1450; p=0.982). In rural LBW children the carriage prevalence was 71% (52/73), compared to the prevalence in rural NBW children which was 83% (334/403; p=0.019).

Conclusion

Gestational age and birth weight did not appear to affect the carriage prevalence of pneumococcus, except for rural LBW children, where it was significantly lower than NBW children. Further analyses may clarify the relationship.

ISPPD-0311
CIGARETTE SMOKE EXPOSURE DOES NOT ALTER PNEUMOCOCCAL AIRWAY CLEARANCE IN EXTRACELLULAR SUPEROXIDE DISMUTASE (EC-SOD) DEFICIENT MICE
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Background and Aims:

Chronic obstructive pulmonary disease (COPD) is a debilitating lung disease caused predominantly by cigarette smoking. COPD patients are also at increased risk of developing pneumonia caused by *Streptococcus pneumoniae*. The pathogenesis of COPD is marked by oxidative stress whereby key lung antioxidant defences including extracellular superoxide dismutase (EC-SOD), are dysfunctional. EC-SOD−/− mice fail to effectively clear other respiratory pathogens, however the role of EC-SOD in pneumococcal airway clearance is poorly understood. The following study aimed to determine whether pneumococcal airway clearance is altered in EC-SOD−/− mice exposed to cigarette smoke (CS).

Methods:

Age-matched female C57BL/6 (wild type) and EC-SOD−/− mice were exposed to air (SHAM) or CS over 8-weeks. Following exposure, *S. pneumoniae* (EF3030, 10⁶ CFU) were delivered to the lungs (intranasally under anaesthetic) and mice were sacrificed 7 days post infection (resolution phase). Pneumococcal load and the total number of inflammatory cells were assessed in the bronchoalveolar lavage (BAL) fluid.

Results:

*S. pneumoniae* was detected in the nasal tissue at comparable levels in both CS/SHAM wild type and EC-SOD−/− mice. The total number of BAL fluid inflammatory cells were unaffected by chronic CS exposure in wild type or EC-SOD−/− mice. Pneumococci were not consistently detected in the BAL fluid irrespective of exposure (CS/SHAM) or mouse genotype.

Conclusion

EC-SOD genetic deletion and chronic CS exposure does not alter nasopharyngeal loads or the resolution of BAL fluid inflammation following acute pneumococcal lung infection. The combination of CS exposure and loss of EC-SOD did not delay pneumococcal lung clearance *in vivo*.

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ISPPD-0685
RISK FACTORS OF PNEUMOCOCCAL CARRIAGE IN CHILDREN UNDER 5 YEARS OF AGE IN INDONESIA

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Background and Aims:
Pneumococcal conjugate vaccines (PCV) have not been introduced in Indonesia. Burden of vaccine-preventable disease is unknown because there is no surveillance system for pneumococcal disease. We evaluated nasopharyngeal (NP) carriage of S. pneumoniae in children <5 years of age in Southwest Sumba (SS) and Gunungkidul districts, Indonesia.

Methods:

We enrolled children <5 years old during vaccination clinics from February to May 2017. NP swabs were collected, evaluated for pneumococcal carriage, and isolates serotyped using PCR. We evaluated factors associated with pneumococcal carriage using logistic regression.

Results:

From 1233 children <5 years (323 <1 years and 910 >1 years), S. pneumoniae carriage was detected for 707 (58%) children (85% carriage in SS and 30% in Gunungkidul, p<0.01). Using multivariate logistic regression, adjusted for district and age, factors associated with pneumococcal carriage included presence of other children aged <5 years in the household (OR 1.31 95%CI: 0.9-1.9), rhinorrhea (OR 1.8 95%CI: 1.3-2.5), and cough (1.1 95%CI: 0.8-1.7). All households in SS and 30% in Gunungkidul used wood for cooking. To date, 94 pneumococcal isolates were serotyped: 49 (52%) were serotypes covered by PCV13, with types 6B 19F, 23F being most common. Types 34, 11A, 15B were the most common non-PCV13-types. Serotyping and susceptibility testing are ongoing.

Conclusion

We identified dramatically different pneumococcal carriage rates between the two districts. Presence of other children in the household and respiratory illness were significant predictors of pneumococcal carriage. PCV13 covers more than half of circulating serotypes among children in the two districts in Indonesia.
We carried out e-mail questionnaire survey to members of Japanese Society for Pediatric Infectious Diseases to investigate current PCV13 and PPSV23 vaccination status on each of hospitals for asplenia. We collected 18 serum samples from asplenic children in Chiba Children’s Hospital. Serotype specific IgG levels against PCV13 (non-PCV7) serotypes were measured by WHO approved enzyme-linked immunosorbent assay.

**Results:**

In total, 92 hospitals completed the questionnaire, 36/92 (39%) hospitals regularly take care of asplenic patients. PPSV23 was recommended in 33/39 hospitals for asplenic children, and PCV13 was recommended in 25/39 hospitals for children aged ≥6 years as off-labeled. In immunological study, 11/18 (61%) children had received PPSV23 and 5/18 (28%) children received PCV13. The patients who had only received PPSV23 had lower geometric mean IgG concentrations than the age-matched controls.

**Conclusion**

Asplenic children aged outside routine PCV13 vaccination (≥ 6 years) didn’t have enough PCV13 serotype-specific IgG levels for prevent IPD. The necessity of official recommendation of pneumococcal vaccine schedule for asplenic children was confirmed through this study.

**ISPPD-0302**

**EFFECT OF ENVIRONMENTAL CONDITIONS ON THE GROWTH OF PNEUMOCOCCAL SEROTYPES**

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**Background and Aims:**

Pneumococcus inhabits the nasopharynx, where it is typically exposed to variable oxygen conditions and temperatures of 30-35°C. However, pneumococcus can experience different conditions due to environmental variations or invasive infection. We evaluated how changes in temperature and oxygen level influenced the growth of different isolates of pneumococcus.

**Methods:**

We performed growth experiments on 56 different pneumococcal serotypes (clinical and carriage isolates) under aerobic, aerobic with additional catalase and anaerobic conditions at 30-39°C. Bacteria were grown for 24 hours in a microplate reader, reading the optical density (OD) at 600 nm every 30 minutes, after shaking. Data were analyzed in R (groFit). For adaptation experiments, we grew isolates aerobically or anaerobically at 30°C and 37°C to mid-log phase prior to starting the experiment.

**Results:**

Both clinical and carriage isolates reached the highest OD at lower temperatures (30-33°C). Clinical isolates had the shortest lag phase at 37°C. The majority of the isolates grew to the highest OD with the addition of catalase, grew well under anaerobic conditions, and grew poorly in ambient air. Our preliminary adaptation experiment shows evidence of adaptation to both temperature and oxygen level. For instance, isolates adapted to 37°C grew slower and to a lower density than the isolates adapted to 30°C when we tested both at 30°C.
Conclusion

The isolates grew best under conditions that mimicked the normal habitat and origin of the isolates in terms of temperature and oxygen and show evidence of environmental adaptation. This phenomenon could influence the transition from colonization to invasive infection.

HOST-PATHOGEN INTERACTIONS

ISPPD-0610
COMPREHENSIVE ANALYSIS ON HOST/BACTERIAL FACTORS INVOLVING SECONDARY PNEUMOCOCCAL PNEUMONIA AFTER INFLUENZA VIRUS INFECTION
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Background and Aims:

It has been well-known that secondary pneumococcal infection occurs after influenza virus infection. Recent reports indicated that it is due to the temporary defects in the immune reaction against pneumococcal infection after flu infection, however, it has not been completely clarified. In this study, we have screened the factors involving secondary pneumococcal infection in mice using microarrays of Streptococcus pneumoniae and mouse.

Methods:

C57/BL6 mouse was used for secondary pneumococcal infection model. Influenza virus (H1N1, A/New Caledonia) was nasally inoculated, followed 5 days later by nasal pneumococcal inoculation (S. pneumoniae D39). Body weight and survival of mice was recorded daily. Lung specimens were obtained from sacrificed mice, and total RNA was extracted from lung specimens and applied for whole-genome DNA microarray of S. pneumoniae and mouse.

Results:

In secondary pneumococcal infection model, mice showed decreased body weights and survivals after pneumococcal infection, and prominent inflammation was observed in lungs. DNA microarray against mice whole-genome indicated that the up-regulations of interferons and IL-10 were confirmed as previously reported, and genes involving innate immunity were down-regulated only in co-infection groups. In pneumococcal factors, some novel pneumococcal genes involved only in the secondary infection were identified. Secondary pneumococcal infection model using knockout strains of the newly identified gene revealed that each of them play certain roles to establish fatal secondary pneumococcal infections.

Conclusion

Host/bacterial factors involved only in secondary infections are quite interesting under the traditional concept of infections, however, it requires further study to reveal whole mechanisms of secondary pneumococcal infections.
ISPPD-0356
DISRUPTION OF THE TIGHT JUNCTION COMPLEX WITH RELEASE OF ZO-1, OCCURS DURING TRANSMIGRATION OF PNEUMOCOCCI THROUGH DIFFERENTIATED HUMAN BRONCHIAL EPITHELIAL CELLS
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Background and Aims:
We developed a pseudostratified human airway epithelial tissue (HAE) model with air-liquid interface (ALI) to study colonization and epithelial transmigration of pneumococci (SP). The aim was to identify cellular responses to SP including the disruption of tight junction (TJ) proteins.

Methods:
Human bronchial epithelial cells (four donors) were cultured for 60 days with an ALI until establishment of a differentiated cell monolayer. TIGR4 SP was inoculated apically at different multiplicity of infection (MOI) and incubated for 30 hours. SP were counted (cfu/ml) at the apical side (“colonizing”) and in the basolateral compartment after transmigration. Trans-epithelial resistance (TEER), confocal microscopy (e.g. TJ) and ELISA for ZO-1 levels in supernatant were performed at different time points.

Results:
Along the path from SP colonization to transmigration, there was a distinct dynamic of epithelial response. Whereas TEER did not change during colonization, it significantly decreased during transmigration indicating loss of integrity of the epithelial barrier. Accordingly, significantly higher ZO-1 levels were detected in supernatants of HAE cells when there was transmigration (p = 0.001, Fig. 1). ZO-1 levels distinguished transmigration from non-transmigration with an area under the curve of 0.77. If analysis was restricted to samples with transmigrating pneumococci, neither the inoculated SP concentrations nor the incubation time had a significant effect on the quantitative ZO-1 levels in supernatant.

\[ \text{different donors (do1,do2,do3,do5) transmigration no vs. yes} \]
\[ \text{minus 0MOI (total samples n=50)} \]
\[ \text{infections SN15, SN17, SN54, 50day old cells} \]

![Graph showing ZO-1 levels](image)

\* P-value = 0.0012

* P-value by Mann Whitney test
Conclusion

This differentiated HAE model simulates epithelial response to pneumococci including ZO-1 detection in the supernatant upon transmigration. Further studies are necessary to explain this mechanism i.e. whether this reflects degradation or hyperexpression of ZO-1 induced by SP.

ISPPD-0105
IN VIVO AND COMPARATIVE GENOMIC ANALYSIS REVEALS THE PHENOTYPIC AND GENOTYPIC FACTORS DRIVING SEROTYPE 1 REPLACEMENT IN THE GAMBIA

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Background and Aims:

Streptococcus pneumoniae serotype 1 is one of the leading causes of invasive pneumococcal disease (IPD) in West Africa. Recently, a rare example of clonal replacement was observed, where the ST3081 clone of serotype 1 replaced the predominant ST618 clone as the main cause of IPD in The Gambia. The aim of this study is to identify the phenotypic and genomic factors driving the observed clonal replacement.

Methods:

Using whole genome sequence analysis and clinically relevant models of in vivo infection, we identify distinct genetic and phenotypic characteristics of the emerging ST3081 clone.

Results:

We showed that ST3081 is significantly more virulent than ST618 in invasive pneumonia models and is carried at higher densities than ST618 in models of nasopharyngeal carriage. We also identified ST-specific accessory genes and a unique ST-specific fixed mutation in the pneumococcal toxin pneumolysin which is associated with increased haemolytic activity in ST3081.

Conclusion

We provide evidence that, within the same serotype 1 clonal complex, biological properties differ significantly from one clone to another in terms of virulence and host invasiveness. These differences may be the result of key genetic differences within the genome.

ISPPD-0182
DIVERSE PNEUMOCOCCAL STRAINS DRIVE A MAIT CELL RESPONSE THROUGH MR1-DEPENDENT AND CYTOKINE-DRIVEN PATHWAYS
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Background and Aims:
Mucosal Associated Invariant T (MAIT) cells represent an innate T cell population of emerging significance. These abundant cells can recognize ligands generated by microbes utilizing the riboflavin synthesis pathway, presented via the MHC-like molecule MR1 and binding of specific T cell receptors (TCR). They also possess a functional programme (shared by innate T cell populations expressing CD161) allowing microbial sensing in a cytokine-dependent, TCR-independent manner. We aimed to determine whether MAIT cells recognise pneumococci and assess the genomics and transcriptomics of the pneumococcal riboflavin operon (Rib genes).

Methods:
We examined the expression of Rib genes in pneumococci at rest and in response to metabolic stress using RNA sequencing, and linked this to MAIT cell activation in vitro. We analysed 571 diverse pneumococcal genomes from 39 countries dating back to 1916, and 824 genomes of 69 different non-pneumococcal Streptococcus species genomes for evidence of Rib gene sequences.

Results:
We observed robust recognition of pneumococcal strains at rest and following stress, using both TCR-dependent and TCR-independent pathways. The pathway used was highly dependent on the antigen-presenting cell, but was maintained across a wide range of clinically-relevant strains. The riboflavin operon was highly conserved among pneumococci, and different versions of the riboflavin operon were also identified in other streptococcal species.

Conclusion
These data indicated an important functional relationship between MAIT cells and pneumococci, which may be tuned by local factors, including the metabolic state of the organism and the antigen-presenting cell that it encounters.

ISPPD-0640
RELATIONSHIP BETWEEN IRON STATUS, INFLAMMATION AND PNEUMOCOCCAL LOAD IN THE FIRST TWO YEARS OF LIFE
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Background and Aims:

Pneumococcal nasopharyngeal (NP) carriage acts as a prerequisite for pneumococcal infections, and iron plays an indispensable role in the establishment and progress of infection. We hypothesize that pneumococcal load is associated with iron status and inflammation.

Methods:

We recruited 120 infants at birth and collected NP samples monthly during the first year, and at months 15, 18, 21 and 24 in the second year. Venous blood was collected at birth, months 2, 5, 12, 18 and 24. NP carriage and load were determined by LytA qPCR whilst iron status was determined by the presence of ferritin in plasma samples.

Results:

Pneumococcal carriage was 29.41% at birth, 91.74% at month 5, 91.59% at month 12, and 71.30% and 77.06% at months 15 and 24 respectively. Mean pneumococcal load was lowest at birth, 0.849 ln copies/µl, 6.713 ln copies/µl at month 11 and 3.609 ln copies/µl at month 24. All babies from birth to 2 months were iron replete and by month 24, 50% were iron deficient (ferritin <12 µg/L or <30µg/L in the presence of inflammation). After adjusting for inflammation, there was some evidence that children who were iron deficient had mean pneumococcal load 0.440 ln copies/µl lower (95% CI -0.883 to 0.003, p-value=0.052) than children who were iron replete. There was very strong evidence that children who had inflammation (crp >5mg/L) had 0.620 ln copies/µl (95% CI 0.360-0.880, p-value <0.001) higher mean pneumococcal load than children who had no inflammation.

Conclusion

Pneumococcal load is associated with inflammation and iron deficiency.

ISPPD-0019

SIGNALS INVOLVED IN THE TRANSITION FROM COLONIZATION TO DISEASE WITH STREPTOCOCCUS PNEUMONIAE

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Background and Aims:

Streptococcus pneumoniae (the pneumococcus) effectively colonizes the human nasopharynx. Colonizing pneumococci form well-organized biofilms. Transition to disease occurs frequently enough that the pneumococcus remains a major influence on human health. Changes in the local environment caused by virus infection or host assaults triggers dispersal from colonizing pneumococci. The resulting biofilm-dispersed pneumococcal population is distinct in its transcriptome and phenotype as compared to biofilm and broth-grown planktonic bacteria counterparts, displaying increased virulence and invasiveness as well as inducing more host inflammation. However, the specific mechanism(s) of transition to disease has been less studied.

Methods:
Previously established *in vitro* biofilm formation and biofilm dispersal models were used to investigate pneumococcal egress after exposure to increased temperature (i.e., mimicking fever). Inhibitors were tested for blocking of dispersal by biofilms of wildtype strains. Deletion mutants were used for testing potential factors involved in dispersal. Viable plate counts and SEM were used to compare wildtype and mutant strains *in vitro*. Experiments utilizing previously established *in vivo* mouse models are ongoing.

**Results:**

Dampened biofilm dispersal in the presence of protease inhibitors implicates a potential role for proteases in heat-induced egress from biofilms. We identify a role for serine/protease HtrA in heat-induced biofilm dispersal, as biofilms formed by a HtrA-negative mutant were unable to respond to heat exposure as compared to wildtype, albeit the formed biofilms were comparable in biomass and structure.

**Conclusion**

Understanding the specific mechanisms involved in the transition to pneumococcal infection provides novel strategies to specifically interfere with disease progression without disturbing normal colonization of the nasopharynx.

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**ISPPD-0445**

**LONGITUDINAL STUDY OF SYSTEMIC AND MUCOSAL TH17 RESPONSES TO PNEUMOCOCCAL ANTIGENS IN CHILDREN COLONISED WITH PNEUMOCOCCUS**

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**Background and Aims:**

Protein pneumococcal vaccine antigens are needed to reduce pneumococcal transmission. CD4⁺Th17 cells may mediate mucosal immunity.

**Methods:**

Adenoids, peripheral blood and nasal swabs from 50 children (2-11yrs) at adenoidectomy and up to 6 subsequent monthly swabs were obtained. Cultures of peripheral blood (PBMC) and adenoidal mononuclear cells (AMNC) were stimulated with candidate antigens (CbpA, Psaa, PspA, Phd, WCA(whole cell antigen), SP1912, SP2108, SP0148) and supernatant IL-17A and IL-22 assayed. Swabs were cultured for pneumococcus. Statistics: ANOVA and unpaired t tests adjusted for multiple comparisons and Pearson's correlation. Described differences had p<0.05.
Results:

22 children (44%) carried pneumococcus at surgery and most subsequently. 28 (56%) carried pneumococcus at least once. All antigens except PhtD; and CbpA, WCV and SP1912 induced both cytokines in PBMC and AMNC, respectively. Colonised children’s unstimulated AMNC produced significantly more cytokines and CbpA, WCV and SP1912-stimulated AMNC induced higher IL-22 responses in uncolonised children, but subsequent carriage status was not predicted by these responses. Unexpectedly, PBMC IL-17A responses to all 3 SPXXXX antigens and IL-22 to SP1912 were positively correlated with numbers of subsequent pneumococcal positive swabs and, among initially uncolonised children, those who subsequently became colonised had higher cytokine responses to SP1912 (only) than those who didn’t.

Conclusion

Colonisation with pneumococcus appears to be associated with increased spontaneous mucosal (AMNC) production of Th17 cytokines and AMNC IL-22 responses to some antigens are higher in uncolonised children. However, children with higher PBMC IL-17A and IL-22 responses to some pneumococcal antigens have more subsequent colonisation. Conceivably they are more colonisation-prone.

Work supported by PATH.

ISPPD-0691
NASOPHARYNGEAL COLONISATION OF STREPTOCOCCUS PNEUMONIAE IN CHILDREN WITH CANCER
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Background and Aims:

Nasopharyngeal colonisation is essential for Streptococcus pneumoniae to cause invasive pneumococcal disease (IPD). However, there is a paucity of literature describing NP colonisation of S. pneumoniae in children diagnosed with cancer who have high burden of IPD.

Methods:

We enrolled children aged between 1 and 18 years diagnosed with haematological or solid organ malignancy receiving active immunosuppressive therapy or have completed immunosuppressive therapy in the preceding 12 months. Nasopharyngeal swabs (NPS) were taken before and after a single-dose of 13-valent pneumococcal conjugate vaccine (PCV13).
Results:

A total of 175 NPS’s were collected from 85 children before and after single dose of PCV13 vaccination, 28-60 days apart. For children receiving active immunosuppressive therapy, 6.8-9.3% of children were colonised with *S. pneumoniae* but this increased to 18.2% six months after cancer therapy is ceased. This is comparable to the CIT group where colonisation rates increased from 18.9% to 23.3% with *S. pneumoniae*. Thirteen percent of the serotypes identified are included in PCV13, 26% included in 23-valent pneumococcal polysaccharide vaccine and 61% were non-typosable or non-vaccine serotypes.

Conclusion

Children receiving immunosuppressive chemotherapy for haematological and non-haematological malignancies are infrequently colonised with pneumococcus despite the known high risk of IPD. A larger study with longer time periods and more sampling time points is required to investigate the effect of vaccination on colonisation and serotypic distribution of *S. pneumoniae* in this vulnerable cohort.

ISPPD-0756

ASSESSING THE ROLE OF PNEUMOCOCCAL NEURAMINIDASES IN IN VITRO AND IN VIVO PNEUMONIA MODELS USING MONOCLONAL ANTIBODIES

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Background and Aims:

*Streptococcus pneumoniae* isolates express up to three neuraminidases (sialidases), NanA, NanB and NanC, all of which cleave terminal sialic acids of glyco-structures on host cell surfaces. As most research has addressed mainly the role of NanA, this study aims at evaluating the contributions of all three neuraminidases in host-pathogen interactions in pneumonia models.

Methods:

We generated two types of monoclonal antibodies (mAbs) that target NanA (all sequence variants), or both NanB and NanC. The effect of mAb-based targeting of neuraminidases was addressed *in vitro* using enzymatic assays and *S. pneumoniae* infection models of primary human tracheal/bronchial epithelial tissue. To study the roles of neuraminidases during pneumonia, mice were passively immunized with mAbs prior to intranasal challenge with *S. pneumoniae*.

Infected human tissues and mouse lungs were stained with peanut lectin (FITC conjugated) which recognizes galactose residues exposed by neuraminidases.

Results:

We found that simultaneous targeting of all neuraminidases was required to inhibit the neuraminidase activity of clinical *S. pneumoniae* isolates *in vitro* and to prevent desialylation of primary human lung tissue. Moreover, all neuraminidases contributed to pneumococcal adherence to human airway epithelial cells.

Neutralizing NanA, NanB or NanC blocked desialylation of the murine respiratory epithelium during pneumonia. Despite this, we did not observe survival benefits, reduction in pulmonary
bacterial load, or significant changes in cytokine responses in mice treated with anti-NanA and anti-NanB/C mAbs.

Conclusion

Inactivation of neuraminidases had no appreciable effect in a lethal pneumonia model in mice.

ISPPD-0078
DEFINING THE VERY EARLY DYNAMICS OF CARRIAGE ACQUISITION OR CLEARANCE FOLLOWING EXPERIMENTAL HUMAN PNEUMOCOCCAL CHALLENGE
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Background and Aims:

The dynamics of establishment of pneumococcal carriage or protection against carriage following pneumococcal (Spn) encounter are unknown. Defining these dynamics could provide new insight in pneumococcal transmission and protective mechanisms. We used the Experimental Human Pneumococcal Challenge (EHPC) model to investigate the first hours and days following exposure.

Methods:

Forty healthy adults were intranasally inoculated with serotype 6B Spn (80,000 CFU in 100uL saline). Volunteers then collected their saliva for bacterial detection (at 0, 1, 2, 4, 8, 12, 24, 36 and 48 hours) and nasal lining fluid to assess mucosal immune responses (at 0, 4, 8, 12, 24 and 48 hours). Samples were stored in a cooled transport bag, and storage temperature and collection times were recorded. We used 6B-specific qPCR assays to measure Spn in saliva.

Results:

Ten out of forty volunteers became carriage-positive, defined by classical microbiology from nasal wash. Preliminary results show presence of pneumococcal DNA in saliva of all carriers (4/4 volunteers) after 24 hours post-inoculation, but not in anyone who was carriage-negative (0/15 volunteers). In contrast, pneumococcal DNA was detected in saliva at one hour post-inoculation in 5/15 carriage-negative volunteers, but not in any carriage-positive volunteers.

Conclusion

We established a novel home sampling method to define the early events after experimental pneumococcal challenge. Preliminary results suggest that stable establishment of carriage can take up to 24 hours. Moreover, two distinct profiles are associated with protection against carriage. Effective mucociliary clearance and phagocytosis by nasal resident cells might complementary contribute to protection against pneumococcal acquisition.

Acknowledgments: BMGF; MRC; NIHR-CRN; Robert Austrian Award.

ISPPD-0718
THE PNEUMOCOCCAL CAPSULE SHEDDING PATHWAY CONTROLS TOLERANT RESPONSE TO LYTIC ANTIBIOTICS

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Background and Aims:

Background: Autolysis is a physiologic hallmark of pneumococcal stationary phase and response to cell wall active antibiotics. Recently the main suicidal autolysin LytA was shown to mediate capsule loss without lysis in response to antimicrobial peptides. We have identified several additional loci affecting the activity of LytA during capsule shedding.

Methods:

Methods: Isogenic mutants in the TIGR4 background were assayed for alterations in capsule shedding in vivo in a murine model of acute pneumonia, and assayed for autolytic response to the cell wall active antibiotics penicillin, vancomycin, and teicoplanin. The mutants were analyzed for alterations in peptidoglycan stem peptide composition by LC/MS.

Results:

Results: Mutants in capsule shedding accessory loci showed marked differences in their ability to shed capsule and their autolytic response to penicillin and vancomycin. In addition, despite no differences in stem peptide composition, one mutant showed an elevated minimum inhibitory concentration of teicoplanin. Capsule shedding was differentially affected in vivo compared to in vitro for the mutant strains. In vivo a greater capsule shedding response correlated with increased virulence in mice.

Conclusion

Conclusions: Autolysis and capsule shedding are two distinct roles for the main suicidal autolysin LytA. Deletion of control mechanisms, composed at least in part of the shedding accessory loci, affects capsule shedding in vivo and in vitro, and leads to altered response to lytic antibiotics which is characteristic of tolerance.

ISPPD-0010
PERIPHERAL BLOOD RNA GENE EXPRESSION IN CHILDREN WITH PNEUMOCOCCAL MENINGITIS: A PROSPECTIVE CASE CONTROL STUDY

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Background and Aims:
Invasive pneumococcal disease (IPD) has increased morbidity and mortality rates among HIV-infected children. We aimed to compare peripheral blood expression profiles between HIV-infected and uninfected children with pneumococcal meningitis and controls, and between survivors and non-survivors, in order to provide insight into the host inflammatory response leading to poorer outcomes.

Methods:

Children aged 2 months to 16 years were enrolled to a prospective case-control observational study in a tertiary hospital in Malawi. The human genome HGU133A Affymetrix array was used to explore differences in gene expression between cases with pneumococcal meningitis (n=12) and controls, and between HIV-infected and uninfected cases, and validated gene expression profiles for 34 genes using real-time quantitative PCR in an independent set of IPD cases (n=229) and controls (n=13). Pathway analysis was used to explore genes differentially expressed.

Results:

Irrespective of underlying HIV infection, cases showed significant upregulation compared with controls of the following: S100 calcium-binding protein A12 (S100A12); vanin-1 (VNN1); arginase, liver (ARG1); matrix metallopeptidase 9 (MMP9); annexin A3 (ANXA3); interleukin 1 receptor, type II (IL1R2); CD177 molecule (CD177); endocytic adaptor protein (NUMB) and S100 calcium-binding protein A9 (S100A9), cytoskeleton-associated protein 4 (CKAP4); and glycogenin 1 (GYG1). RT-qPCR confirmed differential expression in keeping with microarray results. There was no differential gene expression in HIV-infected compared with HIV-uninfected cases, but there was significant upregulation of folate receptor 3 (FOLR3), S100A12 in survivors compared with non-survivors.

![Figure 1: Distribution plot of the differentially expressed genes. The significantly differentially expressed genes are shown in red colour. The significance threshold (p<1.5e-3) is indicated by a dashed red line, and a fold change threshold of more than 2 is shown by the dashed vertical lines. The green line shows p<0.05. (A) Shows results for unadjusted p values, (B) results for BH-adjusted p-values and (C) Bonferroni-adjusted p-values, which represent an overcorrection. BH: Benjamin and Hochberg.](image-url)
Figure 2 Validation of RNA transcription profile differential expression using real-time quantitative PCR. Relative gene expression in cases compared with controls for 34 genes assessed. The black line shows the box plot median. The red dot shows the mean, and the Welch two-sample t-test p value is shown on the top right corner.

355
Conclusion

Children with IPD demonstrated increased expression in genes regulating immune activation, oxidative stress, leucocyte adhesion and migration, arginine metabolism, and glucocorticoid receptor signalling.
ISPPD-0131
PNEUMOCOCCAL PURINE NUCLEOSIDE PHOSPHORYLASES ARE REQUIRED FOR GROWTH AND FULL VIRULENCE
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Background and Aims:

Nucleotides are essential for a wide variety of bacterial processes and are biosynthesized by de novo and salvage pathways. Purine nucleoside phosphorylase (PNP) is a key enzyme involved in salvage pathway of purine biosynthesis. PNP catalyses the cleavage of the glycosidic bond of nucleosides in the presence of inorganic phosphate to produce a purine base and sugar moiety. Bioinformatics analysis predicted the presence of two putative pneumococcal PNPs, PNP1 and PNP2 which share 15% amino acid sequence identity. Recombinant PNP1 and PNP2 were purified to homogeneity from E. coli. Kinetic studies indicated that PNP1 catalysed the phosphorolysis of 6-oxopurines, guanosine (K_m = 13.9 µM) and inosine (K_m = 12.7 µM) whereas PNP2 utilized 6-oxopurines and 6-aminopurines as substrates. Both enzymes did not catalyse the phosphorolysis of pyrimidines. PNP2 has a broader substrate specificity compared to PNP1. Site directed mutagenesis of the nucleoside binding residues rendered PNP1 enzymatically inactive, while, mutations in the ribose and phosphate binding sites resulted in substantially lower activity than the wildtype recombinant protein. Growth of the pneumococcal strains deficient in pnp1 or/ and pnp2 was impaired in chemically defined medium. Genetic complementation and addition of nucleoside/nucleobase restored its growth to wildtype level. Mice experiment suggested that PNP1 and PNP2 are required for full virulence. We are currently elucidating the potential role of PNPs in pneumococcal pathogenesis and regulation of pneumococcal nucleotide biosynthesis. This study could provide targets for designing novel therapeutic agents.

ISPPD-0032
GENOME-WIDE ASSOCIATION ANALYSES OF INVASIVE PNEUMOCOCCAL DISEASE ISOLATES IDENTIFY A BACTERIAL MISSENSE MUTATION ASSOCIATED WITH MENINGITIS
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Background and Aims:

Bacterial mutations predisposing pneumococcus to causing meningitis, a more severe form of invasive pneumococcal disease (IPD), are largely unknown. Knowledge of such mutations may improve our understanding of pathogenesis and inform preventive strategies.

Methods:

Pneumococcal isolates from an exploratory sample of IPD patients (n=2054) and an independent confirmatory cohort (n=2518) were sequenced on an Illumina platform. Coding DNA sequence variations were called based on de novo genome assembly. Association between individual variation and meningitis was assessed by a linear mixed-effects model after controlling for population structure and correcting for multiple testing. Phylogenetic analysis of candidate variant was used to detect possible functional selection advantages.
Results:

A pneumococcal pbp1b gene mutation (pbp1bA641C causing amino acid N214T change in the transglycosylase domain of penicillin-binding protein 1b) was significantly associated with meningitis in both the exploratory sample and the confirmatory cohort (FDR adjusted q-value=0.022 and 0.010, respectively). Patients infected by the pbp1bA641C genotype pneumococci showed 2.7-fold higher odds (95% CI 1.6 to 4.6) of meningitis compared to those infected by non-pbp1b641C pneumococci, after controlling for serotype, antibiotic resistance, and patient age. The pbp1bA641C substitution was acquired by six different pneumococcal lineages and the corresponding codon site showed evidence of being under positive selection.

Conclusion

Pneumococcal pbp1b641C allele was associated with meningitis among IPD patients. The underlying mechanism was unlikely to involve linkage with serotype or antibiotic resistance.

ISPPD-0483
DYNAMICS OF PNEUMOCOCCAL NASOPHARYNGEAL COLONISATION DENSITY IN CHILDREN WITH AND WITHOUT PNEUMONIA.
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Background and Aims:

Using archived samples from the Maela birth cohort study, this study investigated pneumococcal nasopharyngeal colonisation density dynamics in ≤2 year olds before and
during episodes of pneumonia, and compared these to asymptomatic controls matched by age, birth season, and colonising serotype.

**Methods:**

Cases fulfilled WHO criteria for severe or very severe pneumonia and had chest X-ray and/or C-reactive protein results indicative of a likely bacterial infection. LytA qPCR assays were performed on specimens spiked with an internal control and extracted following CDC recommended protocols. Swabs tested were pre-pneumonia and pneumonia swabs for each case (<1 month apart) and two swabs for each control (1 month apart). Medians of log-transformed data were compared with the Wilcoxon signed-rank test.

**Results:**

Pneumococcal densities were determined for 264 swabs from 66 cases and controls. In cases where the serotype remained constant between timepoints, higher densities were obtained for the pneumonia swabs compared to controls (6.1 vs. 5.9 log_{10} copies/mL; p=0.02), when the colonising serotype was 19F or 6B (6.6 vs. 5.8 log_{10} copies/mL; p=0.02) and when the case was classified as very severe. If applying the 6.9 log_{10} copies/mL colonisation density cut-off determined in the PERCH study, seven cases and nine controls would be identified as having pneumococcal pneumonia. In cases with no serotype change, positive density changes between swabs were identified compared to controls (logged density ratio 0.2 vs. -0.5; p=0.02).

**Conclusion**

This study highlights the challenges in using nasopharyngeal densities to determine pneumococcal pneumonia. The differences in nasopharyngeal densities associated with serotype warrants further investigation.

**ISPPD-0116**

**TREATMENT OF MATERNAL PNEUMOCOCCAL INFECTION WITH BETA-LACTAMS LEADS TO TLR2/6 DEPENDENT NEUROPROLIFERATION IN THE FETAL CORTEX AND HIPPOCAMPUS AND POST-NATAL BEHAVIOURAL ABNORMALITIES**

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**Background and Aims:**

During maternal infection with *S. pneumoniae*, cell wall (CW) released by b-lactam antibiotic treatment enters the embryonic brain and signals TLR2 to induce neuronal proliferation in the cortical plate leading to subsequent postnatal cognitive disorders. Here we examine the impacts of maternal live infection with ampicillin treatment, the TLR2/6 signaling pathway outcome and how it affects the highly organized layers of the cortical plate and hippocampus. We sought to determine the gestational timing parameters, brain regions of injury, active signaling cascades and extent of abnormal postnatal behavior in mice exposed to ampicillin released CW in utero.

**Methods:**

Pregnant mice were infected on various gestational days and treated twice daily with ampicillin until e16. Embryonic brains from wild type and transgenic mice were analyzed by
stereology, IF staining and western blot to determine signaling pathways and proliferation. Post-natal mice were tested for sociability and spatial memory.

Results:

CW released during ampicillin treatment of maternal pneumococcal infection leads to a significant increase in neurogenesis in the cortex and hippocampus. CW signals TLR2/6 to increase expression of FOXG1, subsequently exporting FOXO1 to the cytoplasm to induce cell proliferation. This cascade of events during gestation leads to mice that are antisocial and suffer from anxiety and memory defects.

Conclusion

During the second trimester of pregnancy, antibiotic released CW/TLR2/6 signaling causes multifocal, abnormal fetal brain architecture and persistent postnatal cognitive disorders.

ISPPD-0017
SEVERITY OF PNEUMOCOCCAL VS. NON-PNEUMOCOCCAL ACUTE OTITIS MEDIA IN CHILDREN
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Background and Aims:

Pneumococcal acute otitis media (AOM) has been previously considered as a more severe disease than that caused by other otopathogens, based on clinical and/or otologic scores. We tested this hypothesis in the pneumococcal conjugate vaccines (PCVs) era.

Methods:

Children <6 years who presented with "severe" AOM episodes with middle ear fluid (MEF) cultures during 2008-2013 were retrospectively identified. "Severe" AOM episodes were considered if tympanocentesis was required, or if spontaneous otorrhea was present. Data were extracted for demographics, clinical and laboratory tests. Children were categorized according to their PCV status as "unimmunized" or "PCV7/PCV13 immunized", and according to their MEF culture results into the "pneumococcal" or the "non-pneumococcal" group. Leukocytosis was defined as white blood cells (WBC) count >15,000/μL, and elevated C-reactive protein (CRP) level was considered as >50 mg/L.

Results:

Of 295 eligible AOM episodes, 106 (36%) were culture positive. Children in the pneumococcal group (65, 61%) had a significantly higher WBC counts and higher CRP levels, were more often <2 years old and were more prone to complicate with acute mastoiditis (AM), compared to children in the non-pneumococcal group, p=0.03, p=0.02, p=0.04 and p=0.03, respectively. In the pneumococcal group, unimmunized children had higher WBC counts when compared with PCV13 immunized children (p=0.04), but there were no appreciable differences in CRP levels between unimmunized and PCV7/PCV13 immunized children.

Conclusion
Pneumococcal AOM is associated with higher leukocytosis and CRP levels than non-pneumococcal AOM. Circulating *Streptococcus pneumoniae* strains causing "severe" AOM in PCV13 immunized children yielded lower inflammatory responses when compared with unimmunized children.

**ISPPD-0778**
**ANTIMICROBIAL MECHANISMS OF ARACHIDONIC ACID AT THE HOST-PNEUMOCOCCAL INTERFACE**

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Background and Aims: *Streptococcus pneumoniae* (pneumococcus) is a significant global pathogen responsible for more than 1 million deaths every year. To survive within the host, this pathogen must evade both innate and adaptive immunity to proliferate and survive. During the innate immune response, the host utilises long chain fatty acids, such as the polyunsaturated fatty acid, arachidonic acid (AA), in the defence against bacterial infection. However, the mechanisms by which AA contributes to bacterial clearance are not well understood.

Methods: Here, we have combined molecular microbiology, lipidomics and a murine model of pneumococcal infection to investigate the contribution of AA to antimicrobial defence.

Results: The concentration of AA increased 44% in response to *S. pneumoniae* infection. Supplementation of THP-1 macrophages with AA increased pneumococcal killing by 50%, compared to un-supplemented macrophages. RNA sequencing of *S. pneumoniae* in the presence of mild AA stress revealed ~4-fold down-regulation of the fatty acid biosynthesis gene cluster. Membrane composition analyses revealed a reduction in the abundance of bacterial synthesised fatty acids and a significant 31% increase in AA incorporated into the bacterial cell, resulting in changes in membrane fluidity and integrity.

Conclusions: Our data show that AA is selectively increased in host serum in response to pneumococcal infection. Increased AA abundance contributes to bacterial clearance through direct antimicrobial activity, predominately mediated by disruption of the pneumococcal membrane via reduced fatty acid production and the physical insertion of an exogenous fatty acid within the pneumococcal membrane.

**ISPPD-0779**
**EXPLOITING ZINC AT THE HOST-PATHOGEN INTERFACE TO DEVELOP A NOVEL PNEUMOCOCCAL TREATMENT STRATEGY**

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Background and Aims: Streptococcus pneumoniae is a major cause of human morbidity and mortality. During infection, zinc plays a critical role in innate immune defence, and dietary zinc status impacts the progression of invasive pneumococcal disease. Despite this, the mechanisms by which zinc exerts toxicity in S. pneumoniae remain poorly understood. This study aimed to characterise the pneumococcal mechanisms for resisting zinc stress, elucidate the impact of zinc stress on bacterial physiology, and harness this knowledge to develop a novel therapeutic treatment.

Methods: Bacterial zinc resistance mechanisms were characterised in S. pneumoniae (strain D39) through a combination of microbial growth, metal ion content and macrophage survival analyses. Metabolomic and transcriptomic analyses revealed the global impact of zinc stress on S. pneumoniae. The use of zinc in combination with cell permeable ionophores and antibiotic treatment was examined in the multidrug resistant 23F strain by antibiotic killing, MIC and MBC assays.

Results: The cation diffusion facilitator family protein, CzcD, was shown to be a zinc export protein crucial for resisting phagocytic cell clearance. Zinc stress impacted multiple pathways in the pneumococcus, including central carbon metabolism and cell wall biosynthesis. Zinc toxicity, mediated by abrogation of zinc efflux or ionophore enhanced uptake, increased the susceptibility of S. pneumoniae to antibiotic treatment in vitro.

Conclusions: This study revealed the molecular and cellular impact of zinc stress on S. pneumoniae and highlights the therapeutic potential of zinc and ionophores as adjuvants to antibiotics as a novel treatment strategy.

ISPPD-0127
UTILISATION OF THE SUGAR RAFFINOSE DICTATES DISEASE PROGRESSION IN STREPTOCOCCUS PNEUMONIAE
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Background and Aims:

Streptococcus pneumoniae strains differ in their capacity to cause invasive versus localised infections, with the underlying mechanisms remaining poorly understood. Previous studies demonstrated that even very closely related strains within the same serotype and sequence type (ST) displayed variations in virulence, related to their isolation site in humans. Serotype 14 ST15 human blood isolates caused pneumonia, while ST15 ear isolates caused otitis media and meningitis, in mice.

Methods:

Strains were characterised using genomic analyses, growth assays, real time RT-PCR and intranasal murine challenges, to determine the impact of raffinose utilisation on disease progression.

Results:

Genomic comparisons between a ST15 blood and ear isolate identified single nucleotide polymorphisms in several genes, including in the raffinose regulator, rafR. Growth assays with raffinose showed that the blood isolate grew better than the ear isolate, whereas no growth difference was observed in glucose. Correspondingly, RT-PCR showed higher expression of raffinose utilisation genes in the blood isolate compared to the ear isolate, in
raffinose supplemented media. Swapping rafR alleles between the blood and ear isolates led to a switch in the above in vitro characteristics. Strikingly, the rafR swapped strains also showed a simultaneous swap in the disease profiles between the blood and ear isolates. Now the rafR swapped blood isolate caused otitis media and meningitis significantly more than the rafR swapped ear isolate, which instead displayed increased capacities to cause pneumonia.

**Conclusion**

These results suggest that variations in the rafR sequence, that affect the ability to utilise raffinose, play a significant role in dictating pneumococcal disease progression.

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**ISPPD-0272**

**NASOPHARYNGEAL CARRIAGE, SEROTYPE DISTRIBUTION AND ANTIMICROBIAL RESISTANCE GENES OF Streptococcus pneumoniae AMONG HEALTHY INFANT IN INDONESIA DURING FIRST YEARS OF LIFE**

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**Background and Aims:**

*Streptococcus pneumoniae* is a common bacterial pathogen responsible for various infections, including pneumonia, bacteremia, meningitis, and acute otitis media, especially in young children. Nasopharyngeal colonization plays an important role in the development and transmission of pneumococcal diseases. Data on *Streptococcus pneumoniae* carriage prevalence and serotype diversity in Indonesia is limited. The aim of this study is to identify the distribution of serotypes *Streptococcus pneumoniae* and characteristics associated with nasopharyngeal carriage among healthy infants during the first year of life.

**Methods:**

Healthy infants were enrolled in two health care centers at 2-3 months of age and nasopharyngeal swabs were collected monthly for 7 months, with a final swab collected at 12 months of age. *Streptococcus pneumoniae* was identified by lytA qPCR, and positive samples were plated onto selective agar. Serotypes were determined by microarray and latex agglutination/Quellung. The presence of select antimicrobial genes will be assessed using data obtained from microarray.

**Results:**

A total of 200 participants were enrolled in this study: 98 participants from urban areas and 102 participants from semi-rural areas. Urban infants experienced a total of 146 carriage episodes of 41 different serotypes and semi-rural infants experienced a total of 186 carriage episodes with 44 serotypes. 34.1% of pneumococci belonged to PCV13 serotypes. The most frequent serotypes were 6B, 19F, 23F, and 15A.
Conclusion

This longitudinal study will provide interesting data on carriage pneumococci in Indonesian infants during the first year of life.

ISPPD-0472
HOST RESPONSES TO STREPTOCOCCUS PNEUMONIAE: CARRIAGE VERSUS INFECTION SEROTYPES
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Background and Aims:

Bronchiectasis, a chronic suppurative lung disease with increasing global recognition, is prevalent in Australian Indigenous children. Streptococcus pneumoniae is often found in the lower airways of children with bronchiectasis. Surveillance studies suggest that pneumococcal serotypes differ in their propensity to cause disease. The aim of our study is to determine if the infection versus carriage phenotype of S. pneumoniae is associated with different immune responses in children with bronchiectasis. Here we present the preliminary workup of our methodology.

Methods:

Immunologic assays for this study were established using peripheral blood mononuclear cells (PBMC) from adult volunteers without respiratory illness, and clinical isolates of S. pneumoniae obtained from pediatric BAL fluid (infection) and nasopharyngeal swabs (carriage). PBMC from nine adult volunteers were challenged in vitro with S. pneumoniae serotypes associated, in Australian children, with a) lower respiratory infection (19F, 15A) and b) mucosal carriage (9V, 7C). Cytokines supportive of Th17 (IL-17α, IL-6), Th1 (IFN-γ), Th2 (IL-13), and early inflammation (TNF-α) were measured in culture supernatants using Dissociation-Enhanced Lanthanide Fluorescence Immunoassays (DELFIA™).

Results:

All 9 adult volunteers produced measurable amounts of IFN-γ, IL-13 (at 72-hours), IL-6 and TNF-α (at 24 hours) to 19F, 15A, 9V and 7C, whilst 5 of 9 adults produced IL-17α (72-hours). Inter-serotype differences were most pronounced with respect to mean IFN-γ production, although the differences were not statistically significant.

Conclusion

This pilot study informs the methodology of our larger study to investigate the role of the host immune response to S. pneumoniae in the pathogenesis of bronchiectasis in Australian Indigenous children.

ISPPD-0101
PRIMING AND MAINTENANCE OF SEROTYPE- AND PROTEIN-SPECIFIC B-CELL MEMORY RESPONSES AFTER NON-VACCINE-TYPE CARRIAGE
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364
Background and Aims:

Infection with *Streptococcus pneumoniae* induces antibodies as well as cell mediated immune responses resulting in clearance of the bacteria, but whether mucosal colonization also induces an immune memory response is unknown. We performed a study to evaluate if pneumococcal colonization in 11 month old children, vaccinated with pneumococcal-10-valent-conjugate-vaccine (PCV10), induces antibody responses and immune memory against carried serotype and/or pneumococcal proteins three years later.

Methods:

Nasopharyngeal pneumococcal carriage was measured by culture and molecular analysis, in eleven month old children (n=330) and has been repeated in a subset (n=68) of these children three years later at age 46-months. Serotype and protein specific humoral and memory B-cell responses were analyzed in serum (MIA, ELISA) and PBMCs (ELISPOT) from 46-month old children who were colonized with non-vaccine-type (NVT) pneumococci when they were 11 months old.

Results:

Of the 68 children who were re-sampled at the age of 46 months, 44 had carried a NVT pneumococcal serotype, including 6C, 11A, 16F, 19A, 23B, and 35F, at 11-month-of-age and were thus included in immune memory analysis. At the age of 46 months 28/68 children were colonized with a NVT, of which 16 were also carrier at 11-months-of-age but of a different serotype.

Conclusion

First we have identified children that carried non-vaccine-type pneumococci after PCV10 vaccination at different ages. In these children the induction and the role of serotype and protein specific antibodies and B-cell memory responses during and after mucosal colonization are currently being analyzed.

ISPPD-0480

A NOVEL LINK BETWEEN SUGAR METABOLISM AND CELL-TO-CELL SIGNALLING IN *S.PNEUMONIAE*

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Background and Aims:

A molecular switch transitions *S. pneumoniae* from asymptomatic colonizer to pathogen during nasopharyngeal colonization. In this environment, communication between bacterial cells is achieved through detection of chemical signalling molecules (autoinducers) in a quorum sensing (QS) mechanism. Our research has focused on characterising the Autoinducer-2 (AI-2)/LuxS QS system. We found that this system influence biofilm formation and exogenous AI-2 accelerate progression of disease in *S. pneumoniae*-infected mice. Central to this research has been the observation that AI-2-QS signalling is dependent on FruA and AI-2 enables pneumococci to utilize galactose by upregulating the Leloir pathway.
We have explored the possibility that AI-2 phosphorylated during FruA-mediated uptake in turn phosphorylates GalR, thereby activating the \textit{gal} operon.

**Methods:**

galR mutants were characterised phenotypically by assessing growth in CDM-Gal, expression of Leloir pathway genes by qRT-PCR and production of capsular polysaccharide.

**Results:**

\textit{S. pneumoniae} GalR has been reported to be phosphorylated at residues S317, T319 and T323. Substitution of all three residues with alanine (generating a non-phosphorylatable GalR-isoform) abrogated expression of Leloir pathway genes, and abolished capacity to grow in CDM-Gal. However, substitution of all three residues with aspartate (generating a phospho-mimetic GalR-isoform) did not restore growth capacity.

**Conclusion**

FruA-dependent, AI-2-mediated upregulation of the Leloir pathway is blocked when phosphorylation sites in GalR are mutated to Ala. However, substitution of all three sites with phospho-mimetic Asp did not result in constitutive expression of the pathway. These studies are being extended by analysis of single Ala and Asp substitution mutants and by direct detection of phosphorylated isoforms of GalR-AI-2.

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**ISPPD-0334**

**CD169+ MACROPHAGES AS A THERAPEUTIC TARGET DURING INVASIVE PNEUMOCOCCAL DISEASE**

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**Background and Aims:**

The pathogenesis of pneumococcal disease, includes an early, intracellular phase of bacterial replication in splenic CD169+ macrophages - a significant shift from the accepted paradigm. Here we report treatment of pneumococcal sepsis in mice, using a monoclonal antibody known to block CD169.

**Methods:**

Mice were infected intravenously (IV) with \textit{S. pneumoniae} D39. For blocking experiments, anti-CD169 mAb, or an isotype matched control were administered IV 15 minutes prior to infection. All experiments investigated signs of disease, blood counts and distribution of bacteria in the spleen by confocal microscopy.

**Results:**
Four hours following infection pneumococci were found to replicate in splenic macrophages of control mice, while mice pre-treated with antibody did not form foci of infection in CD169+ macrophages. Mice pre-treated with antibody, were less bacteraemic 24 hours post-infection, whereas all control mice developed disease. At the endpoint, significantly more mice in the mAb treated group were clear of cultivable bacteria in the blood, and spleen, whereas all control mice contained bacteria. Overall, mice treated with blocking antibody survived significantly better than control mice.

**Conclusion**

We conclude that CD169 is crucial to the pneumococcal-host interaction underpinning bacteraemia, and that modulation of this interaction may be employed as a therapeutic strategy.

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**ISPPD-0646**

**PNEUMOCOCCAL CLEARANCE BY MACROPHAGES SHOWS CIRCADIAN VARIATION**

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**Background and Aims:**

The pathogenesis of experimental sepsis by intravenous infection with *Streptococcus pneumoniae* is defined by early clearance of bacteria by splenic macrophages and concomitant replication within CD169+ macrophages from which invading bacteria then enter the bloodstream. As previous work had shown the impact of the circadian cycle on pneumococcal infection (Shackelford and Feigin, Science, 1973), we aimed to test if the refinement of our understanding the pathogenesis of infection could define the specific events under circadian control.

**Methods:**

Mice were infected intravenously with *S. pneumoniae* D39 either during the day or the night, and blood and spleen samples were taken at 6h, 24 and 72h. To test functionality of splenic macrophages, organotypic slice cultures were prepared from mouse spleens and supernatant samples were taken at 6h intervals. Cytokine analysis was performed using the Bio-Rad 23-plex-assay.

**Results:**

*In vivo* data showed at 6h hours after challenge higher pneumococcal counts in spleens of mice infected in the night with respect to mice infected in the day. This difference is indicative of impaired macrophage clearance in the spleen and correlated with a significant difference in survival. The day-infected mice with the lower bacterial counts showed at the 6h time point higher cytokine levels, with respect to night-infected mice. Cytokine analysis in organotypic slice cultures confirmed that cytokine production by cultured macrophages showed a circadian rhythm.

**Conclusion**
We conclude that circadian rhythm regulation of baseline macrophage activation and cytokine production influences significantly the susceptibility and outcome of pneumococcal infection.

ISPPD-0130
PNEUMOCOCCAL COLONIZATION ON THE HUMAN NASOPHARYNGEAL EPITHELIUM RESULTS IN HOST JUNCTIONAL-PROTEIN RECRUITMENT AND DIFFERENTIAL GENE EXPRESSION DEPENDENT ON BACTERIAL TRAFFICKING
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Background and Aims:
Colonization of the respiratory tract by Streptococcus pneumoniae is a prerequisite for invasive pneumococcal disease but our mechanistic understanding of this process is incomplete. We postulated that initial contact with the epithelial barrier is an important determinant of the outcome of colonization.

Methods:
We have used an Experimental Human Pneumococcal Carriage Model (EHPC) to visualize carriage of S. pneumoniae and related this to the pattern of bacterial trafficking to epithelial cell-derived responses. In vitro, pneumococcal adherence, invasion and transmigration assays were undertaken using Detroit 562 cells. Epithelial transcriptomes in response to pneumococcal challenge were analyzed by DESeq2, XGR and Ingenuity Pathway Analysis.

Results:
We found evidence of pneumococcal adherence and micro-colony formation at the epithelial cell surface, activation of innate signalling and junctional protein association in vivo. This was mirrored in vitro where the pattern of bacterial trafficking and bacterial replication appeared to dictate the shape of the epithelial-derived response. Pneumococcal-epithelial interactions in vivo and in vitro enhanced surface CD107a expression. In vitro this was associated with up-regulated pro-inflammatory IL-8 and IL-6 expression, and pneumolysin appeared critical for RIP-mediated NFKB activation, regulation of IFN signalling and cytokine signalling.

Conclusion
Pneumococcal colonization is associated with micro-colony formation and epithelial junction protein association. The pattern of pneumococcal interactions with the epithelium influences the human innate immune response, regulated in part by pneumolysin. How this response relates to bacterial clearance and the recruitment of both immune cells to the mucosal surface needs further investigation.
THE INFLUENCE OF B CELL DEPLETION THERAPIES ON THE SUSCEPTIBILITY TO STREPTOCOCCUS PNEUMONIAE INFECTIONS

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Background and Aims:

B cell depletion using monoclonal antibody to the B cell surface marker CD20 is an effective treatment for autoimmune diseases and B cell malignancies. However, how B cell depletion affects antibody responses to pathogens has not been investigated.

Methods:

We have investigated the effects of B cell depletion on natural IgM, colonisation and Prevnar mediated immunity to \textit{S. pneumoniae} using mouse models of infection in mice treated with anti-CD20, and in vitro assays of antibody responses.

Results:

B cell depletion reduced natural IgM recognition of \textit{S. pneumoniae} when measured by flow cytometry by >50% (p = 0.029), but did not increase susceptibility of naïve mice to \textit{S. pneumoniae} pneumonia. When measured by whole cell ELISA or flow cytometry IgG recognition of \textit{S. pneumoniae} was markedly reduced in sera from mice that were B cell depleted prior to nasopharyngeal colonisation with \textit{S. pneumoniae} or to vaccination with Prevnar compared to B cell replete mice. Furthermore, when challenged with \textit{S. pneumoniae} after reconstitution of total IgG to normal levels, previously B cell depleted mice had reduced colonisation or vaccination induced protection compared to controls (eg for Prevnar vaccination 58% of B cell depleted mice developed sepsis compared to 8% of controls).

Conclusion

In conclusion, these studies demonstrate that B cell depletion therapy can have strong negative impacts on antibody-mediated immunity to \textit{S. pneumoniae} which may predispose to respiratory infection. Future work will focus on the effects of different types of anti-CD20 antibody and the impact of the route of administration in this context.

SYSTEMATIC REVIEW OF PNEUMOCOCCAL CONJUGATE VACCINE (PCV) IMMUNOGENICITY IN INFANTS COMPARING PRODUCTS (PCV10 VS PCV13) AND SCHEDULES (2+1 VS 3+0)

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Background and Aims:

WHO recommends PCV10 or PCV13 for routine immunization programmes in all countries using 2+1 or 3+0 schedules. We sought to determine if product or schedule affect immunogenicity.

Methods:

We conducted a systematic literature review and meta-analysis of PCV10 or PCV13 serotype-specific immunogenicity using 2+1 or 3+0 regimens. We compared geometric mean concentration (GMC) of IgG antibodies and proportion of subjects responding (reaching the assay-specific correlate of protection (CoP)) after the primary series and after dose 3.

Results:

Schedule Comparison: While 3 primary doses induced higher GMCs than 2 primary doses, the third dose was more immunogenic for all serotypes except 3 and 19A when given as 2+1 than as 3+0. The proportion responding was similar by serotype, although 3+0 was superior after primary immunization for 6A, 6B and 23F and 2+1 was superior after dose 3 for 6B.

Product Comparison: Product preference depended on serotype and schedule. For shared serotypes, the proportion responding was similar between products; for GMCs, PCV13 was superior for serotypes 6B and 23F regardless of schedule and serotypes 1 and 7F in 2+1, while PCV10 was superior only in 3+0 for 5 and 19F. For serotypes 3, 6A and 19A (only in PCV13), PCV13 had superior GMCs and percent responding, irrespective of schedule.

Conclusion

Schedule preference depends on whether greater immunogenicity is important early in infancy (3+0 better) or later (2+1 better). Differences between the vaccines were schedule dependent for shared serotypes, but PCV13 was better than PCV10 for serotypes only in PCV13.

ISPPD-0528
PERSISTENCE OF HUMORAL IMMUNITY TO VACCINE-RELATED AND VACCINE SEROTYPES IN FINNISH CHILDREN AFTER IMMUNIZATION WITH 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10)
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Background and Aims:
The clinical impact of PCV10 on invasive pneumococcal disease (IPD) in Finnish children has been evaluated after its introduction into the national vaccination programme in 2010. Compared with reference cohort the incidence rate of IPD due to vaccine-related serotypes 6A and 19A has decreased in vaccine-eligible children <24 months of age, but not to serotype 19A in children ≥ 24 months of age. This study aimed to investigate whether the observed age-related waning of protective immunity against serotype 19A could be related to persistence of circulating antibody levels.

Methods:

The study cohort consisted of 186 children born in 2008-2010 in the Hospital District of Southwest Finland and who participated in the Steps to the Healthy Development and Well-being of Children study. The children had received PCV10 with either 2+1 or 3+1 schedule in the Finnish Invasive Pneumococcal Disease (FinIP) Vaccine Trial, conducted in 2009–2012. IgG against pneumococcal capsular polysaccharides of vaccine and vaccine-related serotypes 6A and 19A were measured in post-vaccination serum samples collected at the ages of 13 (N=28-42), 24 (N=63-69), and 36 months (N=54-68) by multiplex immunoassay. Results were expressed as geometric mean concentrations GMC (µg/ml).

Results:

Conclusion

During the follow–up from 13 to 36 months of age the GMCs of antibodies to vaccine-related serotypes 6A and 19A remained at the same level, and were in the same ranges after the 2+1 and 3+1 vaccination schedules.

ISPPD-0721
EXPLORING IMMUNOLOGICAL ASSAYS TO ASSESS RESPONSES TO PNEUMOCOCCAL POLYSACCHARIDE AND CONJUGATE VACCINES IN HIV
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Background and Aims:

Assessing responses to pneumococcal (Pn) vaccination is important in determining immunogenicity. The aim of this project was to qualify and compare the whole vaccine and
serotype IgG subclass response to the pure polysaccharide vaccine Pneumovax-23® (PPV-23) and polysaccharide-protein conjugate vaccine, Prevenar-13® (PCV-13).

Methods:

Multiplexed Luminex assays measured total IgG and IgG1-4 Pn-serotype specific antibodies in patient sera to 11 Pn serotypes and PPV-23 and PCV-13 vaccine conjugated beads in an HIV-infected cohort at the University Hospitals Birmingham.

Pn-specific values were assigned to IgG1 and IgG2 for the reference serum 007sp from 89-SF.

Results:

PPV-23 vaccination produced proportionally higher IgG2 responses than IgG1, IgG3 or IgG4. PCV-13 vaccination produced equivalent IgG1 and IgG2 responses followed by lesser IgG3 and the IgG4 responses. IgG3 responses were proportionately higher in the PCV-13 than PPV-23 cohorts. The Pn-specific IgG4 responses were limited for both the PPV-23 and PCV-13 cohorts. Whole PPV-23 and PCV-13 beads performed well in ROC analysis with the Pn-specific serotype IgG assays. This may offer a cheaper test but lacks the detail of serotype diversity.

Conclusion

This study has demonstrated differences in IgG subclass responses to PPV-23 and PCV-23 vaccines which challenges previous thinking that a plain polysaccharide response is predominantly IgG2 and conjugate vaccine IgG1. New serotype specific assays demonstrate that responses to individual serotypes vary widely between vaccines, however, this granularity cannot be visualized in combined serotype assays.

ISPPD-0379
PRELIMINARY ASSIGNMENT OF SEROTYPE SPECIFIC IgA VALUES TO 007sp

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Background and Aims:

A new pneumococcal reference serum for laboratory use (007sp) was established in 2011. Serotype specific IgG assignments have been published [1-3] but no IgA values have been assigned. We undertook preliminary assignment of serotype specific IgA levels by cross-assignment from the previous standard, 89SF.

Methods:

89SF and 007sp were run side by side with 007sp as the unknown a minimum of 40 times and values (micrograms/ml) were derived for serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. The antibody concentrations were estimated using a linear mixed-effects ANOVA model after natural log transformation. Confidence intervals (95% CI) were estimated using the variance components.

Results:
Binding curves for 007sp exhibited good parallelism and reproducibility with the 89SF standard curves permitting the assignment of serotype specific values. Figure 1 illustrates the serotype specific IgA level in 007sp compared to the original assignments in 89SF.

**Conclusion**

Increasing interest in mucosal mechanisms for inhibiting NP carriage suggests that measuring serotype specific IgA may be of importance in the future. This study assigns preliminary values for IgA to 007sp. We also attempted to assign IgM values but 007sp IgM exhibited non-parallelism to 89SF precluding assignment of values


**ISPPD-0201**

**AUTOMATED COUPLING OF PNEUMOCOCCAL POLYSACCHARIDES TO BEADS FOR USE IN A MULTIPLEX ASSAY**

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**Background and Aims:**

Quantification of *Streptococcus pneumoniae* serotype-specific IgG concentrations is needed in the clinical setting for patient management, in particular those with immunodeficiency’s, as well as for clinical trials. Bead-based multiplex assays can be used to determine the serological immune responses to pneumococcus. One of the biggest constraints for pneumococcal bead assays is the conjugation of polysaccharide to bead, which is an intensive and lengthy process. The ThermoFisher Scientific Kingfisher Flex system offers...
automatic, plate-based handling of magnetic beads which could provide a hands-off way to conjugate polysaccharide to bead.

**Methods:**

Pneumococcal polysaccharides for serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F were conjugated to poly-l-lysine, a linker molecule, and then to Magplex microspheres using the manual in-house method or the Kingfisher Flex. Following conjugation, beads were analysed using a Bioplex system and Bioplex Manager software.

**Results:**

A protocol mirroring the manual in-house protocol was built on the Kingfisher with two changes: centrifugation and orbital shaking were done in the Kingfisher using the medium and slow speeds, respectively. All 12 serotypes were successfully conjugated to Magplex beads using the Kingfisher and results were comparable to manually conjugated beads ($R^2$ range from 0.9792 (Pn7F) to 0.9997 (Pn5)).

**Conclusion**

The Kingfisher Flex system is faster and easier than manual conjugation when conjugating pneumococcal polysaccharide/poly-l-lysine to Magplex beads. Automation of this process will have a significant impact on assay throughput and will decrease the turnaround times for results which could positively impact on patient management.

**ISPPD-0166**

**PNEUMOCOCCAL STRAIN ΔPEP27 IMMUNIZATION CONFERS RESPIRATORY COLONIZATION RESISTANCE VIA NON-CANONICAL WNT SIGNALING AND IL-17A PATHWAYS**

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**Background and Aims:**

Dysregulation in microbial composition causes colonization resistance capacity as a result of antibiotic resistant strains, allowing infection by opportunistic pathogens. Respiratory pathogens use specific virulence mechanism as a diverse factor to subvert colonization resistance by triggering inflammation. Thus intrusions to prevent colonization present a new platform as preventive and therapeutic targets. Being known that Δpep27 reduced the bacterial burden serotype independently and conferred broad protection against *Streptococcus pneumoniae* with higher IL-17 induction. Thus, we suggest that harnessing Th17 immune response in the mucosal compartment is an effective strategy to mediate an effective respiratory vaccine. However, the underlying mechanism that triggers the Th17 immune response via mucosal vaccine remains unknown.

**Methods:**

Balb/c mice immunized intranasally with pep27 mutant were characterized by configuring molecular biological techniques using real-time PCR and western blot analysis based on the sequence diversity of the bacterial genomic expression.

**Results:**
In the present study, we confirmed that Δ
pep27 immunization provides non-specific colonization resistance in the lung via induction of non-canonical Wnt and subsequent interleukin (IL)-17 secretion. RNA-sequencing and quantitative real-time PCR (qPCR) analyses of Δ
pep27 immunized mouse lungs signified the induction of non-canonical Wnt signaling. In addition, Δ
pep27 immunization activated nuclear factor of activated T cell (NFAT) and induced IL-17A secretion, thus inhibiting S. pneumonia, Staphylococcus aureus and Klebsiella pneumoniae. Moreover, IL-17 neutralization or NFAT inhibition impaired bacterial colonization, indicating that non-canonical Wnt signaling is involved in pulmonary colonization resistance.

Conclusion

Δ
pep27 immunization can provide respiratory colonization resistance via non-canonical Wnt signaling and IL-17A pathways.

ISPPD-0098
A NEW SERUM PANEL FOR CALIBRATING PNEUMOCOCCAL OPSONOPHAGOCYTIC ASSAYS FOR 11 NON-PCV13 SEROTYPES
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Background and Aims:
Incidence of invasive pneumococcal diseases caused by 11 non-PCV13 serotypes and non-PPV23 serotypes has increased recently. Changes in serotype prevalence may be caused by serotype replacement and capsular switching. Multivalent vaccines against more than 13 serotypes are under development. To assess the immunogenicity of these vaccines, opsonophagocytic assay (OPA) are needed. Moreover, sera with known OPA values will be useful for assay calibration. There is no available serum panel for 11 non-PCV13 serotypes. Therefore, we developed a new Ewha QC Serum Panel B in this study.

Methods:
Serum samples from healthy adults with PPV23 vaccination were lyophilized and aliquoted into >150 vials per serum. The new panel comprises 20 serum samples (21-40). Multiplexed OPA was performed 5 times for 20 calibration serum samples and 15 times for standard serum 007sp.

Results:
Geomean opsonic indices and 95% confidence interval were determined for each calibration serum sample and 007sp for 11 serotypes (Figure
Conclusion

An international collaborative study will be conducted to determine consensus values for the 11 serotypes. The Ewha QC Serum Panel B will help calibrate pneumococcal OPAs. The serum samples can be obtained by contacting either Kyung-Hyo Kim (kaykim@ewha.ac.kr).

ISPPD-0465
IMMUNOMODULATORY EFFECTS OF VITAMIN D ON THE HOST INFLAMMATORY RESPONSE
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Background and Aims:

Vitamin D (vitD) has a number of important biological effects, particularly on the immune system. Epidemiological evidence suggests that low vitD levels are associated with an increased risk of respiratory infection. We aimed to examine the immunomodulatory effects of vitD in the context of bacterial and viral infection.

Methods:

Healthy adults (N=12) were recruited into the study and blood samples collected into heparinised tubes. Peripheral blood mononuclear cells (PBMCs) were isolated and stimulated with heat-killed pneumococcal bacteria (serotype 19F, HK19F), pneumococcal whole cell antigen (WCA), respiratory syncytial virus (RSV) or co-stimulated with WCA-RSV in the presence or absence of vitD. Expression of key surface markers on lymphoid cells and cytokine secretion was measured.

Results:

VitD reduced IL-17A production (p=0.001) and the number of Th17 cells (p=0.016) in response to WCA stimulation. IFN-γ and IL-22 were also reduced (p=0.001) while IL-10 was increased by vitD (p=0.001). A similar effect was observed for HK19F. In the context of RSV and pneumococcal-RSV co-stimulation assays, significantly higher levels of cytokines (IL-6, IFN-γ, TNF-α) were detected compared to stimulation with either pathogen alone. VitD reduced IFN-γ (p=0.002), IL-6, IL-8 and TNF-α levels in PBMC supernatants (p=0.001) as well as modulated the expression of TLR2, TLR4 and TLR7 in the context of bacterial and/or viral challenge.

Conclusion

VitD can modulate the host response following stimulation with pneumococcal and/or RSV. Further studies are needed to fully characterise the role of vitD in maintaining protection against bacterial and viral infection.

ISPPD-0498
PREDICTORS OF NON-RESPONSE TO THE 7-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY FIJIAN INFANTS

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Background and Aims:

While pneumococcal conjugate vaccines (PCVs) are highly immunogenic, effectiveness varies across populations. Understanding predictors of poor immunological responses to PCVs may inform which vaccinated children may experience increased risk of pneumococcal
disease. This post-hoc analysis describes the predictors of non-response to the 7-valent PCV (PCV7).

Methods:

Demographic, pneumococcal nasopharyngeal carriage and immunological data from a phase 2 randomised controlled trial of Fijian infants receiving 0, 1, 2, or 3 doses of PCV7 in the first year of life was used in a univariate and multivariable model to identify predictors of non-response to PCV7 at 12 months of age. Non-response was defined as inadequate responses to at least 4 vaccine serotypes, measured using serotype-specific correlates of protection for both immunoglobulin G (IgG) and opsonophagocytic indices (OI).

Results:

In 364 infants, receiving a single PCV7 dose and being of indigenous Fijian descent was highly predictive of non-response by IgG (aOR 3.59, 95%CI: 1.79-7.18; \( p < 0.001 \)) and OI (aOR 1.94, 95%CI: 1.14-3.30; \( p = 0.014 \)). Receiving 2 doses predicted non-response by OI only (aOR 2.02, 95%CI: 1.16-3.46; \( p = 0.011 \)), whilst being male predicted non-response only by IgG (aOR 1.83, 95% CI: 1.07-3.14; \( p = 0.028 \)).

Conclusion

These results suggest that indigenous infants who receive fewer than three doses of PCV in infancy may not be fully protected from pneumococcal disease. In the context of exploring reduced-dose PCV schedules (1+1), indirect protection is crucial for maintaining individual protection, particularly for children living in high transmission settings, and perhaps those of certain ethnic groups. Further research on the predictors of PCV non-response is needed.

ISPPD-0090

ALVEOLAR T-HELPER 17 RESPONSES TO STREPTOCOCCUS PNEUMONIAE ARE PRESERVED IN ART-UNTREATED AND TREATED HIV-INFECTED MALAWIAN ADULTS

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Background and Aims:

HIV-infected adults are at an increased risk of pneumococcal pneumonia than their HIV-uninfected counterparts. Alveolar T helper 17 cells have been shown to be critical in conferring protection in murine models of pneumococcal lung infection. We therefore explored whether chronic HIV infection is associated with impaired Th17 responses against Streptococcus pneumoniae in the lung.

Methods:
We recruited 30 HIV-uninfected healthy controls, 23 asymptomatic HIV-infected adults not on ART, and 40 asymptomatic HIV-infected adults on ART (Median time 3.5yrs), in whom we collected bronchoalveolar lavage fluid. We measured alveolar CD4+ T cell immune responses following stimulation with pneumococcal cell culture supernatant (CCS) using flow cytometry-based intracellular cytokine staining.

Results:

We found that the proportion of alveolar CD4+ T cells producing IL-17A following stimulation with pneumococcal CCS was similar between HIV-uninfected controls and ART-naïve HIV-infected adults (0.10% vs. 0.14%; p=0.9273). In contrast, the proportion and relative absolute counts of CD4+ T cells producing IL-17A in response to pneumococcal CCS were higher in ART-treated HIV-infected adults compared HIV-uninfected controls (0.22% vs. 0.10%, p=0.0166; 5420 vs. 1902 cells/100ml BAL fluid; p=0.0519). The increase in relative absolute numbers of IL-17A-producing alveolar CD4+ T cells in ART-treated individuals was not correlated with the peripheral blood CD4+ T cell count (r=-0.1876, p=0.1785).

Conclusion

Alveolar Th17 responses against *S. pneumoniae* are preserved in HIV-infected adults. This suggests that there are other mechanisms that render HIV-infected individuals more susceptible to pneumococcal pneumonia.

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**ISPPD-0056**

**THE INFLUENCE OF AGE ON ANTI-PNEUMOCOCCAL PROTEIN ANTIBODY LEVELS**

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**Background and Aims:**

*Streptococcus pneumoniae* is a leading cause of respiratory infections and invasive diseases. Children and elderly are most susceptible for severe pneumococcal infections. One of the most important mechanisms to protect against infection is the humoral immune response. In this study, we measured the humoral immune response against pneumococcal proteins to see if differences in antibody levels against proteins can explain susceptibility of certain age groups.

**Methods:**

Serum and saliva samples were collected from healthy 11-month-old children (n=100), 24-month-old children (n=100), parents of young children (n=100), adults without young children (n=100) and elderly (n=100). IgG and IgA levels were measured using an unencapsulated pneumococcal ELISA.

**Results:**

Eleven-month-old children had the lowest IgG and IgA antibody levels in serum and saliva. This level was increasing in 24-month-old children. Parents had the highest antibody levels, whereas adults and elderly had comparable amounts of antibodies. Antibody levels were correlated with daycare attendance and presence of siblings, suggesting that antibodies against pneumococcal proteins are a good measure for exposure. Antibody levels do not show a strong decrease in the elderly. However, preliminary Western blot data suggest that...
elderly have a different antibody profile against pneumococcal proteins than adults, more comparable with the profiles seen in children.

Conclusion

In conclusion, young children have low pneumococcal protein antibody levels, which might explain their higher susceptibility for \textit{S. pneumoniae}. Elderly had antibody levels comparable to adults, indicating that other factors are responsible for a higher susceptibility. The specificity, avidity and functionality of their antibodies will be investigated.

**ISPPD-0267**

SYSTEMS BIOLOGICAL ANALYSIS OF ANTIBODY RESPONSES IN THE ELDERLY AFTER RECEIVING PNEUMOCOCCAL POLYSACCHARIDE AND CONJUGATE VACCINES

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\textsuperscript{4}Emory University and Stanford University, Emory Vaccine Center & Stanford Pathology- and Microbiology & Immunology, Atlanta & Stanford, USA

Background and Aims:

Understanding the immunological determinants of the magnitude and persistence of pneumococcal immunity in the geriatric population is crucial to determine the optimal vaccination strategy.

Methods:

Subjects between the ages of 60-89 years, naïve to prior pneumococcal vaccination, were randomized to receive either PPSV23 or PCV13. Circulating IgG, IgM, and IgA antibody titers to all PCV13 and PPSV23 serotypes were measured by Luminex before and 1, 6 and 24 to 36 months after vaccination. High dimensional flow cytometric analysis of the innate immune response to vaccination and an analysis of the transcriptional signatures induced by vaccination were performed. Additional pneumococcal vaccinations were allowed after the 6 month visit per current ACIP guidelines.

Results:

Of 66 subjects, 59 had serology performed at 24 to 36 months. Only 35% (21/59) of subjects had received additional pneumococcal vaccines. A detailed analysis of the magnitude and persistence of binding antibody titers and opsonophagocytic titers following vaccination was performed. Ongoing analysis is aimed at assessing molecular signatures of vaccination that correlate with, and predict the magnitude and persistence of, antibody responses to vaccination.

Conclusion

Pneumococcal vaccination induces robust antibody titers and significant innate immune responses. Definition of the early molecular correlates of the antibody response is currently in progress.
ISPPD-0234

NO HYPORESPONSIVENESS TO SEROTYPE 3 WITH REPEATED DOSES OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV) – AN ANALYSIS OF 9 PEDIATRIC CLINICAL TRIALS

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Background and Aims:

Post-licensure studies in children have reported varying degrees of PCV13 effectiveness against invasive pneumococcal disease (IPD) caused by *Streptococcus pneumoniae* serotype 3 in vaccinated individuals and some have reported limited herd effect for serotype 3 in the 2-6 years following PCV13 introduction. We examined the immune response to serotype 3 across nine pediatric studies to determine if the observed effect of PCV13 on serotype 3 IPD epidemiology was due to hyporesponsiveness, a concern raised by lower IgG geometric mean concentrations seen after the booster dose in some studies.

Methods:

We calculated the geometric mean fold rise (GMFR) of opsonophagocytosis assay (OPA) titers from after the primary series to post-booster dose in the 9 pediatric clinical studies for which paired OPA data were available. The studies were conducted in the United States, Europe or Asia and assessed PCV13 or control in a 2+1 or 3+1 regimen (see Figure).

Results:

The GMFR from one-month post-primary series to one month post-booster dose and 95% CI are shown in the figure. A booster response to serotype 3 was observed in 9 out of 11 analyzed groups from the 9 included pediatric studies. In these studies, serotype 3 GMFRs were within the range seen for some other PCV13 serotypes.

<table>
<thead>
<tr>
<th>Study #</th>
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<tr>
<td>2</td>
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</table>

Figure. Geometric Mean Fold Rises from one-month post-infant series to one month post-booster dose and 95% CI. *In study 7, infants were randomized to receive PCV13 in one of 3 dosing regimens.
Conclusion

These data show no evidence of hyporesponsiveness to *S. pneumoniae* serotype 3 following administration of multiple doses of PCV13.

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**ISPPD-0103**

**REVERSE IMMUNOLOGY AS A TOOL TO IDENTIFY BROADLY RECOGNIZED PNEUMOCOCCAL PROTEINS TARGETED BY HUMAN T-CELLS**

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**Background and Aims:**

To understand the mode of action of future universal protein-based pneumococcal vaccines T-cell mechanisms, which are implied in protection against pneumococcal colonization, should be unraveled. In contrast to high-throughput protein arrays for serology, basic antigen tools for T-cell studies are not available yet. Here we apply reverse immunology to predict and verify broadly recognized human T-cell epitopes for a semi-large array of pneumococcal proteins.

**Methods:**

Hundred pneumococcal proteins of diverging subcellular localization were selected for *in silico* prediction of T-cell immunogenicity based on HLA-DR binding and absence of cross-reactivity against human proteins (Epivax). For 20 potentially T-cell immunogenic proteins, peptides predicted to bind >4 of 8 common HLA-DRB1 alleles were synthesized, pooled per protein and tested in T-cell assays using PBMCs from a panel of healthy adults and (ex-) pneumococcal pneumonia cases.

**Results:**

Peptide pools of 19/20 proteins evoked T-cell responses in healthy adults. Most frequent responses (in ≥ 25% of 20 donors tested) were found for SP_0117 (PspA), SP_0468 (putative sortase), SP_0546 (BlpZ), SP_1650 (PsaA), SP_1923 (pneumolysin), SP_2116 (PcsB), and SPR_0907 (PhtD). Healthy adults and cases had diverging patterns of protein immunodominance and cytokine profiles (IFNg, TNFa, IL-13 and IL17A) against single peptides.

**Conclusion**

We demonstrated proof of principle for a reverse immunology approach to screen human pneumococcus specific T-cell responses at a semi-large proteome scale. Currently in depth T-cell analyses are ongoing in pneumococcal carriers and (ex-) cases of various age groups to further understand the specificity and mechanistic role of naturally acquired T-cell immunity to pneumococcal proteins.
INDIGENOUS POPULATIONS WORLD-WIDE

ISPPD-0321
IMPACT OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE AND PREDICTORS OF PNEUMOCOCCAL CARRIAGE IN WESTERN AUSTRALIAN ABORIGINAL PEOPLE
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2Telethon Kids Institute, Wesfarmers Centre of Vaccines & Infectious Diseases, Perth, Australia
3Charles Darwin University, Menzies School of Health Research, Darwin, Australia
4PathWest Laboratory Medicine WA, Division of Microbiology & Infectious Diseases, Perth, Australia

Background and Aims:
In 2011 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 in Western Australia (WA); however invasive pneumococcal disease rates have remained high in Aboriginal people. Since PCVs alter the distribution of pneumococcal serotypes carried in the nasopharynx, we assessed the impact of PCV13 on carriage, emerging serotypes, and risk factors for carriage.

Methods:
Between 2008 and 2014 we collected nasopharyngeal swabs (NPS) and demographic, health and environmental information from Aboriginal people across WA. 1500 pre-PCV13 and 1385 post-PCV13 NPS were cultured and pneumococcal isolates serotyped by Quellung reaction. Risk factors for pneumococcal carriage were analysed by logistic regression.

Results:
Pneumococcal prevalence was 67% among under-5s and 53% among 5-14-year-olds post-PCV13, compared with 72% and 49% pre-PCV13. PCV13-nonPCV7 serotype prevalence decreased from 14% to 6% in under-5s (p<0.01) and from 8% to 6% at 5-14 years (p>0.05). Among under-5s, the top 25% serotypes pre-PCV13 were 6C, 19A, 16F compared to 11A, 16F and 15B post-PCV13.

Risk of pneumococcal carriage increased with increasing age until 12 months (OR 4.19, 95% CI 2.39-7.33), with nasal discharge (OR 2.49, 2.00-3.09), remote location (OR 2.21, 1.67-2.92) and household crowding (OR 1.36, 1.11-1.67). Recent antibiotic use reduced risk of carriage (OR 0.48, 0.33-0.69). Isolates of serotypes 19A (6%), 19F (2%) and non-serotypeable isolates (2%) were resistant to penicillin. Isolates of serotypes 23F and 7B were frequently resistant to cotrimoxazole, erythromycin and tetracycline (82-87% for 23F, 93-100% for 7B).

Conclusion
Carriage of PCV13-nonPCV7 serotypes decreased in children post-PCV13 introduction. Crowding and young age remain risk factors for carriage in Aboriginal people.
A DESCRIPTIVE STUDY OF A SEROTYPE 1 SEQUENCE TYPE 306 INVASIVE PNEUMOCOCCAL DISEASE OUTBREAK IN THE AUSTRALIAN INDIGENOUS POPULATION

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⁴National Centre for Immunisation Research & Surveillance, Discipline of Paediatrics and Child Health, Sydney, Australia
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Background and Aims:

Serotype 1 (ST1) invasive pneumococcal disease (IPD) is rare in Australia. An outbreak of ST1 IPD occurred between 2010 to 2013 primarily in remote locations of Northern and Central Australia. Both conjugate and polysaccharide pneumococcal vaccines were in use with some limitations at the time. Here we describe the outbreak and the response.

Methods:

Descriptive analysis using nation-wide surveillance data for 2003-2014 and more detailed state-based data for outbreak region and timeline identification. Molecular characterisation was provided by Queensland Health. Real-time multi-jurisdictional teleconferences were conducted. In addition to promoting routine pneumococcal vaccines, outbreak response vaccination strategies were adopted in some areas.

Results:

The identified outbreak-regions included Western Australia, Northern Territory and parts of Queensland where ST1 increased from 2% of all IPD to over 18% during 2010-2013 (n=245). During 2011, the ST1 incidence rate ratio was 30.7 in the outbreak-regions compared to the remainder of Australia. 76% of outbreak cases were Indigenous with a median age of 15 years. The most common presentation was pneumonia and overall mortality was low. Where vaccination information was recorded, 26% of cases had received polysaccharide vaccine within the previous 5 years. No children fully vaccinated with a ST1-containing conjugate vaccine developed IPD.

Conclusion

The ST1 IPD outbreak primarily affected a vulnerable Indigenous population in Australia. Real-time inter-jurisdictional collaboration was useful in monitoring natural progression of the outbreak and considering possible interventions. ST1-containing conjugate vaccines provided protection against ST1 disease in children. Developing specific vaccine recommendations to apply in outbreak situations would help better manage such outbreaks.
Background and Aims:

Australia introduced 7-valent pneumococcal conjugate vaccine (7vPCV) for Indigenous infants in 2001, replaced by 13vPCV in 2011. Funding of the 23-valent pneumococcal polysaccharide vaccine (23vPPV) for Indigenous at-risk groups was progressively expanded from 1986, including all Indigenous adults 50+ years from 2000. This study examines the epidemiology of invasive pneumococcal disease (IPD) in Indigenous Australians.

Methods:

Analyses were performed on IPD notifications collected through the National Notifiable Diseases Surveillance System from 2002 to 2016. 2,835 (10.75%) of 26,381 cases were reported as Indigenous. Serotype data was available for 94% of these cases.

Results:

Between 2002 and 2016 IPD incidence decreased in Indigenous children and increased in Indigenous 50+ adults. There was an outbreak of serotype 1 in 2011-2012 which decreased following introduction of infant 13vPCV. In 2016, 71% of IPD in the Indigenous population was due to non-PCV serotypes.
Conclusion

IPD remains a significant health burden for the Indigenous population despite vaccination programs. IPD incidence in those aged 50+ years has steadily increased over the past decade. Non-PCV serotypes currently account for the greatest proportion of disease.

ISPPD-0699
SEROTYPE-SPECIFIC PNEUMOCOCCAL COLONIZATION PREVALENCE AND DENSITY AMONG AMERICAN INDIANS IN THE PCV13 ERA USING PCR AND MICROARRAY

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²Centers for Disease Control and Prevention, Arctic Investigations Program, Anchorage, USA
³St. George’s- University of London, Institute for Infection and Immunity, London, United Kingdom
⁴London Bioscience Innovation Centre, BUGS Bioscience, London, United Kingdom

Background and Aims:
Molecular methods may offer new insight into vaccine-related, serotype-specific changes in pneumococcal colonization prevalence and density in the PCV-use era.

Methods:
A cross-sectional study from January 2010-March 2012 evaluated the impact of a PCV7-to-PCV13 switch (in March 2010) on NP colonization prevalence among American Indians. A random sample of 1177 NP swabs from children <5y (N=586) and adults ≥18y (N=591) were selected from pre-PCV13 (N=194 <5y, N=197 ≥18y), Year-1 post-switch (N=197 <5y, N=198 ≥18y) and Year-2 post-switch (N=195 <5y, N=196 ≥18y). Swabs underwent broth enrichment culture and lytA qPCR (Ct <40 considered positive). Microarray was performed on plate sweeps of culture(+) and/or qPCR(+) STGG following a culture step. Mean colonization density (the number of DNA copies relative to a standard curve expressed as log₁₀ copies/mL) was compared across periods.

Results:
There were 356 (30%) culture(+) swabs and 417 (35%) lytA qPCR(+) swabs. A microarray serotype result was available for 75% (346/459) of swabs positive by either method. Mean densities were higher for culture(+) vs. culture(-) swabs (children: 8.4 vs. 7.6; adults: 7.9 vs. 7.2, p<0.01 for both) and for microarray(+) vs. microarray(-) swabs (children: 8.4 vs. 7.7; adults: 7.9 vs. 7.1, p<0.01 for both). Mean pneumococcal densities were similar pre- vs post-switch for adults and children (p≥0.05). Among culture(+) and/or microarray(+) participants, mean PCV13-type densities were similar pre- vs post-switch in children and adults (p≥0.05).
Conclusion

Culture(+) and microarray(+) swabs have higher density than culture(-) and microarray(-) swabs. Residual PCV13-type carriage is of similar density compared to pre-PCV13.

Background and Aims:

Streptococcus pneumoniae colonization of the nasopharynx is common in young children and is a pre-requisite for pneumococcal disease. Nasopharyngeal colonization is an important key to the burden of pneumococcal disease and its prevention limits spread of pneumococci. Our study investigated nasopharyngeal carriage of S. pneumoniae and three other commonly carried pathogens (Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus) in healthy children in Central Lombok, West Nusa Tenggara, prior to introduction of pneumococcal vaccination program in Indonesia.

Methods:

This cross-sectional study was carried out in 2016 among 101 healthy children aged 12-24 months living in urban and semi-rural communities. Nasopharyngeal swabs were collected according to WHO recommendations, and bacteria were detected by real-time quantitative PCR. Pneumococcal serotyping was conducted by microarray, with a representative isolate also typed by latex agglutination/Quellung.

Results:

The pneumococcal carriage prevalence of study subjects was 50.5% (51/101), with 52.9% (27/51) in urban and 47.1% (24/51) in semi-rural children. The most common pneumococcal serotypes in descending order were 6A, 6B, 23F, 15B/C, and nonencapsulated pneumococci. Of a total of 53 pneumococci identified, 28 (53%) belonged to PCV13 serotypes. The carriage prevalence of other colonizing pathogens was 25/101 (25.7%) for H. influenzae, 52/101 (51.5%) for M. catarrhalis, and 7/101 (6.9%) for S. aureus.
This study provides important baseline data on S. pneumoniae carriage prior to the large-scale introduction of a pneumococcal vaccination program in Indonesia. In Lombok, approximately half of young children carry pneumococcus, and PCV13 serotypes are common.

ISPPD-0247

SHOULD HIGH RISK INFANTS RECEIVE A 4-DOSE EARLY COMBINATION SCHEDULE OF 10-VALENT PNEUMOCOCCAL HAEMOPHILUS INFLUENZAE PROTEIN D CONJUGATE VACCINE PLUS PREVENAR13? PREV-IX_COMBO a RCT.

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⁹Northern Territory Dept Health, Center for Disease Control, Darwin, Australia
¹⁰Royal Darwin Hospital, Paediatrics, Darwin, Australia

Background and Aims:

Otitis media (OM) commences within weeks of birth and persists throughout childhood in almost all Aboriginal infants living in remote areas of the Northern Territory (NT). Non-typeable Haemophilus influenzae (NTHi) and Streptococcus pneumoniae are major pathogens.

Methods:

Eligible Aboriginal infants were allocated (1:1:1) at 28 to 38 days of age, to i) Synflorix™ at 2,4,6 months (SSS), ii) Prevenar13™ at 2,4,6 months (PPP), or iii) Synflorix at 1,2,4 months plus Prevenar13 at 6 months (SSSP).

Results:

In groups i, ii and iii we had 68, 71 and 66 sera at 2 months, 65, 58 and 66 at 4 months, and 117, 115 and 120 at 7 months, respectively. Early vaccination provided superior above threshold GMCs at 2 and 4 months of age (Figures 1 and 2). At 7 months the SSSP schedule achieved superior or equivalent GMCs to all serotypes other than 6A (Figure 3). 

HiD assays are ongoing.
Pneumococcal immunogenicity of the early combination schedule (SSSP) was superior overall to standard schedules (SSS or PPP), other than for 6A. Of note, the SSSP group had superior GMCs for serotypes 3, 6B, 19F and 23F. Determination of overall superiority awaits results of anti-HiD assays.

**Conclusion**

Pneumococcal immunogenicity of the early combination schedule (SSSP) was superior overall to standard schedules (SSS or PPP), other than for 6A. Of note, the SSSP group had superior GMCs for serotypes 3, 6B, 19F and 23F. Determination of overall superiority awaits results of anti-HiD assays.

**ISPPD-0759**

CHARACTERISTICS OF STREPTOCOCCUS PNEUMONIAE CARRIAGE ISOLATES RECOVERED FROM GUARANI INDIGENOUS CHILDREN LIVING CLOSE TO A MAJOR URBAN AREA IN THE SOUTHEAST REGION OF BRAZIL

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²Fundação Oswaldo Cruz, Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil
Background and Aims:

Indigenous people are at increased risk of pneumococcal diseases, and monitoring of pneumococci circulating in their communities is of high importance to assess the impact of pneumococcal conjugate vaccines.

Methods:

Forty-eight pneumococcal isolates recovered from the nasopharynx of asymptomatic Guarani children (up to 5 years old) living in villages in the Southeast region of Brazil, before the introduction of PCV10 in the national immunization program, were analyzed. Capsular types, antimicrobial susceptibility profiles and MLST genotypes were determined.

Results:

The most frequent serotypes were 6C and 19A (twelve isolates each), followed by 15C (eight) and 6B (three). The most common genotypes were ST3930 (comprising all serotype 6C isolates) and ST733 (comprising ten serotype 19A isolates). Three genotypes included more than one serotype: ST6349 (four 15C isolates and one each of 15B, 19A and 23F), ST338 (three 15C isolates and one 24F), and ST387 (two 23B and one 23F); suggesting capsular switching events. Ten (20.83%) isolates were penicillin nonsusceptible (MIC ranging from 0.12 to 2 μg/ml), and they were represented by ST387 (serotypes 23B and 23F), ST338 (serotypes 15C and 24F), ST6350 (serotype 14), ST2878 (serotype 19A), ST6349 (serotype 19A) and ST7076 (serotype 6B). Nine ST (comprising 27 isolates) represented clones only detected in Brazil, including the predominant genotype identified (ST3930); and five of them (encompassing 12 strains) were described here for the first time.

Conclusion

The indigenous investigated represent a peculiar population regarding distribution of pneumococcal serotypes and clones, showing a high occurrence of novel and regional genotypes as well as of non-vaccine serotypes.

ISPPD-0039

ANALYSIS OF STREPTOCOCCUS PNEUMONIAE BACTERAEMIC CASES WITH VIEW OF EPIDEMIOLOGY AND CO-MORBIDITIES ASSOCIATED WITH INVASIVE PNEUMOCOCCAL DISEASES IN A TERTIARY CARE CENTER, SRI LANKA


1Teaching Hospital Karapitiya, Microbiology, Galle, Sri Lanka

Background and Aims:

Pneumococcal diseases caused by Streptococcus pneumoniae can be of two main types; invasive (IPD) & non-invasive and both types are still common. This study aimed to describe the epidemiology and co-morbidities associated with IPD with bacteraemia.

Methods:

A retrospective analysis of pneumococcal positive blood cultures since January 2014 to August 2017 was carried out at teaching hospital Karapitiya, Sri Lanka. Data was collected
from the request forms, laboratory records and bed head tickets. Repeated cultures from the same patient were excluded. Penicillin sensitivity was mainly determined by oxacillin disc sensitivity.

Results:

There were 42 pneumococcal positive blood cultures during the period. Among bacteraemic patients, 25(60%) cases of pneumonia, 8 cases of meningitis, 5 cases of sepsis of unknown origin and 2 cases of neonatal sepsis were identified. There was male predominance (71%) and more involvement of extremes of age (36% infants, 19% young children and 24% elderly) in all conditions.

36% bacteraemic patients had associated co-morbidities such as cardiac failure (4), malignancy (4), diabetes (02), chronic lung disease (01), chronic liver disease (01), nephrotic syndrome (01) and surgery (01). 5 patients were managed in the ICU (4 pneumonic and 1 meningitis).

Oxacillin resistance rate was 55% among blood culture isolates. Mortality rate was 14% among bacteraemic patients.

Conclusion

IPD with bacteraemia was more prevalent among infants, young children and elderly with male predominance. Elderly with bacteraemia was often associated with co-morbidities such as cardiac failure and malignancy. Penicillin resistance was 55% among pneumococcal isolates in this setting.

ISPPD-0399
DECREASE IN CO-COLONIZATION WITH MULTIPLE PNEUMOCOCCAL SEROTYPES AMONG WARAO AMERINDIAN CHILDREN FOLLOWING VACCINATION WITH THE 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

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5Radboud University Medical Centre, Department of Pediatrics, Nijmegen, The Netherlands

Background and Aims:

Pneumococcal carriage is a surrogate marker for assessment of PCV coverage and efficacy. It is increasingly recognized that concurrent colonization with more than one serotype of pneumococcus frequently occurs. This study aims to evaluate the impact of the 13-valent pneumococcal conjugate vaccine (PCV13) on pneumococcal co-colonization among Warao Amerindian children from Venezuela

Methods:

Nasopharyngeal swabs were collected from 508 Warao children aged 6 weeks-59 months prior to PCV13 vaccination and from 234 fully vaccinated Warao children after vaccination. Nasopharyngeal swabs, with a semi-quantitative growth of >200 colonies on blood agar
plates, from 126 and 60 children respectively, were used for DNA isolation and the detection of multiple pneumococcal serotypes with a serial multiplex PCR.

**Results:**

Pneumococcal carriage rates in Warao children, pre- and post- vaccination, were respectively 73% (371/508) and 62% (145/234). Vaccinated children carried a lower proportion of PCV13 serotypes as compared with non-vaccinated children (32% or 19/60 vs 64% or 81/126). Vaccinated children had a lower prevalence of pneumococcal co-colonization in comparison with non-vaccinated children (25% or 15/60 vs 60% or 76/126 respectively). Co-colonization in the vaccinated children was mostly with non-vaccine or non-typeable serotypes.

**Conclusion:**

Pneumococcal co-colonization rates in Warao population are very high but vaccination with PCV13 resulted in a significant decrease. This might represent an additional benefit of PCV13 vaccination in this high-risk population because a decrease in co-colonization might interfere with fewer opportunities for horizontal gene transfer avoiding events as capsular switching or acquisition of antibiotic resistance determinants.

**Background and Aims:**

High prevalence rates of ARTI have been registered for the Warao Amerindian children from Venezuela and one-third of the child mortality in this population is attributable to pneumonia. The objective of this study is to evaluate the occurrence of ARTI in children after the introduction of the PCV13 vaccine.

**Methods:**

Warao children < 10 years of age coming from vaccinated and non-vaccinated communities were included in a cross-sectional survey to determine the prevalence of ARTI respectively 2, 3 and 4 years after PCV13 vaccination. Because no hospital or disease records are available, data were obtained through standardized parent questionnaires and physical examinations of the children using the World Health Organization Integrated Management of Childhood Illnesses strategy.

**Results:**

Pneumococcal carriage rates in Warao children, pre- and post- vaccination, were respectively 73% (371/508) and 62% (145/234). Vaccinated children carried a lower proportion of PCV13 serotypes as compared with non-vaccinated children (32% or 19/60 vs 64% or 81/126). Vaccinated children had a lower prevalence of pneumococcal co-colonization in comparison with non-vaccinated children (25% or 15/60 vs 60% or 76/126 respectively). Co-colonization in the vaccinated children was mostly with non-vaccine or non-typeable serotypes.

**Conclusion:**

Pneumococcal co-colonization rates in Warao population are very high but vaccination with PCV13 resulted in a significant decrease. This might represent an additional benefit of PCV13 vaccination in this high-risk population because a decrease in co-colonization might interfere with fewer opportunities for horizontal gene transfer avoiding events as capsular switching or acquisition of antibiotic resistance determinants.
One thousand sixty Warao children were evaluated with 60% coming from vaccinated and 40% from non-vaccinated communities. Respectively 13%, 9.5% and 24% presented with ARTI in the three follow-up periods. Significant differences in ARTI prevalence between children of vaccinated and non-vaccinated communities were observed in the two first periods; 10.8% vs. 18.6% and 7% vs. 11.8% (p<0.05) respectively. Four years after PCV13 vaccination the ARTI prevalence in the two study groups were 27% vs. 23% respectively (no significant difference)

Conclusion

In these communities, where there is no disease registration, a cross-sectional survey shows reduction of ARTI prevalence in vaccinated communities for a period of 3 years. After this period no differences in ARTI prevalence was found for children coming from vaccinated and non-vaccinated communities.

ISPPD-0482

STRENGTHENING PARTICIPANT ENGAGEMENT IN A RANDOMISED CONTROLLED TRIAL OF TREATMENT FOR CHRONIC SUPPURATIVE OTITIS MEDIA IN REMOTE ABORIGINAL COMMUNITIES OF THE NORTHERN TERRITORY, AUSTRALIA

C. Wigger

"Menzies School of Health Research, Child health division, Darwin, Australia"

Background and Aims:

Indigenous children in remote communities experience a high burden of pneumococcal colonisation and disease, particularly associated with otitis media. Since 1991, Menzies in Darwin has undertaken otitis media research (including pneumococcal vaccine trials, pneumococcal surveillance, and antibiotic trials) with over 50 remote Indigenous communities. Positive cross-cultural relationships with communities and families are critical to strengthening participant engagement and addressing the high burden of disease experienced by these children. This report examines the success or otherwise of our research relationships. Our hypothesis is that ear health improvements for Indigenous children is dependent on an approach that ensures that knowledge and understanding are shared, families are respected and supported, health services are culturally safe and provide evidence-based, best quality practice.

Methods:

As research nurses in a randomised controlled trial of treatment for chronic suppurative otitis media (CSOM) in remote Aboriginal communities, we present our informal observations, some key positive factors and anecdotal stories that improve the relationship between researchers and participants which may directly or indirectly influence participants’ desire and ability to participate in the research process.

Results:

The strategies we use to achieve greater engagement of participants and improved relationships between researchers, participants and remote communities will be described.

Conclusion

Engaging and retaining remote Indigenous participation in clinical research trials needs a comprehensive approach which includes building positive relationships with individuals and
strengthening community support. Formally evaluating such approaches should be a part of all clinical research.

INFANT DISEASE AND PROTECTION

ISPPD-0667
NASOPHARYNGEAL COLONIZATION BY STREPTOCOCCUS PNEUMONIAE AND SEROTYPE DISTRIBUTION AMONG CHILDREN IN INDIA PRIOR TO VACCINE INTRODUCTION
N. Arora1
1International Clinical Epidemiology Network INCLEN, INCLEN Executive Office IEO, New Delhi, India

Background and Aims:

Pneumococcal conjugate vaccine (PCV) was recently recommended for routine use in India’s Universal Immunization Programme. The goal of this study was to determine the prevalence of nasopharyngeal colonization (NP) among children <5yrs prior to PCV introduction in India.

Methods:

A cross-sectional study was conducted from December 2016 to June 2017 in Palwal, Haryana. Cases included children with suspected pneumonia, meningitis or bacteremia visiting primary care clinics. Community children were those attending daycare centers. NP swabs collected were sent to the WHO reference laboratory at Vellore for testing using culture, serotyping and PCR.

Results:

Among 429 enrolled children, 93 cases (53% male, median age 21mo) revealed 66.7% (62/93) Spn-positive NP swabs. Receipt of prior antibiotics among cases was negligible. Among 336 community children (50% male, median age 25mo), 52.7% (177/336) were Spn-colonized. The proportion colonized with PCV13-type serotypes (culture-based) was 24.7% (23/93) and 20.8% (82/336) among cases and community children respectively. PCR identified an additional 10 (7 cases, 3 community) as Spn-colonized and 87 (23.6%) as having multiple serotypes. Pneumococcal colonization (culture+PCR combined) was significantly higher among cases (74.2%) than among community children (53.6%; p<0.005), while PCV13-serotype colonization was similar (35.5% vs 26.2%, respectively).

Conclusion

Pneumococcal colonization was common in this region prior to vaccine introduction and appeared to be higher among symptomatic children. Continued colonization studies in primary care settings will be important to monitor vaccine impact.

ISPPD-0378
AETIOLOGY OF BACTERIAL MENINGITIS AMONG CHILDREN LESS THAN FIVE YEARS OLD IN COTE D’IVOIRE: FINDINGS OF HOSPITAL-BASED SURVEILLANCE 2010-2016
Background and Aims:

Bacterial meningitis is one of the major diseases that affects children under 5 years old in Cote d’Ivoire. In a bid to curb the burden of paediatric meningitis, Cote d’Ivoire introduced the *Haemophilus influenzae* type b (Hib) conjugate vaccine and the thirteen-valent Pneumococcal Conjugate Vaccine (PCV13) in 2009 and 2014 respectively. Here we describe the epidemiological characteristics of paediatric bacterial meningitis in Cote d’Ivoire from 2010 to 2016.

Methods:

A total of 2761 children under 5 years with suspected bacterial meningitis were recruited from 2010 to 2016. Out of this total, 1160 had cerebrospinal fluid (CSF) specimens collected that were microbiology culture negative at the site, and sent to the WHO regional reference laboratory (RRL). A molecular method was used to detect the presence and serotyping of pathogens in the culture negative CSF.

Results:

From the 2761 cases of suspected meningitis were reported, and CSF was collected in 42% (1160/2761) of the suspected cases. *Streptococcus pneumoniae* was the main pathogen causing paediatric bacterial meningitis, which accounted for 2.5% of positive cases. PCV13 serotypes 5, 18C, 19F and 6A/B were still being detected post PCV13 introduction. We noted the re-emergence of 2 cases of *Haemophilus influenzae* non-typable (Hi-NT) post Hib vaccine introduction.

Conclusion

Despite the widespread use of the PCV13 and Hib vaccines, pneumococcal vaccine types and Hib are still an important cause of bacterial meningitis among children in Cote d’Ivoire. This reinforces the need for strengthening laboratory surveillance for enhanced monitoring of vaccine impact.
Background and Aims:

Invasive pneumococcal diseases [IPD] are responsible of a wide spectrum of infections in children. Our aim is to characterize the demographics, clinical spectrum, serotypes and outcomes of infants younger than 6 months of age with IPD in Colombia, after the introduction of universal pneumococcal immunization with pneumococcal conjugated vaccine 10-valente [PCV-10].

Methods:

Descriptive study of case series of infants younger than 6 months from a Pediatric Network of 10 hospitals in Bogotá, Colombia between 2008 and 2016.

Results:

From 416 patients included in our IPD Network, 66(15.87%) were infants younger than 6 months with 39(60%) males, 36(54.5%) younger than 3 months, 64(96.97%) without history of underlying conditions. Thirteen of 18 infants documented pneumococcal immunization according to their age and 2 infants with 3 doses developed meningitis. Pneumonia was the main diagnosis followed by meningitis in infants younger than 3 months and bacteremia in infants older than 3 months. Serotyping was performed in 40 infants (60.6%), 25 of them (62.5%) fully identified. Serotype 3 was the most common serotype showing the highest Pediatric Intensive Care Unit (PICU) admission and mortality, followed by 19A, 6B and 19F. Penicillin resistance was documented in 6 of 52 (11.5%) infants. Overall mortality was 18.2% with higher mortality in those infants older than 3 months.

Conclusion

Infants younger than 6 months of age from our network showed serious IPD especially pneumonia with elevated PICU admission and mortality mainly among infants older than 3 months and those with serotypes not included in the PCV-10.
YEARS OLD, 2008-2016, IN 10 HOSPITALS OF BOGOTA COLOMBIA.- RED NEUMOCOLOMBIA
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2Grupo para el control de la resistencia bacteriana en Bogotá- GREBO., Cundinamarca, Bogotá, Colombia
3Asociación Colombiana de Infectologia, Cundinamarca, Bogotá, Colombia
4Universidad Nacional de Colombia, Cundinamarca, Bogotá, Colombia
5Fundación Hospital Pediátrico la Misericordia, Cundinamarca, Bogotá, Colombia
6Fundación Hospital Infantil Universitario de San José, Cundinamarca, Bogotá, Colombia
7Universidad de la Sabana, Cundinamarca, Bogotá, Colombia
8Clínica Infantil Colsubsidio, Cundinamarca, Bogotá, Colombia
9Fundación Cardiointfantil-Instituto de Cardiología, Cundinamarca, Bogotá, Colombia
10Sociedad Colombiana de Pediatría, Cundinamarca, Bogotá, Colombia
11Clínicas Colsanitas, Cundinamarca, Bogotá, Colombia
12Hospital Militar Central, Cundinamarca, Bogotá, Colombia
13Hospital Santa Clara, Cundinamarca, Bogotá, Colombia
14Hospital el Tunal, Cundinamarca, Bogotá, Colombia
15Hospital Universitario Clínica San Rafael, Cundinamarca, Bogotá, Colombia
16Clínica el Bosque, Cundinamarca, Bogotá, Colombia

Background and Aims:
Invasive pneumococcal disease (IPD) is an important cause of infant morbidity and mortality. In Colombia PCV10 is administered since 2012. In patients over 5 years old, IPD has been related to risk conditions. There are few case series in the literature that describe the characteristics of the IPD in children over 5 years old.

Methods:
Descriptive, ambispective study (2008 - 2016) in pediatric patients with IPD treated in 10 hospitals in Bogotá. We analyzed the data of patients between 5 and 18 years, for the period from 2008 to 2016. Demographic, clinical and microbiological variables were analyzed.

Results:
416 cases of IPD were recorded. 103 cases (24.5%) are patients between 5 and 18 years old. 61.2% (63) are male. 69% (71) are under 10 years old and 31% (32) are older than 10 years. The diagnosis was pneumonia in 70 cases (68%), bacteremia in 16 (15.5%) and meningitis in 14 (13.6%). The average hospital stay was 15 days. 36.9% (38) of the patients were admitted to the ICU. Serotype was obtained in 77 (74.7%). The most frequent serotypes were 19A (27.3%), 3 (15.6%), 14 (14.3%), 1 (11.7%) and 19F (3.9%). 37 patients (35.9%) had some predisposing factor, being SLE more frequent (7).

Conclusion
Streptococcus pneumoniae is a cause of invasive disease in children over 5 years old, especially if they have predisposing factors. The distribution of serotypes is similar to that found in other age groups. Vaccination should be implemented, especially in patients with risk factors.
Background and Aims:

Community-acquired pneumonia represents an important health problem. It is the leading cause of infant mortality in children under 5 years. *S. pneumoniae* is the main bacterial pathogen. In Colombia, PCV10 has been administered since 2012.

Methods:

Case series study from 2008-2016. Cases of pneumococcal pneumonia were taken in pediatric patients in 10 hospitals in Bogotá. Epidemiological, microbiological and clinical information was obtained. This study was approved by the ethics committee of each institution.

Results:

282 patients were included, 115(41%) under 2 years. In 2014-2016 the most frequent serotypes were 19A with 28(29.1%), 3 with 16(16.6%) and 14 with 10(10.4%) isolates. In the last period we observed a higher number of deaths, the need for PICU and complicated pneumonia compared to the initial period: Table 1.

**Table 1. Pneumococcal pneumonia cases**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Complicated pneumonia n(%)</td>
<td>23(20.7)</td>
<td>18(24)</td>
<td>40(41.6)</td>
</tr>
<tr>
<td>Penicillin resistance n(%)</td>
<td>9(8.1)</td>
<td>1(1.3)</td>
<td>16(16.6)</td>
</tr>
<tr>
<td>PICU n(%)</td>
<td>33(29.7)</td>
<td>30(40)</td>
<td>45(46.8)</td>
</tr>
<tr>
<td>Death n(%)</td>
<td>9(8.1)</td>
<td>5(6.6)</td>
<td>12(12.5)</td>
</tr>
</tbody>
</table>
Near half of serotype 3 and 19A required management in PICU. (Table 2).

Table 2. Description according to serotype 2008 - 2016

<table>
<thead>
<tr>
<th>Serotypes</th>
<th>14</th>
<th>19A</th>
<th>1</th>
<th>3</th>
<th>Other serotypes</th>
<th>Without serotyping</th>
<th>n=49</th>
<th>n=36</th>
<th>n=32</th>
<th>n=21</th>
<th>n=34</th>
<th>n=89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated pneumonia n(%)</td>
<td>13(26.5)</td>
<td>10(27.7)</td>
<td>10(31.2)</td>
<td>9(42.8)</td>
<td>9(26.4)</td>
<td>30(33.7)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PICU n(%)</td>
<td>13(26.5)</td>
<td>15(41.6)</td>
<td>10(31.2)</td>
<td>10(47.6)</td>
<td>15(44.1)</td>
<td>45(50.5)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Mortality n(%)</td>
<td>5(10.2)</td>
<td>4(11.1)</td>
<td>0</td>
<td>4(19)</td>
<td>5(14.7)</td>
<td>8(8.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin resistance n(%)</td>
<td>6(12.2)</td>
<td>8(22.2)</td>
<td>0</td>
<td>1(4.7)</td>
<td>5(14.7)</td>
<td>6(6.7)</td>
<td></td>
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</tbody>
</table>

Conclusion

In the last period, an increase in the number of pneumonia cases and greater severity in relation to circulating serotypes was observed.

ISPPD-0230
COMPLICATED PNEUMONIA FROM S. Pneumoniae IN 10 PEDIATRIC HOSPITALS IN BOGOTÁ, COLOMBIA; 2008 – 2016
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2 Red Neumocolombia, Cundinamarca, Bogotá, Colombia
3 Asociacion Colombiana de Infectologia, Cundinamarca, Bogotá, Colombia
4 Hospital Militar Central, Cundinamarca, Bogotá, Colombia
5 Sociedad Colombiana de Pediatria, Cundinamarca, Bogotá, Colombia
6 Clinica Infantil Cols subsidio, Cundinamarca, Bogotá, Colombia
7 Fundación Hospital Pediátrico la Misericordia, Cundinamarca, Bogotá, Colombia
8 Universidad Nacional de Colombia, Cundinamarca, Bogotá, Colombia
9 Fundación Hospital Infantil Universitario de San José, Cundinamarca, Bogotá, Colombia
10 Grupo para el control de la resistencia bacteriana en Bogotá- GREBO, Cundinamarca, Bogotá, Colombia
11 Universidad de la Sabana, Cundinamarca, Bogotá, Colombia
12 Fundación Cardi infantil-Instituto de Cardiología, Cundinamarca, Bogotá, Colombia
13 Hospital Santa Clara, Cundinamarca, Bogotá, Colombia
14 Hospital el Tunal, Cundinamarca, Bogotá, Colombia
15 Hospital Universitario Clinica San Rafael., Cundinamarca, Bogotá, Colombia
16 Clinica el Bosque, Cundinamarca, Bogotá, Colombia

Background and Aims:

Complicated pneumonia from S. pneumoniae remains an important problem and cause of morbidity and mortality worldwide. In Colombia, PCV10 has been administered since 2012. Red Neumocolombia monitors invasive pneumococcal disease in pediatric patients in Bogotá since 2012.

Methods:
Ambispective case series study (2008-2016) in pediatric patients admitted to 10 hospitals in Bogotá with criteria of complicated pneumonia (parapneumonic effusion, empyema, and necrotizing pneumonia). Epidemiological and clinical characteristics were described.

Results:

Of 282 patients diagnosed with pneumonia, 81 patients (28.7%) had complicated pneumonia. In 2008-2011, the condition corresponded to 23/111 (20.7%) of the cases; in 2011-2013, 18/75 (24%); and 2014-2016, 40/96 (41.6%) cases. The percentage of cases of complicated pneumonia increased in the last period. 57 (70.3%) patients required PICU, 11 (13%) patients died. 7 (63.6%) of the patients who died were under 24 months of age (Table 1).

**Table 1.** Complicated pneumonia characteristics

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Most common serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>7 (30.4)</td>
<td>1 (5.5)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>19A</td>
<td>0</td>
<td>0</td>
<td>10 (25)</td>
</tr>
<tr>
<td>1</td>
<td>4 (17.4)</td>
<td>4 (22.2)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1 (5.5)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Other serotypes</td>
<td>0</td>
<td>2 (11.1)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Not serotyped</td>
<td>12 (52.1)</td>
<td>10 (55.5)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>PICU</td>
<td>18 (78.2)</td>
<td>12 (66.6)</td>
<td>27 (67.5)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (17.3)</td>
<td>1 (5.5)</td>
<td>6 (15)</td>
</tr>
</tbody>
</table>

Conclusion

In recent years, as in other countries, there has been an absolute increase in cases of complicated pneumonia, with a higher percentage in relation to the total number of cases of pneumonia. There is a higher death rate and requirement for PICU, associated with an increase in serotypes 3 and 19A compared to previous years.

**ISPPD-0115**

**CURRENT ACCESS TO INFANT PNEUMOCOCCAL CONJUGATE VACCINES IN AFRICA AND THE EASTERN MEDITERRANEAN REGION**

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²Pfizer, Vaccines, Paris, France
³Pfizer, Vaccines, New York, USA

Background and Aims:

Africa/Eastern Mediterranean countries include the world’s poorest nations. Access to pneumococcal conjugate vaccines (PCVs) through National Immunization Programs (NIPs) has been possible through local or donor funding programs such as Gavi, the Vaccine Alliance. When implemented as part of a NIP, PCVs have significantly reduced pneumococcal disease. However, implementation and coverage is variable across the region. We aimed to review access to PCVs in this region.

Methods:
We classified access to national immunization programs (NIP) as: no PCVs available or PCVs available; and for the latter, as nationally-funded NIP, Gavi-funded NIP, or no public funding. Vaccine access, birth cohort size and PCV uptake estimates were obtained from publicly available sources.

Results:

Across 67 countries, defined by WHO regions, representing 49 million of the world’s estimated 135M births, we found 5 countries were without PCV access, and among the remaining 62 countries, 16 were nationally-funded, 38 were Gavi-funded, and 8 were without public funding. PCV uptake was consistently high (>70%) in both public- (13/16 countries) and Gavi-funded (29/38 countries) NIPs. We estimate that the NIPs protected 32.6M infants, of which 28.4M were under Gavi-funding. Over 16M infants remain without access: in the 5 countries without PCVs and in the 8 countries without public funding.

Conclusion

PCVs are available in Africa/Eastern Mediterranean countries, and Gavi-funded programs comprise the majority of NIPs, although access gaps remain. As a number of countries approach transition from Gavi support, financing mechanisms may still be needed for these countries to introduce and maintain PCV NIPs, facilitating access for vulnerable infants.

Background and Aims:

Asia is a geographically and economically diverse region, and where pneumococcal conjugate vaccines (PCVs) were introduced as part of National Immunization Programs (NIPs), significant reductions in pediatric pneumococcal disease have been observed. Despite efforts to increase PCV introduction and uptake globally, implementation in Asia lags behind other regions. We aimed to review access to PCVs in Asia.

Methods:

Asia region countries were classified as: no PCVs available or PCVs available; and for the latter, as publicly-funded NIP, Gavi-funded NIP, or no public funding. Vaccine access, birth cohort size and PCV coverage estimates obtained from publicly available sources.

Results:

Of 24 countries, 2 were without access to PCVs and of the remaining 22, 7 were publicly-funded NIPs, 9 were Gavi, and 6 were without public funding (Figure 1). In 2017, of 50 million infants born annually in this region, an estimated 12.4M were protected by PCVs. The majority of protected infants (9.6M) were from countries with publicly-funded NIPs with high coverage rates (≥70%). Over 37.6M infants remain without access to PCVs.
Conclusion

While PCVs are available throughout most of Asia, vaccination programs and coverage rates vary. While 12.4M children benefit from the protection of PCVs, 37.6M children await access to lifesaving vaccines. Access to PCVs through a NIP is ideal to secure high PCV coverage. Local and global support is needed to ensure countries introduce and maintain PCVs to improve public health.

ISPPD-0062
ANTIBODY RESPONSES TO 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV13) IN NON-PREGNANT WOMEN IN THE HIGHLANDS OF PAPUA NEW GUINEA
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¹Papua New Guinea Institute of Medical Research, Infection and Immunity Unit, Goroka, Papua New Guinea
²University of Western Australia, Division of Paediatrics- School of Medicine, Perth, Australia
³Telethon Kids Institute, Head- Ear Health, Perth, Australia
⁴Telethon Kids Institute, Vaccine Trials Group, Perth, Australia

Background and Aims:

Streptococcus pneumoniae remains a leading cause of serious illness in young infants in PNG, who are colonized by pneumococci at an average age of 17 days old. A possible approach to protect young infants before scheduled infant immunization is to vaccinate the mother during her last weeks of pregnancy; however, the safety and immunogenicity of PCV13 in PNG adults is unknown. The aim of this pilot study was to evaluate responses to PCV13 in non-pregnant women from the highlands of PNG.
Methods:

50 non-pregnant women (18-45 yrs old) were vaccinated with PCV13. Venous blood was collected before and 1 month after vaccination. Side effects were monitored over a 24-48 hour period after vaccination. PCV13 serotype-specific antibody responses were measured by an established ELISA protocol. Functional antibody responses as correlates of protection are being assessed in Perth, Australia.

Results:

48 of the 50 women enrolled completed the study. No severe adverse effects were reported. Geometric mean antibody titers (GMT) significantly increased after vaccination for all PCV13-serotypes (P<0.001) in all participants. A high proportion of women (79-100%) had seroprotective levels of >1 μg/ml before vaccination for all serotypes, except for serotype 3. After vaccination, 96-100% of women had seroprotective levels. Serotype 3 proportions doubled from 19 to 38%.

Conclusion

PNG women of child-bearing age have high naturally acquired pneumococcal antibody titers. Vaccination induces even higher titers. Analysis of functional responses is underway to evaluate whether vaccination induces antibodies with a higher opsonophagocytic activity, which would be important to mediate protection in newborns.

ISPPD-0680
SEROTYPE DISTRIBUTION AND SUSCEPTIBILITY PATTERN OF STREPTOCOCCUS PNEUMONIAE IN INVASIVE DISEASE AND NASOPHARYNGEAL CARRIAGES PRE-VACCINE INTRODUCTION IN CUBA
G. Toraño-Peraza1, I. Luis-Gonzalvez2, M.E. Toledo-Romani3, N. Linares-Pérez2
1Tropical Medicine Institute “Pedro Kouri”, National Reference Laboratory, Havana, Cuba
2Finlay Vaccine Institute, Clinical Research and Impact Evaluation, Havana, Cuba
3Tropical Medicine Institute “Pedro Kouri”, Epidemiology, Havana, Cuba

Background and Aims:

Cuba has a new heptavalent PCV under advanced clinical development and its introduction in children 1-5 years old is scheduled in 2018. We report the results of serotyping and antibiotic susceptibility testing performed on isolates from invasive pneumococcal (IPD) and nasopharyngeal (NP) carriages in Cuban hospitalized children, pre-vaccine introduction

Methods:

A total of 353 isolates from IPD and 80 from the nasopharynx of hospitalized children £ 5 years old with clinical pneumonia were recovered prospectively during 2013-2016. Typing of isolates was done using capsular swelling method with the Pneumotest reagent set. Antimicrobial susceptibility was determined following CLSI methods

Results:

The higher proportion of isolation from IPD was collected in children among 12-59 years old (annual average 30.2; Range 20.0-40.4); 85.8 % of them belonged to the follow seven serotypes, in order of frequency: 14, 19A, 6A, 19F, 6B, 3 and 23F. Serotypes 6B, 6A, 19F y 23F were the most associated to antimicrobial resistance: penicillin (16.7%), ceftriaxone
(3.15%), macrolides (62.7%), trimethoprim-sulfamethoxazole (40.3%) and chloramphenicol (7.4%). The proportion of NP colonization in hospitalized children was 13.76% and the serotype and resistance profile was similar to the pattern of IPD isolates, but 19A was the predominant (25%) and 100% of β-lactamase susceptibility was demonstrated. Non vaccine serotypes representing 23.7% of all isolation from nasopharynx

**Conclusion**

Our data predict more than 50% coverage of the circulating *S. pneumoniae* in Cuba with the new heptavalent conjugate vaccine and could be useful for evaluating the serotype distribution in support of their introduction.

**ISPPD-0429**

**EPIDEMIOLOGAL CHANGES IN PEDIATRIC PNEUMONIA AND MENINGITIS FOLLOWING INTRODUCTION OF UNIVERSAL VACCINATION WITH PNEUMOCOCCAL VACCINE 13-V (PCV13v) IN ARGENTINA: HOSPITAL-BASED ANALYSIS IN ROSARIO, ARGENTINA**

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²Hospital de Niños Victor J. Vilela, Pulmonology, Rosario, Argentina
³Hospital de Niños Victor J. Vilela, Laboratory, Rosario, Argentina
⁴Hospital de Niños Victor J. Vilela, Radiology, Rosario, Argentina
⁵National Institute for Infectious Diseases, Bacteriology, Buenos Aires, Argentina
⁶National Institute for Infectious Diseases, Bacteriology, Buenos Aires, Argentina

**Background and Aims:**

In January 2012 PCV13v was introduced in Argentina using 2+1 schedule and catch-up program until 2 yo. Vaccination coverage for 1st and 3rd doses were 96.6% and 85.3% in 2013, 87.6% and 82.3% in 2016 respectively. We used our surveillance program to evaluate the changes that occurred in hospitalizations for community acquired pneumonia (CAP), consolidated pneumonia (CP), empyema (EMP) and meningitis (M), following the introduction of PCV13v.

**Methods:**

Rates of CAP, CP, EMP and M/10⁴ hospital discharges were compared between pre vaccine period (preVp) 2008-2011, and post vaccine period (postVp) 2013-2016 in children <13 yo. Bacterial-confirmed EMP and M were analyzed to evaluate frequency changes in their etiologies.

**Results:**

From preVp to postVp, hospitalization rates due to all-cause CAP decreased significantly by 11.1 (95%CI: 0.4;20.6), 8.6% (38.9;56.8), 47.5% (37.9;55.6) and 41.9% (30.2;51.7) in children <1, 1, 2 to 4, and 5 to 12 yo, respectively. Hospitalization rates for CP declined 4.7%, 64.6% (51.3;74.2), 55.1% (42;65.3) and 45.3% (29.1;57.8) in such age groups, respectively. EMP rates declined significantly 46.2% (13.8;66.4), in children 2 to 4 yo. Hospitalization rate for pneumococcal M decreased by 33.4% (0;77.5).
Pneumococcus caused 75.4% vs 25.7% \((p=0.002)\), and 40.9% vs 15.1% \((p=0.064)\) of culture positive EMP, and M in preVp and postVp respectively.

**Conclusion**

Hospitalization rates declined significantly in children from all ages with all-cause CAP, in those >1 yo with CP and in those 2 to 4 yo with EMP, after introduction of PCV13v. The relative importance of pneumococcus as bacterial agent of EMP and M decreased markedly.

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**ISPPD-0277**

**BACTERIAL ETIOLOGY OF MIDDLE EAR FLUID IN INDIAN CHILDREN WITH RECURRENT OTITIS MEDIA INFECTION**

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²Manipal Hospital, Department of pediatrics, Bangalore, India

**Background and Aims:**

Recurrent Otitis Media is one of the common infections of childhood. The causative bacterial pathogen is one of the major risk factor of recurrent infection. With limited availability of Indian data, we performed this study to identify the bacterial pathogens

**Methods:**

Otitis media cases were diagnosed based on clinical criteria. 36 Middle ear fluid(MEF) samples were collected by Tympanocentesis and cultured for pathogens. 78% of the cases had 3 previous episodes of otitis media in the past 6 months whereas the rest 22% of the cases had 4 episodes in the last 6 months. All the patients were on antibiotic coverage at the time of sample collection. 16s rDNA PCR and \(S.pneumoniae\) qmPCR was performed on genomic DNA samples and serotyped by PCRSeqTyping

**Results:**

Conventional culture showed no growth in any of the samples. 16s rDNA PCR could identify bacterial pathogens in 33 out of 36 MEF specimens. Five samples showed mixed reads in 16s rDNA sequencing. The organisms identified were Neisseria sp other than \(N.meningitidis(n=7)\), \(N.meningitidis(n=8)\), Lactococcus sp\(n=4\), \(S.pneumoniae(n=2)\), \(P.aeruginosa(n=2)\), \(H.influenza(n=1)\), \(S.infantis(n=1)\), \(S.epidermidis(n=1)\), \(S.auricularis(n=1)\) and Streptococcus sp\(n=1\). qmPCR for \(S.pneumoniae\) was positive in 7 samples. PCRSeqTyping identified Serotype 19A in two samples.

**Conclusion**

The study demonstrates the usefulness of 16s rDNA PCR protocol to identify the bacterial pathogens in MEF by culture-independent method. Neisseria sp. was the predominant pathogen identified followed by \(S.pneumoniae\). The study provides insight to the etiology of bacterial pathogens in recurrent otitis media among Indian children for first time.

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**ISPPD-0436**

**IMMUNOGENICITY AND REACTOGENICITY/SAFETY OF THE PNEUMOCOCCAL NON-TYPEABLE HAEMOPHILUS INFLUENZAE PROTEIN D-CONJUGATE VACCINE (PHID-CV) IN HIGH-RISK PEDIATRIC GROUPS: A LITERATURE REVIEW**
Background and Aims:

The pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV, GSK) is indicated for immunization against invasive pneumococcal disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in children <5 years of age. We performed a review of the available literature to assess the immunogenicity and reactogenicity/safety of PHiD-CV in pediatric populations at high risk of pneumococcal disease.

Methods:

A literature search was conducted within the MedMeme and PubMed databases for abstracts and articles published between 1 January 2011 and 30 August 2017 (Figure 1).

Results:

Data for the following high-risk conditions were available: prematurely born infants, children with acute lymphoblastic or myeloid leukemia, infants infected with or exposed to HIV *in utero*, and children with asplenia, splenic dysfunction (including sickle cell disease), or complement deficiencies. 554 children at high risk were included in the total vaccinated cohorts of the 5 eligible studies. Study population characteristics, objectives, and conclusions are summarized in Figure 2.
Conclusion

This literature review indicated that in the analyzed studies PHID-CV provided adequate immunogenicity and had an acceptable reactogenicity/safety profile in children in the high-risk groups assessed. This is reassuring for physicians considering PHID-CV vaccination in these children.
ISPPD-0650
EFFECTIVENESS OF 7-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINES (PCV7, PCV13) AGAINST VACCINE-TYPE PNEUMOCOCCAL OTITIS MEDIA (VTP-OM) IN ISRAEL

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2Ben-Gurion University of Negev, The Faculty of Health Sciences, Beer-Sheva, Israel
3Soroka University Medical Center, Pediatric Infectious Disease Unit, Beer-Sheva, Israel

Background and Aims:

Post-implementation studies of PCV effectiveness against VTP-OM are lacking due to difficulties in obtaining appropriate samples. In 2009, Israel introduced PCV7 (at 2, 4 and 12 months) and, starting November 2010, gradually replaced PCV7 with PCV13. We conducted a case-control evaluation of PCV7 and PCV13 effectiveness against complex VTP-OM requiring cultures.

Methods:

VTP-OM cases, defined by isolation of pneumococcus from tympanocentesis or spontaneously draining pus, were identified through active surveillance in children 4-35 months in southern Israel. Isolates were serotyped by Quellung and classified as PCV7-type or PCV13-type. We included cases identified during October 2009 through December 2011 (PCV7 period) and January 2012 through July 2013 (PCV13 period). Controls were children 4-35 months with rotavirus-negative gastroenteritis during the same time. We estimated vaccine effectiveness (VE) as one minus the VTP-OM odds ratio for 1 or >2 PCV doses vs. no PCV, adjusted for ethnicity, age (months) and time, using logistic regression.

Results:

During PCV7 and PCV13 periods, we identified 89 and 161 VTP-OM episodes caused by PCV7 and PCV13 serotypes, respectively. VE was 63.2% for PCV7 against PCV7-type OM, 72.7% for PCV13 against PCV13-type OM; and 80.1% for PCV13 against PCV13-unique OM serotypes (Table). One dose of either PCV7 or PCV13 was not effective.

Table. Vaccine effectiveness (95% CI) against VTP-OM by PCV product, schedule, serotype group, and time

<table>
<thead>
<tr>
<th>Serotype group</th>
<th>PCV7 types</th>
<th>PCV7+6A</th>
<th>Unique 5 PCV13 types</th>
<th>PCV13 types</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV7 1 dose vs. 0</td>
<td>9.4% (118, 62.4%)</td>
<td>3.6% (118, 57.3%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PCV7 ≥ 2 doses vs. 0</td>
<td>63.2% (21.5, 82.8%)</td>
<td>51.1% (2.1, 75.6%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PCV13 1 dose vs. 0</td>
<td>-22.6% (-7.39, 82.1%)</td>
<td>19.8% (-250, 83.5%)</td>
<td>52.8% (-66.6, 86.6%)</td>
<td>-</td>
</tr>
<tr>
<td>PCV13 ≥ 2 doses vs. 0</td>
<td>91.9% (39.1, 98.9%)</td>
<td>83.1% (13.1, 95.4%)</td>
<td>72.7% (8.9, 91.8%)</td>
<td>-</td>
</tr>
</tbody>
</table>

Conclusion

PCV7 and PCV13 are effective in preventing VTP-OM episodes caused by corresponding vaccine serotypes among children 4-35 months old.
ISPPD-0417
PERSISTENCE OF PCV7 AND PCV13 SEROTYPES IN PEDIATRIC INVASIVE PNEUMOCOCCAL DISEASE IN PORTUGAL AFTER MORE THAN A DECADE OF VACCINE USE
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Background and Aims:
In Portugal, pneumococcal conjugate vaccines (PCVs) have been available since 2001 but only in June 2015 was PCV13 included in the National Immunization Plan (NIP). We aimed to characterize isolates causing invasive pneumococcal disease (IPD) in 2012-2016.

Methods:
A total of 230 isolates recovered from children (<18 years) diagnosed with IPD in 61 hospital laboratories and pediatric departments located throughout Portugal between July 2012 and June 2016 were characterized by serotyping and antimicrobial susceptibility testing.

Results:
The number of isolates recovered in each epidemiological year was approximately constant, except 2015-16 where there was a decrease of 27% relative to the average of previous years. 37 different capsular types, as well as non-typable isolates were detected. Serotypes not included in any PCV (NVTs) accounted for half of the isolates (50%, n=115). Serotypes 15B/C, 10A, 24F, 8, 12B were the most frequent NVTs, represented by >10 isolates each. Serotypes 14 (n=26), 1 (n=18), 3 (n=15), 7F (n=13), 6B (n=13) and 19A (n=10) were the most frequent PCV serotypes. Overall, 23% of the isolates were penicillin non-susceptible (PSNP). Resistance to erythromycin (ERP) was expressed by 22% of the isolates and simultaneous PNSP and ERP was found in 14%.

Conclusion
The lower number of isolates received 2015-16 possibly reflects a reduction in IPD due to PCV13 introduction in the NIP. PCV13 serotypes are still expressed by half of isolates responsible for IPD. The data presented here emphasizes the potential role of PCV13 in the NIP in further diminishing pediatric IPD.

ISPPD-0291
PREVALENCE AND CHARACTERISTICS OF CHILDREN WITH OTITIS MEDIA WITH EFFUSION IN VIETNAM
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²Institute of Tropical Medicine- Nagasaki University, Department of Pediatric Infectious Diseases, Nagasaki, Japan
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⁴Khany Hoa Health Service, Vice director, Nha Trang, Vietnam
Background and Aims:

Otitis media with effusion (OME) is defined as the presence of fluid in the middle ear without signs and symptoms of acute ear infection. About 90% of the children experienced OME before 24 months of age. OME is the most common cause of hearing impairment among children in developing countries. Association between nasopharyngeal pneumococcal carriage in the community and OME had not been evaluated. The aim of this study was to investigate prevalence of OME and its association with nasopharyngeal pneumococcus carriage.

Methods:

In October 2016, 320 children under 24 month of age, were randomly recruited for ear examination and demographic data collection from three communes in Nha Trang, central Vietnam. OME was diagnosed with the presence of middle ear fluid by digital pneumatic otoscope. Nasopharyngeal pneumococcal carriage was also tested. The point prevalence of OME in this community was estimated. Adjusted odds ratio (aOR) was calculated using multivariable logistic regression model to estimate the effect of pneumococcal carriage on OME.

Results:

Among 272 children who was successfully diagnosed in both ear, 47 children were diagnosed of having OME. The estimated prevalence of OME in this community was 17.2% (95% confidence interval: 12.7 - 21.6%). Ever been to nursery (aOR 18.28 [5.50-60.78]), living in rural area (aOR 4.14 [1.70-10.9]), and pneumococcal carriage positive (aOR 3.51 [1.44-8.53]) were positively associated with having OME by univariate and multivariable logistic regression model.

Conclusion

We elucidated the prevalence of OME and its association with nasopharyngeal pneumococcal carriage in Nha Trang, Vietnam.
Methods:

Cerebrospinal fluid (CSF) specimens were collected in suspected meningitis from 2010 to 2016. CSF specimens were subjected to culture, rapid antigen test and molecular examination to detect pneumococcus, meningococcus and Haemophilus influenzae. Antibiogram, serotyping and whole-genome sequencing were performed on pneumococcal isolates.

Results:

There were 1013 suspected and 115 laboratory confirmed meningitis cases during the surveillance period. Pneumococcus, meningococcus and H. influenzae accounted for 66.0% (76/115), 26.1% (30/115) and 7.8% (9/115) of the laboratory confirmed cases respectively. Most of the suspected 63.1% (639/1013) and confirmed 57% (66/115) cases were among infants. The pneumococcal case fatality rate was 28%; it is higher than meningococcal mortality (5%). In the post-PCV13 era, vaccine serotypes accounted for 55% of pneumococcal meningitis case. Five children who had meningitis attributed to vaccine serotype had received PCV13 prior to disease onset. Four children that had H. influenzae type b (Hib) meningitis had been vaccinated. All twelve serogrouped meningococci belonged to serogroup W. The predominant lineage was ST618 (n = 7) found among serotype 1 isolates. An ST2167 lineage that included serotypes 19A and 23F resistant to trimethoprim and sulfamethoxazole.

Conclusion

Pneumococcus is associated with high mortality and remains the leading cause of meningitis. The persistence of Hib meningitis is also concerning. These findings highlight the importance of monitoring of vaccine-preventable bacterial meningitis.

ISPPD-0246

LOW PREVALENCE OF PNEUMOCOCCAL ACUTE OSTEOARTICULAR INFECTIONS (PAOAIs) DURING A 17-YEAR-PERIOD IN CHILDREN FROM EL SALVADOR (ES): 2000-2017

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2Hospital Nacional de Niños "Dr. Carlos Sáenz Herrera", Servicio de Infectología Pediátrica, San José, Costa Rica

Background and Aims:

The prevalence of PAOAIs in children prior to PCVs introduction was low, and even after, very few reports have looked at its epidemiology and microbiology. In ES, universal PCV7 (3+1) and PCV13 (2+1) were introduced for infants in Jan-2010 and Jan-2011, respectively. Nationwide, around 99% of children with invasive pneumococcal infections (IPIs) are managed at our institution. This is the first study in Central America and the Caribbean looking specifically at PAOAIs at a main referral center.

Methods:

Retrospective chart and laboratory review of pts <13 years hospitalized with a culture-confirmed PAOAI at the only national pediatric tertiary referral hospital in ES. We defined
PAOAI as septic arthritis (SA) and acute osteomyelitis (AO). Study period: Jan-01-2000 to Sep-30-2017.

Results:

Among 276 pts with an IPI during this 17-year-period, only 3 (1.08%) had a SA and none AO. 2 episodes occurred pre PCV7/13 introduction. Ages were: 11, 12 and 60 months, respectively. All were male pts; one had an underlying medical condition (malnutrition). Arthrocentesis was performed in 3 pts. All 3 isolates were grown from joint fluid cultures. Penicillin/cefotaxime resistance was 66.7%(2/3) and 0%, respectively. Serogroup (but not serotype) determination was available in 2/3 pts (serogroups 6 and 18). Only the child with serogroup 18 had 2 previous doses of PCV13. None developed complications or sequelae.

Conclusion

The overall prevalence of PAOAIIs in children from ES prior and post-PCV introduction is much lower than other reports from main referral centers in both developed and developing countries.

ISPPD-0703
HIGH FATALITY RATES ASSOCIATED WITH INVASIVE PNEUMOCOCCAL DISEASE (IPD) IN PATIENTS <6 MONTHS OF AGE IN EL SALVADOR (ES): PERIOD 2000-2017
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2Hospital Nacional de Niños Benjamín Bloom, Servicio de Infectología Pediátrica, San Salvador, El Salvador

Background and Aims:

Few studies analyzing IPD in infants <6 months of age have been published from developing countries, including Latin America. In ES, universal PCV7 (3+1) and PCV13 (2+1) were introduced in Jan-2010 and Jan-2011, respectively. Nationwide, around 99% of children with an IPD are managed at our institution. We describe the first Central American and Caribbean study analyzing IPD in this age group.

Methods:

Retrospective chart and laboratory review of hospitalized pts <6 months with a culture-confirmed IPD episode at the only national pediatric tertiary referral hospital in ES. Study period: Jan-01-2000 to Sep-30-2017.

Results:

Among 276 pts <13 years hospitalized with an IPD episode during this long period, 65 (23.6%) were < 6 months. Median age was: 3 months; 3 (4.6%) newborn pts were identified: 1-wk, 1-wk, and 3-wks-old, respectively. 39/65 (60%) pts were male. The most common clinical presentations were: meningitis 43 (66.2%), sepsis 13 (20%), and pneumonia/empyema 9 (13.8%) pts. Penicillin/cefotaxime resistance was 17.2% (10/58) and 5.6% (3/54), respectively. 55 (84.6%), 3 (4.6%), and 7 (10.8%) episodes occurred pre PCV7, during PCV7-PCV13 transition, and post-PCV13 introduction. Fatality rate was 40% (26/65 pts). Among the 26 fatalities, the more common clinical diagnosis was: meningitis 14 (53.8%), sepsis 11 (42.3%) pts, and pneumonia/empyema 1 (3.8%) pt, respectively.
Conclusion

IPD in infants <6m from ES is associated with high fatality rates. Following PCV7/PCV13 introduction in ES, a decrease of IPD cases in this age group was observed.

ISPPD-0669
PNEUMOCOCCAL SEROTYPE SURVEILLANCE AMONG CHILDREN IN INDIA: THE BASIS STUDY
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¹Christian Medical College, Clinical Microbiology, Vellore- Tamil Nadu, India

Background and Aims:

Pneumococcal conjugate vaccine (PCV) was recently introduced in select states in India. The goal of BASIS was to characterize the distribution of serotypes causing IPD among children under 5 years in different regions in India prior to vaccine introduction.

Methods:

BASIS consisted of active (prospective enrolment of children) and passive (retrospective pneumococcal isolate collection) surveillance in 13 sites in 9 states. Children aged <5yrs with features of pneumonia, meningitis or bacteremia were enrolled. Blood, cerebrospinal fluid or other sterile body fluids were collected and processed as per standard protocols. Pneumococcal isolates were serotyped by the Quellung method at the WHO reference laboratory at Christian Medical College, Vellore.

Results:

Between September 2015 and June 2017, 2,821 children with suspected IPD were enrolled at the seven active sites, yielding 141 pneumococcal isolates. Median age of all cases was 12 months, and 60% were males. Prior antibiotics were reported in 26% of all cases. IPD cases presented with pneumonia (54%), bacteremia/sepsis (27%), meningitis/meningoencephalitis (16%), pleural effusion/empyema (10%), nephrotic syndrome (9%) and other syndromes (9%). An additional 106 pneumococcal isolates were identified from passive sites. Among the total 247 pneumococcal isolates, common serotypes included 14 (17%), 19A (10%), 5 (9%), 6B (9%), and 19F (7%). PCV13-serotype prevalence was 76%. In-hospital mortality among all IPD cases was 7% (10/141), and 6-month post-discharge mortality among those followed up was 10% (7/71).

Conclusion

The BASIS study provides important nationally-representative data to support introduction of PCV in India and evaluate the impact on pneumococcal serotype distribution.
INTERACTION WITH VIRUSES AND OTHER BACTERIA

ISPPD-0342
AGE-DEPENDENT DISSIMILARITY OF THE BACTERIAL NASOPHARYNGEAL AND MIDDLE-EAR MICROBIOTA IN CHILDREN WITH ACUTE OTITIS MEDIA
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2University of Zurich, University of Zurich, Zurich, Switzerland
3University of Lausanne, Institute for Work and Health, Lausanne, Switzerland

Background and Aims:
Acute otitis media is usually caused by otopathogens ascending to the middle ear from the nasopharynx. However, it is unknown if the nasopharyngeal microbiota of children with acute otitis media can serve as an age-dependent or independent proxy for the microbial communities of the middle ear fluid as there is a lack of next generation sequencing studies simultaneously analyzing the microbial communities of the two sites.

Methods:
Within this study, we performed 16S rRNA next generation sequencing on a total of 286 nasopharyngeal swabs collected between 2004 and 2012 from Swiss children (0-6 years) with acute otitis media. In addition, 42/286 children had spontaneous tympanic membrane perforation and, therefore, additional middle ear swabs could be analyzed, too.

Results:
Our results showed that alpha (Richness, SDI and Evenness) and beta diversity measurements of the nasopharyngeal bacterial microbiota showed a clear dependency of the increasing age of the children. Bacterial richness and personalized profiles (measured by beta dispersion) were higher and more frequent in more aged children, respectively. Dissimilarity values based on the binary distance matrix of the microbiota patterns of NP and MEF correlated with increasing age, too. In general, positive (PPVs) and negative predictive values (NPVs) of the most abundant OTUs in the NP were moderately and well predictive for their presence in the MEFs, respectively.

Conclusion
As compared to culturing, microbiota studies are more complete and may detect less known bacteria related to AOM. This is crucial to better understand AOM pathogenesis.

ISPPD-0460
ASSOCIATION OF HUMAN RHINO VIRUS WITH STREPTOCOCCUS PNEUMONIAE IN CHILDREN WITH AND WITHOUT HIV FROM EASTERN INDIA
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1Indian Institute of Technology-Kharagpur, School of Medical Science & Technology, Kharagpur, India

Background and Aims:
Upper respiratory tract viruses and bacteria often interact with each other causing severe respiratory infections. Human rhinovirus and pneumococcus are the most common causes of the common cold and bacterial pneumonia, respectively. HIV-infected children are at increased risk of severe disease from complicated respiratory infections. This study looked at the association of rhinovirus with pneumococcus in the nasopharynx of HIV-infected children.

Methods:

We conducted a nested case-control study on children with and without HIV within a larger prospective cohort study on the impact of PCV-13 in HIV infected children from West Bengal, India. Multiplex real time PCR was run on 80 random banked nasopharyngeal swabs collected from 40 children with HIV (CLH) and 40 without HIV (HUC) for detection of rhinovirus (5'untranslated region) and pneumococcus (lytA). Association between rhinovirus and pneumococcus was determined by logistic regression and between pneumococcal density and rhinovirus, by ordered logistic regression.

Results:

The median age of children in both groups was 3. CLH had increased likelihood of co-infection of rhinovirus with pneumococcus in their nasopharynx as compared to HUC. Odds ratios were 18.75 (p=0.011, 95% CI 1.9-180) in CLH, while in HUC they were 1 (p=1, 95%CI=0.2-4.9). The association between rhinovirus and pneumococcus increased with increase in log density of pneumococcus in CLH and HUC with coefficients 2.62 (p=0.025,95%CI0.32-4.9) vs. 1.63 (p=0.27,95%CI=-1.2-4.5), respectively.

Conclusion

HIV infected children have increased co-infection of rhinovirus and pneumococcus in their nasopharynx.

ISPPD-0722
BASELINE RESULTS FROM THE TRANSMISSION OF PNEUMOCOCCUS(TOP) STUDY, USING LIVE ATTENUATED INFLUENZA VACCINE(LAIV) IN 2-YEAR-OLDS TO STUDY FAMILIES IN A RANDOMISED PROSPECTIVE STEPPED-WEDGE DESIGN

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2University of Exeter, Computer Science, Exeter, United Kingdom
3St George's University of London, Paediatric Infectious Disease Research Group, London, United Kingdom
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5University of Oxford, Oxford Vaccine Group- Department of Paediatrics, Oxford, United Kingdom
6University of Southampton, NIHR Clinical Research Facility, Southampton, United Kingdom
7Pfizer Vaccines, Na, Collegeville PA, USA

Background and Aims:
Interrupting transmission of vaccine serotypes underlies the effectiveness of pneumococcal conjugate vaccine programmes at population level. *Streptococcus pneumoniae* (Sp) nasal colonisation density varies widely between individuals and over time; its relationship to infectiousness is unknown.

We are using LAIV to modify the density of pneumococcal nasal carriage in LAIV-naive 2-year-olds and then assessing the impact of this rise on household transmission rates.

**Methods:**

500 families are recruited, and the index 2-year-old is randomised 1:1 to receive LAIV either at day 0 or day 28; saliva and nasopharyngeal samples (NPS) are collected from participants every 14 days over 2 months. Samples are analysed for Sp using real-time quantitative PCR (*lytA*) and considered positive when the threshold cycle (Ct) value is less than or equal to 35.

**Results:**

**First 25% of participant families**

<table>
<thead>
<tr>
<th></th>
<th>Participants</th>
<th>Families</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consented</td>
<td>421</td>
<td>124</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Average participants/family</td>
<td>3.43</td>
<td></td>
</tr>
<tr>
<td>Families with sample collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) within protocol-defined period (56 days +/- 7)</td>
<td>93(49-63)</td>
<td></td>
</tr>
<tr>
<td>b) &lt;49 days</td>
<td>25(31-48)</td>
<td></td>
</tr>
<tr>
<td>c) &gt; 63 days</td>
<td>2(64-70)</td>
<td></td>
</tr>
<tr>
<td>NPS collected</td>
<td>1945</td>
<td></td>
</tr>
<tr>
<td>Saliva samples collected</td>
<td>2134</td>
<td></td>
</tr>
</tbody>
</table>

**Day 0 Bristol NPS data**

<table>
<thead>
<tr>
<th></th>
<th>Median carriage density (Log10 gene copies/ml (range))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index child</td>
<td>3.28(0.68-4.13)</td>
</tr>
<tr>
<td>Sibling</td>
<td>2.74(0.79-4.81)</td>
</tr>
<tr>
<td>Mother</td>
<td>1.06(0.68-2.03)</td>
</tr>
<tr>
<td>Father</td>
<td>1.19(0.66-4.29)</td>
</tr>
</tbody>
</table>

**Conclusion**

These data confirm study feasibility including high participation and completion rates per protocol. Pneumococcal carriage rates in all age groups are slightly higher than in our previous studies. This study exemplifies novel use of live attenuated vaccines as experimental probes in human challenge experiments to elucidate the biology of colonisation and transmission.
INFECTION MONONUCLEOSIS
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Background and Aims:

Nasopharyngeal pneumococcal colonization varies according to region and community. In Ukraine the rate of S. pneumoniae carriage in healthy children under 5 years of age is approximately 35%-54% (Chernyshоvа L,2015). The aim of this study was to analyze the association between acute Epstein-Barr virus (EBV) infection, upper respiratory tract viral infections (URI) and nasopharyngeal (NP) colonization with S. pneumoniae.

Methods:

We observed 191 patients 0-5 y.o.- 64 children with EBV primary infection and 127 children with URI. We tested for the presence of 10 common respiratory viruses by real-time PCR; S. pneumoniae was isolated by culture methods. Serotyping was performed using the multiplex PCR. We tested anti-VCA IgM & IgG as markers for acute EBV

Results:

The occurrence of S. pneumoniae NP colonisation in children with primary EBV was significantly higher (70.3%) than in the children with URI (21.3%). Most prevalent S. pneumoniae serotypes in children with acute EBV were 14 (50%) followed by 23F (12.5%) and 6 (9.4%), in children with URI – 19F (27.6%), 6A/B (15,7%), 23F (7,8%). A 6,25% children with EBV have been shown to carry more than one serotype S. pneumoniae.

Conclusion

Our study suggests that there is a high incidence of S. pneumoniae coinfections in children admitted with EBV primary infection. Streptococcus may be a secondary pathogen or have a synergistic effect in the inflamed or damaged tonsillar and pharyngeal tissue.

THE EFFECT OF HOOKWORM CO-INFECTION ON PNEUMOCOCCAL CARRIAGE AND INVASIVE DISEASE

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Background and Aims:

Hookworm infections are highly prevalent in sub-Saharan Africa and South East Asia, where the incidence of invasive pneumococcal disease is also high. Hookworms are gastrointestinal nematodes that normally reside within the small intestine of their host for months or years, causing long-lived chronic infection. In addition, hookworm larvae migrate through the lung, which is associated with significant tissue damage. Chronic helminth infections promote an immunoregulatory environment, which is associated with increased numbers of T regulatory (Treg) cells and higher levels of the immunosuppressive cytokines, TGF-β and IL-10, which can alter the immune response to bystander pathogens. Resistance to pneumococcal disease is based upon a delicate balance between Treg-driven immune tolerance and pro-inflammatory responses which may clear infection but can also lead to tissue damage, providing a route for bacterial dissemination. Thus, the tissue damage caused by larval
migration through the lung and the immunoregulation associated with adult hookworms in the small intestine may influence pneumococcal disease progression.

Methods:

Our lab is currently investigating the effect of hookworm (Nippostrongylus brasiliensis and Heligmosomoides polygyrus) co-infection on pneumococcal disease progression using mouse models of pneumococcal carriage and pneumonia.

Results:

Our preliminary data suggest that both lung migration and chronic gastrointestinal infection caused by these helminths leads to increased mortality in mouse pneumococcal pneumonia models and may also promote seeding of the bacterium from the nasopharynx to the lungs in pneumococcal carriage models.

Conclusion

These studies suggest that hookworm co-infections can worsen disease outcome in pneumococcal pneumonia and promote progression from carriage to disease.

ISPPD-0189

NASOPHARYNGEAL CARRIAGE OF STREPTOCOCCUS PNEUMONIAE IN HEALTHY CHILDREN

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Background and Aims:

Streptococcus pneumoniae (pneumococcus) is a transient coloniser of the human nasopharynx (NP) and mostly resides asymptomatically. Healthy children provide the best reflection of pneumococci circulating within a community. Pneumococcal vaccines have successfully reduced the carriage of vaccine-types, however these are being replaced by non-vaccine types. Vaccine elimination of pneumococci is thought to affect the nasopharyngeal microbiota. Staphylococcus aureus and Haemophilus influenzae are of great interest as they are capable of replacing pneumococci in several disease aetiologies. In light of the routine use of pneumococcal vaccines in the childhood immunisation scheme of Hong Kong, we aim to study pneumococcal carriage in healthy children and understand its associations with prominent commensals of the NP.

Methods:

Nasopharyngeal swabs (N = 601) were collected from children between 2-14 years of age, between January 2014 and February 2015. Specimens were cultured on selective media to isolate S.pneumoniae, S.aureus and H.influenzae. Organisms were identified using appropriate biochemical tests. S.pneumoniae isolated were serotyped.

Results:

The carriage rates of S.pneumoniae, S.aureus and H.influenzae were 10.6% (N=64), 22.1% (N=133) and 1.0% (N=6) respectively. Serogroup 15 was the most common (20.3%, N=13), followed by Serogroup 6 (17.2%, N=11), 23A (12.5%, N=8) and 11A/D (6.25%, N=4). A
significant negative association was found between \textit{S.pneumoniae} and \textit{S.aureus} (OR 0.4, 95% CI 0.18-0.9, p < 0.05).

\textbf{Conclusion}

Carriage rate of \textit{S.pneumoniae} and \textit{S.aureus} have remained steady compared to previous studies. A large proportion of \textit{S.pneumoniae} belonged to non-vaccine serotypes. The negative association between \textit{S.pneumoniae} and \textit{S.aureus} suggests antagonism between the organisms which warrants further investigation.
It is vital to monitor the epidemiology of pneumococcal serotypes and resistance to better understand the selective pressures of antibiotic prescribing and help guide the future vaccine scheduling in PNG.

MICROBIOLOGY

ISPPD-0023
REVERSED ANTIMICROBIAL RESISTANCE IN PNEUMOCOCCI BY HAMLET- A HUMAN MILK PROTEIN-LIPID COMPLEX
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Background and Aims:

Multi-drug resistance in Streptococcus pneumoniae (pneumococci) remain a leading and major cause of death worldwide, making it one of the priority pathogens listed by the WHO against which new treatment alternatives are urgently needed. Using natural molecules as medication is one possible alternative and human breast milk is a suitable candidate due to its known anti-infectious properties. We have purified a protein-lipid complex from human milk termed HAMLET that has bactericidal activity against a range of bacterial species including pneumococci. This activity is high in vitro but the efficacy of HAMLET alone in vivo is not optimal. This project aimed to develop a new way of treating antibiotic resistant infections using HAMLET.

Methods:

In pneumococci, membrane and intracellular events was detected using fluorescent methodology. Bacterial survival was measured using the broth micro-dilution method.

Results:

Sublethal concentrations of HAMLET induced membrane depolarization, without causing death. Beside membrane depolarization, HAMLET triggered a series of events involving changes in intracellular ion levels and binding to a set of intracellular proteins and molecules. Mechanistically, HAMLET-induced membrane depolarization in the absence of cell death increased membrane permeability, facilitating the entry of molecules. HAMLET and antibiotic combination treatment of resistant isolates resulted in re-sensitization with subsequent bacterial death to the antibiotic they were resistant to.

Conclusion

HAMLET facilitated the entry of antibiotics and their access to antibiotic targets. These results support the idea of developing HAMLET into an antibiotic adjuvant that have the potential to solve the problem of antimicrobial resistance in pneumococci.

ISPPD-0146
DOES SAMPLING THE OROPHARYNX IN ADDITION TO THE NASOPHARYNX IMPROVE PNEUMOCOCCAL DETECTION IN ADULTS USING MOLECULAR METHODS?
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Background and Aims:

The WHO recommends collection of both oropharyngeal (OP) and nasopharyngeal (NP) samples for pneumococcal carriage studies in adults using standard culture-based methods. As molecular methods are increasingly used in carriage studies, we examined whether sampling both the NP and OP improves pneumococcal detection in adults using molecular methods. Previous work highlighted commensal streptococci in OP samples can cause spurious identification and serotyping results, here we use an approach minimising false positives.

Methods:

Paired NP and OP samples (n=508 each) were collected from adults as part of the New Vaccine Evaluation Project in Fiji. NP and OP samples were initially screened using lytA qPCR. lytA positive OP samples were additionally screened by bguR and piaB qPCR, only proceeding for further testing when positive by lytA plus bguR or piaB. Final identification of pneumococci and molecular serotyping was performed using microarray following a culture amplification step.

Results:

Overall, 65 (13%) of 508 adults carried pneumococci, 43 (66%) of the carriers had detectable pneumococci in the nasopharynx only, 14 (22%) had detectable pneumococci in the oropharynx only, and 8 (12%) had pneumococci in both sites. Compared with NP sampling alone, combined NP and OP sampling did not significantly improve detection of pneumococcal carriage (51/508, 10% vs. 65/508, 13%; p=0.200). The results were similar for vaccine and non-vaccine serotypes, with no significant improvement in detection with the addition of OP sampling (p=0.452 and p=0.370, respectively).

Conclusion

OP sampling (in addition to NP sampling) did not significantly improve detection of pneumococci using molecular methods.
Background and Aims:

S. pneumoniae resistant to antimicrobials is a public health threat. Pneumococcal colonization is a precursor of invasive disease. Mozambique introduced PCV10 in April 2013. We evaluated the impact of PCV10 on AMR pneumococci colonizing the upper respiratory tract.

Methods:

We used data from two cross-sectional surveys, 2012-2013 (pre-PCV10) and 2015-2016 (post-PCV10), among children aged six weeks to 59 months. Participants included HIV-infected children presenting for routine care at outpatient clinics and a random sample of HIV-uninfected children from the community. We collected vaccination history and nasopharyngeal swabs. Swabs were cultured, and isolates underwent serotyping and antimicrobial susceptibility testing. CLSI 2017 guidelines breakpoints were used to determine AMR. We compared AMR-pneumococcal carriage prevalence pre- and post-PCV10 introduction by HIV status.

Results:

Among 243 HIV-uninfected and 336 HIV-infected children with pneumococcal carriage pre-PCV10, 191 (79%) and 303 (90%) carried pneumococci resistant to ≥1 drug, respectively. Resistance to trimetoprim-sulphamethoxazole, tetracycline, and erythromycin were most common. In HIV-uninfected colonized children, tetracycline and erythromycin resistance decreased from 24% (58/243) and 14% (34/243) pre-PCV10 to 16% (44/280 fully-vaccinated carriers) (P=0.018) and 8% (22/280 fully vaccinated carriers) (P=0.024) post-PCV10. No declines in AMR-pneumococci were observed among colonized HIV-infected children for any of the antimicrobials tested. PCV10-types were associated with tetracycline (OR: 3.25 [95%CI: 3.48-4.50]) and erythromycin resistance (OR: 11.9 [95%CI: 5.25-27.0]).

Conclusion

Impact of PCV10 on reducing erythromycin- and tetracycline-resistant pneumococcal colonization was observed in HIV-uninfected children. PCV10 is an important intervention for prevention of carriage and illness due to AMR-pneumococci.

ISPPD-0743

PNEUMOCOCCAL SEROTYPE DISTRIBUTION AND ANTIMICROBIAL SUSCEPTIBILITY FOR CHILDREN OF 2017 IN SUZHOU, CHINA BEFORE THE INTRODUCTION OF PCV13

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Background and Aims:

In order to estimate the potential impact of pneumococcal vaccines in children in Suzhou and provide the basis for vaccination strategies, we carried out a prospective study to investigate the distribution of pneumococcal serotypes and antimicrobial susceptibility of *Streptococcus pneumoniae* from hospitalized children <14 years in Suzhou, China.

Methods:

From January 2017 to early August 2017, we prospectively collected *S. pneumoniae* from Soochow University Affiliated Children's Hospital (SCH). The antibiotic susceptibility, serotypes of *S. pneumoniae* strains were identified by E-test, Quellung reaction or and multiplex PCR.

Results:

A total of 569 *S. pneumoniae* isolates were obtained, from CSF (n=3), blood (n=1), bronchial lavage fluid (n=18), sputum (n=516), and otorrhea (n=30). Isolates from males were approximately 1.5 times that of females, and most of the isolates were from children under 5 years (84%). Potential vaccine coverage rates with PCV7, PCV13, and PPSV23 were 58.7%, 76.6%, and 73.6%, respectively. The most common serotype was 19F (29.9%), followed by 19A (9.7%), 6B (9.5%), 14 (9.3%), 23F (9.1%). Although majority of the isolates were resistant to erythromycin, clindamycin, tetracycline, and sulfamethoxazole, most of the strains were sensitive to penicillin, vancomycin, and levofloxacin. For PCV13 isolates, antibiotics resistant rates are generally higher or similar to other strains.

Conclusion

Serotypes 19F was the most common serotype detected in children in Suzhuo, China. PCV 13 vaccine coverage was high. It is likely that PCV13 will have a substantial impact on antimicrobial resistance in China.

ISPPD-0199
UNDERESTIMATION OF ANTIMICROBIAL RESISTANT S. PNEUMONIAE BY CONVENTIONAL SEROTYPING OF MULTIPLE-SEROTYPE-CARRIAGE IN HEALTHY CHILDREN IN MALAWI: RISK OF PNEUMOCOCCAL VACCINE DRIVING RESISTANT STRAIN EMERGENCE

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Background and Aims:

Increasing access to antibiotics and the recent introduction of pneumococcal vaccines into EPI schedules makes robust surveillance for emergence of drug-resistant pneumococci a clinical and public health imperative. During community-based pneumococcal carriage surveillance in Malawi, concordance was assessed between conventional microbiological drug susceptibility testing (DST) and detection of resistance genes by molecular serotyping microarray. Through identifying antimicrobial resistance (AMR) the frequency of AMR non-vaccine serotype (AMR-NVT) pneumococcus co-colonised with vaccine serotype (VT) was investigated.

Methods:

Nasopharyngeal samples were collected from children 3-10 years old following WHO recommendations. Sample selection criteria based on microarray results included presence of two unique pneumococcal serotypes, absence of non-pneumococcal species and detection of AMR profile with ≥1 tetM, mefA, cat, or ermB gene detected. A single isolate from the same sample was subject to DST by disc diffusion and E-test, per EUCAST recommendations, for susceptibility to tetracycline, macrolides and chloramphenicol.

Results:

Amongst 120 screened samples, 80 fulfilled the selection criteria. Amongst these, 56% (46/80) were discordant (AMR by microarray but DST-sensitive to all tested antibiotics). Discordance included 35 isolates with tetracycline and 23 with macrolide resistance. 14% (11/80) of samples carried an AMR-NVT with a VT.

Conclusion

Conventional DST underestimates AMR in multiple-serotype-carriage samples, likely due to AMR strains present at low abundance and not detected by culture of single isolate. AMR-NVT co-colonised with VT increases risk of pneumococcal vaccines driving emergence of AMR-NVT in settings with high prevalence of co-colonisation. DNA microarray enables the detection of this emergence where a gene mutation has been identified.

ISPPD-0537

THE ROLE OF TRANSFORMATION IN SHAPING THE DISTRIBUTION OF GENOMIC ISLANDS ACROSS PNEUMOCOCCAL POPULATIONS

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Background and Aims:
Genomic islands (GIs) are stretches of DNA present in only a subset of a bacterial population, and encode much phenotypic variation, such as serotypes and antibiotic resistance. They can be exchanged between strains through recombination mechanisms, such as transformation. This process can insert or delete GIs, depending on the donor and recipient genotypes, if an homologous recombination spans the GI's integration site and includes sufficiently long flanking homologous arms.

**Methods:**

An experimental assay was implemented in which the relative rates of GI insertion and deletion by transformation could be quantified. Mathematical models, representing different mechanistic hypotheses, were fitted to the data.

**Results:**

GI insertion rates declined geometrically with the GI’s size. Although most efficient for shorter GIs, transformation-mediated deletion frequencies did not vary consistently with GI length, with removal of 10 kb GIs approximately 50% as efficient as acquisition of base substitutions. Fragments of two kilobases, typical of transformation event sizes, could drive all these deletions independent of GI length.

**Conclusion**

This suggests transformation is unlikely to have evolved as an efficient means of acquiring novel gene cassettes, and is consistent with the low observed frequency of serotype switching, which necessitates the import of long stretches of DNA. Transformation is likely an effective mechanism for removing deleterious GIs, such as prophage, IS elements and other parasitic mobile elements. The strong asymmetry of transformation, favouring the elimination of GIs over their import, suggests non-mobile accessory loci must be under selection if they are maintained in a population.

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**ISPPD-0538**

**CHARACTERISATION OF A NOVEL PHASE VARIABLE RESTRICTION-MODIFICATION LOCUS**

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**Background and Aims:**

Restriction-modification (R-M) systems have an important role in defense against infection by mobile genetic elements. Additionally, epigenetic consequences of the different patterns of methylation caused by the SpnIII phase-variable type I R-M have been shown to affect phenotypes such as virulence. This work aims to characterize a second type I phase-variable R-M system, SpnIV, encoded by the translocating variable R-M (tvr) locus.

**Methods:**

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425
Mutagenesis was used to produce strains in which different components of the *tvr* locus were altered. These were characterized through a series of assays, including methylation-sensitive whole genome sequencing.

**Results:**

A novel rearrangement mechanism was inferred involving segments of DNA encoding target recognition domains, which determine the R-M system’s specificity, being shuffled laterally between two types of direct repeats within the locus. This process typically occurs over hours, although this varies in rate between strains, and appears to be regulated by a toxin/antitoxin-like system. By targeting an important recombinase gene, we have been able to explore the range of permutations different versions of the locus can achieve through construction of multiple ‘locked’ mutants. Methylation-sensitive sequencing identified the motifs targeted by the full diversity of target recognition domains found across the species, and also aided the identification of regulatory mechanisms that ensure only one specificity subunit within the *tvr* locus is active at once.

**Conclusion**

The *tvr* locus can drive many different patterns of methylation, which vary both within and between strains, giving it the potential to substantially influence both gene expression and dynamics of mobile genetic element transmission between pneumococci.

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**ISPPD-0330**

**INVASIVE STREPTOCOCCUS PNEUMONIAE SEROTYPE 35B IN SOUTH AFRICA, 2005-2016**

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**Background and Aims:**

Since pneumococcal conjugate vaccine (PCV) introduction in children, vaccine serotype invasive pneumococcal disease (IPD) declined with non-vaccine serotype replacement, including serotype 35B disease. Novel serotype 35D, non-reactive with factor serum 35a and harbouring a disrupted *wciG* gene, was recently described in the USA and Australia. We aimed to describe 35B and detect putative 35D in South Africa.

**Methods:**

We reviewed IPD cases reported through national, laboratory-based surveillance. Incidence rates per 100,000 population were calculated for 2005-2008 (pre PCV) and 2016. MLST-defined genotypes were determined for 64 35B’s. A convenience sample of 33 35B isolates, spanning 2005-2016, were re-serotyped using Quellung. Of these, 10 with whole genome data, and additional 35B genomes (n=35) without Quellung re-serotyping, were investigated for a disrupted *wciG* gene.
Results:

Surveillance identified 45,852 IPD cases: 376/31,513 (1%) were originally 35B by Quellung and 57% (214/376) were penicillin non-susceptible. All-age IPD incidence declined 60% (95% CI, 58%-62%; rates: 7.1 to 2.8). 35B incidence increased 4.5-fold in children aged <5 years (95% CI, 2.25-9.04; rates: 0.08 to 0.36) and doubled in adults aged ≥25 years (95% CI, 1.20-3.21; rates: 0.05 to 0.10). Serotype 35B’s were predominantly penicillin-non-susceptible ST361 and single-locus variants (30/64, 47%) or penicillin-susceptible ST9813 (12/64, 19%). 4/33 (12%) putative 35D’s (isolated in 2011, 2012, 2013) were identified phenotypically; three had unrelated wciG disruptions and genotypes. The additional 35B genomes revealed no wciG disruptions.

Conclusion

Serotype 35B incidence increased significantly post PCV, and almost half belonged to penicillin non-susceptible clone ST361. Putative 35D was detected at low frequency in unrelated lineages post PCV.

Background and Aims:

The nasopharynx is a complex and dynamic environment, where *Streptococcus pneumoniae* interact with the host immune system as well as other colonising bacteria, including potential pathogens such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*. The aims of this study were to estimate the carriage prevalence of those bacteria in young children in Indonesia, and to examine interactions between these bacterial species.

Methods:

302 healthy children aged 12-24 months were enrolled in community health centres in Bandung (West Java), Lombok (West Nusa Tenggara), and Padang (West Sumatra) regions of Indonesia. Nasopharyngeal swabs were collected using a flocked, nylon swab and stored according to World Health Organization recommendations, and bacterial species detected by qPCR.

Results:
Overall carriage prevalence was 49.5% for *S. pneumoniae*, 27.5% for *H. influenzae*, 42.7% for *M. catarrhalis*, and 7.3% for *S. aureus*. Positive associations were observed for pneumococcus and *M. catarrhalis* (OR 3.1 [95% CI 1.91 – 4.94]), and *H. influenzae* and *M. catarrhalis* (OR 2.34 [95% CI 1.40 – 3.91]), and a negative association was found between *M. catarrhalis* and *S. aureus* (OR 0.06 [95% CI 0.01 – 0.43]). Densities of pneumococci, *H. influenzae*, and *M. catarrhalis* were positively correlated when two species were present.

**Conclusion**

Positive associations between carriage and density between pneumococci, *H. influenzae*, and *M. catarrhalis* suggest a synergistic relationship among these species with potential clinical implications.

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**ISPPD-0301**

EVALUATING THE ADDED VALUE OF OROPHARYNGEAL SWABS FOR DETECTION OF PNEUMOCOCCAL CARRIAGE IN ADULTS, KENYA


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**Background and Aims:**

Nasopharyngeal (NP) specimens are the gold standard for pneumococcal colonization detection in children, but consensus is lacking on ideal specimen(s) for detection of adult carriage. Current guidelines recommend both NP and oropharyngeal (OP) swabs. We evaluated the added value of OP specimens in an adult carriage study.

**Methods:**

Pneumococcal carriage was assessed during 2012 as part of multi-year cross-sectional studies evaluating 10-valent pneumococcal conjugate vaccine (PCV10) impact. Adults with children aged <5 years were recruited from a community in rural Kenya. For each participant, NP and OP swabs were collected and stored separately. Each swab was cultured for pneumococci; serotypes were determined by Quellung. We compared pneumococcal isolation rates between NP and OP specimens and the contribution of OP for PCV10-type carriage detection.

**Results:**

Of 557 adults (median age=33.9 years; range 16.4, 72.6 years), 283 (50.8%) were colonized. Pneumococci were detected from both OP and NP specimens for 131 (23.5%) and only from NP in 119 (21.4%). OP swabs alone yielded an additional 33 (5.9%) positives. PCV10-type carriage was isolated from NP or OP swabs in 9.7% (54/557) of subjects; 4.7% (26/557) had PCV10 in NP swabs only. In 0.9% (5/557) of subjects was PCV10-type carriage identified only in OP swabs.

**Conclusion**
In this setting, inclusion of OP swabs minimally increased microbiologic detection of overall and PCV10-pneumococcal carriage. The added cost and benefit of collecting OP specimens could justify excluding their use for future adult carriage studies.

ISPPD-0660
OPTIMISATION OF PNEUMOCOCCAL CARRIAGE DETECTION BY COMBINED DIRECT AND CULTURE-AMPLIFIED QUANTITATIVE PCR
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Background and Aims:

The impact of conjugate and potentially 3rd generation protein antigen pneumococcal (Sp) vaccines depends greatly upon effects on carriage and transmission in young children. Conventional culture detection methods lack sensitivity.

Methods:

We compared the performance of culture, direct lytA qPCR without (direct-DqPCR) and with a preceding 24h culture-amplification (CAqPCR) step in nasal swab STGG samples stored frozen, from two groups of healthy toddlers attending daycare in Coimbra, Portugal in 2011 and 2012. We performed microarray serotyping on DNA extracts from the cultures.

Results:

Sp detection rates by culture (Cx) were lower(60.1%) than by DqPCR(66.1%) with 36(7%) Cx-DqPCR+ and 9(1.7%) Cx+DqPCR- samples(n=516). Rates by CAqPCR were higher(75.8%) than by DqPCR(68.3%) with 60(12%) D-CA+ and 6(1.2%) D+CA- samples for a combined overall detection rate of 80.4%(n=496). Increases in DNA following CA varied widely (101-107) but were not predicted by serotype. A subpopulation with small increases were mostly non-typeable or Sp-like strains. High density DqPCR samples tended to increase less on CA suggesting a saturation effect in culture.

Conclusion

Performing both DqPCR and CAqPCR on STGG nasal swab samples achieves optimal sensitivity in pneumococcal carriage studies and identifies which samples contain viable organisms. DqPCR permits evaluation of carriage density over a wide (6-7 log10) range that is very difficult to achieve using dilutions and quantitative cultures. We also confirm that relative abundance of mixed serotypes in microarray detection assays done using DNA extracts from lawn cultures are not confounded by consistent differences between rates of growth of different serotypes.

Supported by an investigator-led grant from Pfizer.
ISPPD-0386
QUALIFIED MEASURE OF PERFORMANCE OF NASOPHARYNGEAL VERSUS OROPHARYNGEAL SAMPLING FOR DETECTION OF S. PNEUMONIAE CARRIAGE AMONG ADULTS WITH CULTURE AND MOLECULAR METHODS
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Background and Aims:

Pneumococcal carriage studies are valuable tools in understanding population biology, transmission dynamics and vaccine impact. WHO guideline recommends, sampling of nasopharynx only for detecting pneumococci in infants and children. The date on the role of Oropharyngeal sampling in adults though convenient, is limited and conflicting. We assessed efficiency of NP vs OP sampling in identifying and quantifying S. pneumoniae in a single cohort of pre and post Hajj pilgrims from India.

Methods:

Using flocked swabs, paired NP (1614) and OP (n=1614) samples were harvested from 807 pilgrims with an interval of 40±5 days. Swabs were placed in STGG medium and frozen at −80°C till processing. Pneumococcal carriage was detected by culture and qmPCR. Serotyping was performed with Quellung, PCRseqTyping and mPCR-FAF.

Results:

In NP samples, carriage detection in pre and post Hajj cohorts by culture was 5.6 and 7.8%. qmPCR was positive in 18 and 22%. Whereas, in pre and post OP sample cohorts, culture detection was 7.4 and 8.6%, qmPCR was positive in 20 and 21.3%. Serotypes 5, 6A, 15B and 23A, 24B, 33A were isolated exclusively from NP and OP swabs, respectively. The average genome copies/µl of pneumococci in NP and OP swabs were 296 and 394, correspondingly.

Conclusion

Our study demonstrates that OP sampling was marginally superior to NP sampling. Studies that use a single sample to identify carriage may underestimate pneumococcal carriage rates and miss-out serotypes exclusively present. Sampling from both sites is necessary to obtain accurate information, especially in adults.

ISPPD-0427
BACTERIOLOGY OF MIDDLE EAR FLUID FROM INDIAN CHILDREN WITH RECURRENT OTITIS MEDIA: A MOLECULAR DETECTION APPROACH
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Background and Aims:

Causative bacterial pathogens are one of the major risk factor of recurrent Otitis media in children. Prior antibiotic administration in these children often results in negative culture. With the scarcity of available Indian data, we performed this study to identify the bacterial etiology.

Methods:
36 Middle ear fluid (MEF) samples were collected by tympanocentesis from children below 5 years. 78% of the cases had 3 previous episodes of otitis media in the past 6 months whereas the rest 22% of the cases had 4 episodes in the last 6 months. All of them were on antibiotic coverage at the time of sample collection. The clinical samples (MEF no.36) were subjected to bacterial culture, 16s rDNA PCR and qmPCR for *S. pneumoniae*. qmPCR positive samples for *S. pneumoniae* were serotyped by PCRSeqTyping.

Results:

Every single sample was negative by conventional culture whereas 16s rDNA PCR identified bacterial pathogens in 33 out of 36 specimens. The organisms identified in 29 samples were *Neisseria* sp\(\text{(n=7)}\), *Neisseria meningitidis* (n=8), *Lactococcus* sp \(\text{(n=5)}\), *S. pneumoniae* (n=2), *Pseudomonas aeruginosa* (n=2), *Haemophilus influenza* (n=1), *Streptococcus infantis* (n=1), *Staphylococcus epidermidis* (n=1), *Staphylococcus auricularis* (n=1) and *Streptococcus* sp (n=1). Four samples showed mixed reads. qmPCR was also positive for *S. pneumoniae* in 2 samples. PCRSeqTyping identified Serotype 19A in both the samples.

Conclusion

The study demonstrates the usefulness of 16s rDNA PCR and provides insights to the etiology of bacterial pathogens in MEF by culture-independent method.

ISPPD-0516
DEVELOPMENT OF USER FRIENDLY, DEPENDABLE SOFTWARE TO ANALYZE MICROARRAY FEATURE EXTRACTION DATA FOR S. PNEUMONIAE SEROTYPING
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Background and Aims:

Microarray platform offers greater potential in serotyping as compared to conventional typing methods. With specific probes for testing it is potentially quicker, easier and more reliable than established tests. They have a diagnostic prospective in a number of areas including that of infectious diseases. Manual analysis of the system output raw data is labor intensive, time consuming, error prone with interpretation difficulties. To address these issues in-house software was developed and evaluated.

Methods:

Probe identity, processed signal and background subtracted signal were considered and output was derived in the form of percentage. 100% detection of the probes signal was the detection parameter of the serotypes. The percentage occurrence of each serotype was analyzed by measuring the intensity of background signal. The accuracy of the model was evaluated with 53 known individual standard strains and 10 pooled samples, each containing 2 different known standard strains.

Results:

Accurate interpretation of the data was provided by the model for all the standard strains and spiked samples tested.
Conclusion

Use of software enables faster and easier serotype inference of the raw data. The development of in-house software resulted to an error free, economical mode of reporting.

ISPPD-0511
MACROLINE RESISTANCE IN STREPTOCOCCUS PNEUMONIAE AND ITS RELATIONSHIP WITH INVASIVE/CARRIAGE PORTENTIAL OF DIFFERENT SEROTYPES
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²Bangladesh Institute of Child Health, Dhaka Shishu Hospital, Dhaka, Bangladesh

Background and Aims:

Pathogenesis of Streptococcus pneumoniae (Spn) starts with colonization of the nasopharynx (NP), the potential ecological niche where bacteria acquire antimicrobial resistance and virulence factors. However, duration of colonization in NP differs for different serotypes; invasive serotypes reside for shorter period in the NP than noninvasive serotypes. There have been reports on increasing macrolide-resistance of Spn. We investigated the correlation of macrolide susceptibility of serotypes to their invasive potentiality.

Methods:

We selected 384 erythromycin susceptible and 81 non-susceptible invasive isolates. Odds ratio (OR) was calculated and used to estimate the invasive potential (IP) of serotypes through comparison with nasopharyngeal isolates (N=453). Invasiveness of each serotype was calculated with erythromycin resistance by Pearson’s correlation coefficient test.

Results:

Highest ORs were exhibited by serotypes 1(25.08), 12A(19.5), and 7F(12.86), with significant association with invasive disease. Conversely, serotypes with low ORs (<1), 19F, 19A and 23F, were found to be significantly associated with carriage. Serotypes 2, 5, 45 and 38 were associated with invasive disease (IP considered 100%). Analysis of 465 invasive pneumococcal isolates showed that serotypes with low IP/invasiveness were predominantly erythromycin non-susceptible serotypes 19F(44%), 6B(38%), 23F(36%), 19A(35%) and 6A(28%); serotypes with high IP/invasiveness were rarely non-susceptible 1(0%), 1(4%), 5(8%), 12A(0%) and 45(0%).

Conclusion

A strong negative correlation (r = -0.736) was found with invasiveness of serotypes and macrolide resistance. To understand the dynamics of macrolide resistance, we should be vigilant in the post vaccine era and closely monitor trends of macrolide resistant serotypes in the NP besides invasive sources.

ISPPD-0720
DETECTION OF MACROLIDE RESISTANT GENES OF STREPTOCOCCUS PNEUMONIAE ISOLATED FROM NORTHEAST MALAYSIA
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Background and Aims:

Streptococcus pneumoniae is one of the leading causes of the mortality and morbidity worldwide. The dramatic increased in in-vitro resistance of antibiotics particularly beta-lactams and macrolide antibiotics raised the questions on clinical impact of antimicrobial resistance on clinical outcomes. Therefore, this study aims to describe the distribution of macrolide-resistance determinants in S. pneumoniae and to associate with clinical outcomes among patients.

Methods:

A descriptive cross sectional study was conducted in a tertiary teaching hospital, Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia from June 2014 to December 2015. All S. pneumoniae were isolated from clinical specimens. All isolates were subjected to polymerase chain reaction analysis to detect macrolide-resistant determinants. Patients’ clinical data were obtained from clinical notes.

Results:

A total of 113 S. pneumoniae were isolated in the study. 26.5% of the isolates were resistant to erythromycin with MIC range of 0.03 to >256 \( \mu \)g/ml and MIC\(_{90}\) of 32 \( \mu \)g/ml. Among the erythromycin-resistant isolates, \( \text{mef(A)} \) and \( \text{erm(B)} \) gene were detected in 50.4% and 20% isolates respectively. 16.7% of the isolates were found to have both \( \text{mef(A)} \) and \( \text{erm(B)} \) gene and 13.3% with none of the two genes. There were no significant association between presence of macrolide resistance determinants with mortality (\( p = 0.837 \)) or complications (\( p > 0.999 \) for empyema and cardiac complication; \( p = 0.135 \) for subdural abscess)

Conclusion

Macrolide resistant genes were detected among S. pneumoniae isolates. However, there was no significant association between macrolide resistant determinants with clinical outcomes of patients with pneumococcal infection.

Background and Aims:

Streptococcus pneumoniae a major cause of infectious disease worldwide, especially in children. It has a highly diverse polysaccharide capsule and has over 92 serotypes. There have been recent reports on variants of serotype-35B and serogroup-6. Here, we report variants of serogroup-35 found in nasopharynges of Bangladeshi children.

Methods:
Between January 2016 through September 2017, we collected 8,587 nasopharyngeal swabs from children aged 3-35 months with clinical pneumonia. All isolates were serotyped using both antisera-based quellung (Staten Serum Institute, Denmark) and PCR reactions.

Results:

We detected 2001 pneumococcal isolates, 220 of which belonged to serogroup-35. However, we could not determine the serotype of eight isolates of serogroup-35. Amongst five factor sera (fs) of serogroup-35 (35a, 35b, 35c, 29b and 42a), these isolates yielded positive results with all sera except 42a, a combination not currently known (Table: 1). PCR results matched that of serotype 35F, but quellung patterns did not.

Table 1: Serological profile of serotype 35 (35A, 35B, 35C and 35F).

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Pool G</th>
<th>Group 35</th>
<th>fs35a</th>
<th>fs35b</th>
<th>fs35c</th>
<th>fs29b</th>
<th>fs42a</th>
</tr>
</thead>
<tbody>
<tr>
<td>35A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>35B</td>
<td>+</td>
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<td>35F</td>
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<tr>
<td>Atypical 35</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>

Conclusion

We report an atypical serotype in serogroup-35. Future genetic analysis and structural studies of capsular polysaccharide is required to determine this serotype. We should be vigilant and conduct continuous surveillance to track emergence of new serotypes.

ISPPD-0741
RADIOLOGICAL ABNORMALITIES IN CHILDREN WITH COMMUNITY ACQUIRED PNEUMONIA
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Background and Aims:

Streptococcus Pneumonia (SP) is a common cause of community Acquired Pneumonia (CAP) in children. Similar SP serotypes have been reported from nasopharynx (NP) and blood in CAP. Primary endpoint pneumonia (PEP) is a commonly reported radiological
abnormality in SP-CAP. Objective was to find radiological abnormalities in children with CAP with or without SP isolation from their NP.

Methods:

This study was conducted in four teaching hospitals in Uttar Pradesh and Bihar states, India. Here 2/3rd of children are vaccinated against *Haemophilus influenzae* type B but Pneumococcal Conjugate Vaccination has not yet started. Children aged 2-59 months hospitalized with WHO defined CAP were recruited with parental consent. NP culture and SP isolation were done by convectional microbiological techniques. Chest X ray (CXR) was done and interpreted by an independent panel of radiologists.

Results:

From March-December 2017, 337 cases were recruited for NP swab culture. Among these 42(12.46%) were positive for SP and 63.5% for other organisms. SP isolation in ages 2-11 months was 52.4%(22/42); 12-23 months 21.4%(9/42) and 24-59 months 26.2%(11/42). PEP was present in 24% (81/337) and 26.2% SP positive. Other infiltrates were present in 45.7%(154/337) and 45.7% in SP positive. Normal CXR was found in 30.3%(102/337) and 31% in SP positive.

Conclusion

Abnormal as well as normal CXR was found in cases of CAP with NP swab positive for SP. Ongoing serotyping of these isolates would reveal if there is any difference in cases of various radiological abnormalities.

ISPPD-0428

PCR-BASED DISCRIMINATION OF EMERGING STREPTOCOCCUS PNEUMONIAE SEROTYPE 22F AND 33F

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Background and Aims:

Serotyping of *Streptococcus pneumoniae* is important to monitor disease epidemiology and assess the impact of pneumococcal vaccines. Traditionally, the Quellung reaction used serotype-specific antibodies to classify *S. pneumoniae* based on differences in capsular antigens. More recently, PCR-based serotype deduction relying on serotype-specific capsule biosynthesis genes has been broadly applied for pneumococcal surveillance. However, PCR-based serotyping lacks discrimination for certain *S. pneumoniae* serotypes, including the differentiation of serotype 22F from 22A, and serotype 33F from 33A and 37. Serotypes 22F and 33F are emerging serotypes that are absent in the currently licensed 13-valent pneumococcal conjugate vaccine, but present in the new candidate 15-valent formulation. This study validated novel PCR reactions to detect and discriminate *S. pneumoniae* serotypes 22F and 33F.

Methods:

In order to differentiate *S. pneumoniae* serotypes 22F or 33F from genetically similar serotypes, two novel PCR reactions were designed and validated. The specificity of all PCR
targets was evaluated using all 92 different *S. pneumoniae* serotypes, as well as 32 other streptococci. Reproducibility was evaluated using geographically and genetically diverse strains of *S. pneumoniae* serotypes 22F and 22A, or serotypes 33F, 33A, and 37 that were previously characterized by reputable reference laboratories.

**Results:**

Overall, *S. pneumoniae* serotypes 22F and 33F could be accurately and reproducibly detected and discriminated.

**Conclusion**

Such a molecular serotyping approach provides a valuable diagnostic tool that is feasible in any molecular laboratory, to enable pneumococcal serotype surveillance and subsequent assessment of the impact of the new 15-valent candidate pneumococcal vaccine.

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**ISPPD-0702**

**EFFLUX MEDIATED HIGH-LEVEL MACROLIDE RESISTANCE IN STREPTOCOCCUS PNEUMONIAE IS MEDIATED BY MEL AND REGULATED BOTH IN CIS AND TRANS IN A STRAIN-DEPENDENT MANNER**

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**Background and Aims:**

The Macrolide Genetic Assembly (Mega), a 5.1-5.2 kb genetic element related to conjugative transposons and containing the genes *mef*(E) and *mel*, is responsible for efflux-based macrolide resistance in *Streptococcus pneumoniae*. Two varieties of Mega have been characterized, Mega-1 (99bp insertion between *mef*(E) and *mel*), and Mega-2, lacking this insertion. Mega can be inserted in six unique locations in the pneumococcal genome; and while many insertions result in efflux typical low-level resistance, some Mega insertions display a wide range of MIC values and result in high-level resistant strains (erythromycin MICs>16ug/ml-256ug/ml).

**Methods:**

Mega insertion classes displaying high-level resistance were examined and compared to low-level resistant strains using established molecular techniques. Mega cassettes from representative strains were interchanged as well as inserted into a D39 background. Single deletion strains were constructed for *mef*(E) and *mel*, and a strain was constructed containing the *mef*(E) upstream regulatory region joined to the *mel* start.

**Results:**

Replacing Mega-2 with Mega-1 resulted in the downregulation of both *mef*(E) and *mel*. The Mega-2 element in the context of a high-level resistant strain had higher MICs than a low-level resistant strain. These data point to cis and trans acting factors affecting Mega-mediated resistance. In high-level resistant strains, *mel* alone was responsible for mediating high-level resistance and this correlated with high levels of *mel* expression.

**Conclusion**
Unlike typical efflux-mediated low-level resistance (dependent on both mef(E) and mel), mel is upregulated and is required to convey high-level efflux-mediated resistance in pneumococcal strains. Strain background influences low-versus high-level efflux mediated macrolide resistance in S. pneumoniae.

ISPPD-0466
A PNEUMOCOCCAL SEROGROUP 11 CAPSULE VARIANT IDENTIFIED IN THE ASIA-PACIFIC REGION
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⁷The University of Melbourne, Centre for International Child Health-Department of Paediatrics, Parkville, Australia
⁸St. George’s- University of London, Institute for Infection and Immunity, London, United Kingdom
⁹London Bioscience Innovation Centre, BUGS Bioscience, Parkville, United Kingdom
¹⁰The University of Melbourne, Department of Microbiology and Immunology at the Peter Doherty Institute for Infection and Immunity, Parkville, Australia

Background and Aims:
As part of a pneumococcal vaccine impact study in Fiji, we used DNA microarray to conduct pneumococcal serotyping on nasopharyngeal swabs from children. 78 of 2,045 (3.8%) swabs contained pneumococci that typed as ‘11F-like’, a novel genetic variant of serotype 11F. In this study, we aimed to determine the genetic basis of the sequence diversity in the 11F-like capsular polysaccharide (cps) locus and if these changes modify antigenic properties of the capsule.

Methods:
The genomes of two randomly selected 11F-like isolates were sequenced. Phylogenetic analyses were performed for each gene in the cps locus to identify genes that were divergent from reference 11F sequences. Capsular phenotypes were evaluated by serological typing methods (Quellung reaction and latex agglutination).

Results:
Within the 11F-like cps locus, the wcwC and wcrL genes were phylogenetically divergent from reference 11F sequences. We also identified a single nucleotide insertion within a homopolymeric region of the 11F-like gct gene, which restores the open reading frame. In contrast to the 11F capsule, Quellung serotyping of 11F-like isolates confirmed the 11F-like capsule contains glycerol phosphate and lacks N-acetyl-glucosamine. This is due to changes in the 11F-like gct and wcrL genes, which mediate these modifications, respectively. As a result, serological typing methods type these isolates as serotype 11A. Similar 11F-like variants were also identified in Mongolia, Lao PDR and Vietnam.
Conclusion

Our study demonstrates that genetic variants can yield discrepant serotyping results depending on whether a genotypic or phenotypic approach is used. This work has implications for vaccine impact studies that monitor serotype replacement.

ISPPD-0547
GENETIC ANALYSIS OF PENICILLIN BINDING PROTEIN (PBP) 1a, 2b and 2x AMONG INVASIVE STREPTOCOCCUS PNEUMONIAE (SPN) RECOVERED FROM CHILDREN (< 5 YEARS) IN INDIA
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2Pushpagiri Institute of Medical Sciences and Research Center, Pushpagiri Research Center, Tiruvalla, India
3Christian Medical College, Clinical Microbiology, Vellore, India

Background and Aims:
PBPs mediate pneumococcal resistance to penicillin. The aim of this study was to analyze the variations in the pbp gene sequences, amino acid changes and correlate the same against minimum inhibitory concentration (MIC) to penicillin.

Methods:
Ten penicillin (PEN) susceptible (MIC ≤0.06 µg/mL) and ten PEN resistant ( meningitis ≥ 0.12 µg/ml and non- meningitis ≥2 µg/mL) from an ongoing multicentric surveillance study (BASIS) were tested. Pneumococcal DNA was extracted, and sequenced by primers against pbp1A (1197bp), pbp2B (1317bp) and pbp2X (1148bp). The generated sequences were compared with those of the published reference strain R6.

Results:
In the pbp1a sequences, seven (MIC to PEN > 0.25 μg/mL) of the PEN resistant isolates had a Ser352→ Ala mutation in the coding region 352-355 and an Ile358→ Thr mutation next to this region. The PEN susceptible isolates showed a low degree variation (<1%). All resistant isolates showed very minimal pbp2b sequence variation. Compared with the pbp2x gene sequence of the reference R6 strain, 10 isolates (MIC to PEN ≤ 0.05 µg/mL) showed high similarity to the R6 prototype, and the remaining 10 isolates (MIC to PEN ≥ 0.5 µg/mL) had 37 amino acid mutations concentrated within 345 amino acids between codons 257 and 602. No serotype based associations with specific mutations were discernible.

Conclusion
The variations in the pbp1a, pbp2b and pbp2x genes do not form a consistent association with increasing penicillin MIC values. This may explain the low level of complete resistance to penicillin among invasive Spn isolates in India.

ISPPD-0259
ANTIMICROBIAL RESISTANCE DETERMINANTS AND SUSCEPTIBILITY PROFILES OF PNEUMOCOCCAL CARRIAGE ISOLATES RECOVERED FROM HEALTHY CHILDREN IN PERU PRE-PCV INTRODUCTION
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Background and Aims:

Pneumococci’s ecological niche is the nasopharynx of healthy children. Pneumococcal resistance to antimicrobial agents has evolved into a worldwide health problem. Introduction of pneumococcal conjugate vaccines (PCV) has resulted in a decline in carriage of penicillin non-susceptible (PNS) pneumococci. In this study, we examined susceptibility profiles of pneumococcal isolates carried by healthy children in Peru pre-PCV7 introduction in 2009.

Methods:

As part of the Global Pneumococcal Sequencing project (www.pneumogen.net), whole genome sequences were obtained from 516 carriage isolates from children ≤2 in 3 different regions of Peru (2007-2009): coast (Lima, Piura), sierra (Cusco, Abancay, Arequipa, Huancayo), and amazon basin (Iquitos). A CDC bioinformatics pipeline was used to identify core genomic and accessory elements that conferred antimicrobial resistance phenotypes.

Results:

Four-hundred-thirteen (80%) isolates were predicted to be non-susceptible to at least one antimicrobial class, including 160 (31%) isolates resistant to at least three. The highest rates of non-susceptibility were observed against penicillin (50%, MIC≥0.12) and co-trimoxazole (75%, MIC≥1). The coastal region had the highest proportion of multidrug resistant (MDR) isolates (36.1%), significantly higher (p=0.04) than in the amazon basin (25%) and sierra (23.3%). The clones most commonly associated with PNS and MDR were: 19F/CC236(PMEN14) in the coast, 6B/CC90(PMEN2) in amazon basin, and 23F/CC81(PMEN1) in the sierra.

Conclusion

Since PCV7 contains 19F, 6B and 23F, their prevalence and associated MDR are likely to have decreased since the introduction of vaccine; a study of pneumococcal carriage in the same population post-PCV is currently being planned.

ISPPD-0237
MOLECULAR-BASED TESTING METHODS AND BROTH ENRICHMENT TO DETECT PNEUMOCOCCAL CARRIAGE, DENSITY, AND SEROTYPES

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Background and Aims:

To assist with monitoring PCV13 impact, we conducted S. pneumoniae (SP) carriage studies in nine Alaska communities in 2008-2014. Carriage prevalence measurements can be
affected by low-density or multiple-strain colonization that might go undetected using a direct plating method. The current study investigated molecular-based SP identification/serotyping methods and compared them to direct plating.

Methods:

107 (53 positive, 54 negative) previously assessed nasopharyngeal (NP) swabs frozen in STGG media were grown in enrichment broth. On enriched and non-enriched STGG samples, we used \textit{lytA} and \textit{psaA} qPCR for SP detection and no-stop multiplex conventional PCR for serotyping. We assessed SP density using \textit{lytA} qPCR.

Results:

56/107 (52.3%) non-enriched and 78/107 (72.9%) enriched samples were SP positive (both \textit{lytA} and \textit{psaA} positive); SP density was higher in enriched vs. non-enriched samples (9.71E+07 vs. 9.78E+05; p<0.01). Compared with direct plating, we detected increased SP carriage prevalence in enriched samples for persons ≥18 years (24% vs. 65%; p<0.0001). In both non-enriched and enriched samples, SP density was inversely associated with age (p=0.046 and 0.0003, respectively). With enrichment, the number of serotypes identified per person increased (1.02 vs. 2.76; p <0.01) and was inversely associated with age (p=0.006). In enriched samples, SP density was associated with a greater number of serotypes identified per person (p=0.01).

Conclusion

Using molecular methods and no-stop PCR on broth-enriched samples, we detected an increase in SP carriage prevalence and identified additional serotypes. SP density increased with broth enrichment. Specificity of \textit{lytA} and \textit{psaA} for SP detection from NP samples will be determined.

ISPPD-0739
NASOPHARYNGEAL ISOLATION OF STREPTOCOCCUS PNEUMONIAE IN CHILDREN ADMITTED WITH WHO DEFINED COMMUNITY ACQUIRED PNEUMONIA IN NORTH INDIA
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\textsuperscript{2}King George Medical University, Department of Microbiology, Lucknow, India
\textsuperscript{3}Child Health Research Foundation, Department of Microbiology, Dhaka, Bangladesh
\textsuperscript{4}King George Medical University, Department of Community Medicine and Public Health, Lucknow, India

Background and Aims:

Pneumococcal carriage is the precursor for pneumococcal pneumonia. Current study was designed to i) assess pneumococcus isolation rate from Nasopharynx (NP)of children admitted with WHO defined Community Acquired Pneumonia (CAP) at 4 teaching hospitals of Uttar Pradesh(UP) and Bihar and ii) document NP carriage in healthy children in one teaching hospital in Lucknow(UP).

Methods:
Prospective surveillance of pneumonia cases aged 2-59 months residing in pre defined district admitted with CAP after parental consent. Healthy, age-matched, antibiotic naive, controls were recruited at Lucknow. NP was transported in skim milk-tryptone-glucose-glycerol medium and plated onto 5% sheep blood agar containing gentamicin[1]. Isolates were identified based on susceptibility to optochin and bile solubility for the intermediately susceptible isolates. Serotyping was done using Quellung reaction.

Results:

From March-December 2017, 432 pneumonia cases were recruited, of which 96.8% (418/432) had prior antibiotic use. Of these, pneumococcus was isolated from NP swabs in 12.9% (56/432) and other organisms in 63.9% (276/432). Pneumococcus isolation in age categories was: 10.4% (29/280) in 2-11 months; 14.3% (10/71) in 12-23 months and 20.9% (17/81) in 24-59 months. Of 56 isolates, 22 were serotyped till date. Prevalent Serotypes were 6A(n=3), 23F(n=4), 19F(n=3), 9V(n=4), 6B(N=3), 19A(n=1), 16F(n=2), 22F(n=1)& 34(n=1). Among controls, pneumococcus was isolated from 26.9% (21/78) (not serotyped) and other organisms were 54/78 (69.2%).

Conclusion

Low isolation of SP from NP was found among cases and healthy controls, possibly due to high use antibiotic. Vaccine serotypes were commonly found among cases.


ISPPD-0376
CHARACTERIZATION OF NON-VACCINE S. PNEUMONIAE CAUSING INVASIVE PNEUMOCOCCAL DISEASE (IPD) IN INDIAN CHILDREN
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Background and Aims:

Pneumococcal conjugate vaccine with 13 serotypes was recently (May, 2017) introduced into the primary infant immunization program of the nation. Although the use of PCVs are a remarkable public health success, their long-term utility is threatened by non-vaccine coverage, serotype replacement and switching. Knowledge of serotype prevalence, sequence types and their resistance patterns of non-vaccine types is of importance in the backdrop to estimate the impact of PCV

Methods:

124 S. pneumoniae IPD isolates from children <5yrs collected across India from 2009-2017 were included in the study. Isolates were serotyped with quellung and PCRSeqTyping. Analyzing seven housekeeping genes, MLST sequence types were identified. eBURST algorithm was used to identify the clonality. Antibiotic susceptible profile was generated by broth microdilution method

Results:

Of the 124 IPD isolates, 42(33%; blood–31, CSF-11) were non-PCV13 vaccine types. The most common serotypes were 15B(n=7), 20(n=3), 10A(n=3), 16F(n=3) and 24A(n=3). The other NVTs were 8(n=2), 11A(n=2), 17F(n=2), 33F(n=2), 34,28F, 13, 10F, 18A, 35A, 27, 7B,
45,9L,31,25F,36 and 2(n=1each). 11CSF isolates belonged to serotype 15B,34,13,33F,20,35A,27,45,9L,17F and 8. MLST resolved the population into 39 known STs and 5 novel STs. All the 42 isolates were singletons. Tetracycline, cotrimoxazole and erythromycin showed 44, 44 and 30% resistance respectively. Resistance to Penicillin and levofloxacin was not observed.

**Conclusion**

The study reveals the importance of non-vaccine types causing invasive pneumococcal disease. With routine childhood vaccination using PCV13, potential for emergence and expansion of non-vaccine serotypes is of concern. To recognize the elevated NVTs in pneumococcal disease and/or carriage, surveillance studies are needed to document the dynamics.

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**ISPPD-0514**

**COMPARISON OF NASOPHARYNGEAL SWABS WITH NASAL SWABS FOR DETECTING BACTERIAL CARRIAGE IN HEALTHY CHILDREN**

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**Background and Aims:**

*Streptococcus pneumoniae* (Spn) along with *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* are commonly involved in upper respiratory tract infections in children. The recommended sampling site for evaluating healthy carriage is the nasopharynx (NP). However, NP sampling requires training and is not always well tolerated by children. By contrast, collection of nasal (NS) sample is easier and better-tolerated. We characterized NS and NP samples to compare bacterial colonization, load and serotype differences.

**Methods:**

NP (Copan Flock swab) and NS swabs (Dacron swab) were collected from 6-11 months old healthy child in Bangladesh. After culture, bacterial load was determined semi-quantitatively and Spn was serotyped using a quelling-guided PCR.

**Results:**

We investigated 169 NS and NP pairs. Colonization rates in NP and NS for Spn were 68% (CI: 0.61-0.75) and 60% (CI: 0.53-0.68) (p=0.07), for *H. influenzae* 31% (CI: 0.24-0.38) and 22% (CI: 0.16-0.29) (p=0.04), for *S. aureus* 8% (CI: 0.04-0.12) and 9% (CI: 0.05-0.13) (p=0.58) and for *M. catarrhalis* 40% (CI: 0.33-0.48) and 31% (CI: 0.24-0.38) (p=0.03), respectively. No significant difference was found in bacterial density between NP and NS.

Twelve children were positive for multiple pneumococcal serotypes; 10 of these 12 NP and NS pairs were identical and in one NS sample had three serotypes (6A, 3, 4) while the NP counterpart had two (6A, 4).

**Conclusion**
There is no significant difference in bacterial colonization and load between NS and NP. Carriage of multiple Spn serotypes were also similar. For resource poor settings, NS can be a choice for monitoring healthy carriage.

ISPPD-0369
PNEUMOCOCCAL COLONIZATION AMONG ADULTS LIVING IN AN URBAN SLUM IN BRAZIL: A CULTURE- AND PCR-BASED SURVEY
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Background and Aims:

Young children are considered the main reservoir for pneumococci and the main target of pneumococcal diseases. However, they affect individuals from all age groups, representing a major economic burden among vaccine-preventable diseases in adults. Crowding, as seen in slums, constitutes a risk factor for pneumococcal colonization, which is a pre-requisite for the development of pneumococcal diseases and transmission. Our aim was to determine the pneumococcal carriage prevalence among adults living in a slum and to compare different methodologies for pneumococcal detection.

Methods:

From Oct-Nov 2016, we collected oropharyngeal swabs from 385 adults > 18 years old attending one public clinic inside a slum in a major urban area in Brazil. After a broth enrichment (BE) step, we performed three different approaches to detect pneumococci: culture on blood agar plate (BEC), culture on selective medium (BESC; blood agar plate with 5 mg/L gentamicin), and lytA-PCR (BE-lytA).

Results:

We detected 99 (25.7%) pneumococcal carriers. The culture-based methods enabled the detection of pneumococci in 32 (8.3%) adults: 19 (4.9%) by BEC and 24 (6.2%) by BESC. By BE-lytA method, 88 (22.9%) carriers were identified.

Conclusion

Adults living in slums may constitute important reservoirs for pneumococci, since we observed a high (1/4) colonization prevalence. The use of selective medium enhanced pneumococcal isolation, but the molecular method was extremely more sensitive. The use of robust approaches to obtain a more realistic insight about the asymptomatic carrier status is of paramount importance to guide prevention strategies for the adult population.

ISPPD-0046
STRUCTURE OF STREPTOCOCCUS PNEUMONIAE COMGC PILIN REVEALS AN UNUSUAL CONFORMATION
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²University of Copenhagen, Department of Biology Structural Biology and NMR Laboratory, Copenhagen, Denmark
Background and Aims:

Many pathogenic bacteria present long filamentous structures known as pili on their surface. Type IV pili are important virulence factors and have been associated with a wide variety of functions such as adhesion, biofilm formation, and horizontal gene transfer. The respiratory pathogen *Streptococcus pneumoniae* (the pneumococcus) is naturally competent and DNA uptake and transformation are dependent on pneumococcal type IV pili. Competent pneumococci express a competence-inducible *comG* operon encoding proteins required for the assembly of these pili. Among these proteins, the major pilin ComGC was shown to constitute the backbone of the pili but their biogenesis remains elusive. Herein, we characterize the pneumococcal major pilin ComGC and its ability to assemble into type IV pili.

Methods:

The visualization of ComGC was assessed by transmission electron microscopy and immunogold labeling. Labelled ComGC was expressed and purified for nuclear magnetic resonance (NMR). Furthermore, *in vitro* assays including Bacterial Adenylate Cyclase Two-Hybrid (BACTH) system, chemical cross-linking and pilin processing complemented the characterization the pneumococcal major pilin ComGC.

Results:

We report the high resolution NMR structure of N-terminal truncated ComGC revealing a distinct and highly flexible structure. The structure consists exclusively of three α-helical segments and a variable C-terminal domain showing no similarity to previously characterized type IV pilin proteins.

Conclusion

Together, these data provide the first structural evidence of a type IV pilin involved in the assembly of competence-induced pili in Gram positive bacteria and provide initial structural insights to understand the underlying mechanisms of DNA uptake by pneumococci.

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**ISPPD-0464**

**THE USE OF MALDI-TOF MASS SPECTROMETRY FOR RAPID IDENTIFICATION OF OPTOCHIN-RESISTANT *Streptococcus* ISOLATED FROM SPUTUM**

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**Background and Aims:**

Optochin susceptibility is widely used to differentiate *Streptococcus pneumoniae* from other *Streptococcus* groups. Recent studies mentioned some *S. pneumoniae* were resistant to optochin. This strain should be confirmed by bile solubility test. However, it is time consuming and showed subjective results that could lead to misidentification. We used
Matrix Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS) as a rapid identification tool to identify optochin-resistant Streptococcus.

Methods:

We used 201 of optochin-resistant Streptococcus isolated from patients sputum. Overnight culture was prepared on blood agar for identification by MALDI-TOF MS. Interpretation of MALDI-TOF MS results followed Bruker score level criteria. The isolates with score <2.000 were confirmed with recA gene sequencing.

Results:

MALDI-TOF MS-based identification showed S. oralis as dominant suspected species (46.3%), followed by S. mitis (25.4%), S. infantis (10.4%), S. parasanguinis (7.5%), S. anginosus and S. peroris (3.5%), S. sanguinis (2.0%) S. pneumoniae (1.0%), and S. pseudopneumoniae (0.5%). We observed there were different results among isolates with score <2.000 and recA gene sequencing. In addition, MALDI-TOF MS showed various suspected species options for optochin-resistant Streptococcus while optochin-sensitive Streptococcus showed S. pneumoniae as the only species option.

Conclusion

We concluded S. oralis and S. mitis were the most common species identified from sputum isolates. MALDI-TOF MS result is reliable for genus level identification with score <2.000. MALDI-TOF MS-based identification is less sensitive and specific to identify optochin-resistant Streptococcus.

ISPPD-0227
SEROTYPES AND ANTIMICROBIAL RESISTANCE PROFILE OF CLINICAL ISOLATES OF STREPTOCOCCUS PNEUMONIAE: A SINGLE CENTER REPORT FROM SOUTHERN INDIA
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Background and Aims:

Knowledge of serotype is important clinically and epidemiologically as it can influence outcome of the disease, antimicrobial resistance and vaccine coverage. This study was undertaken to estimate the percentage of serotypes included in current vaccines and to determine any association between antimicrobial resistance and serotypes.

Methods:

Pneumococcal isolates from clinical samples between May 2015 and October 2017 were included in the study. Antimicrobial susceptibility tests and molecular serotyping (multiplex PCR) were performed by standard procedures. Association between drug resistance and serotypes was determined using Chi-square test (two-tailed p<0.05 as statistically significant).

Results:
Of the total 134 pneumococcal isolates, majority were from respiratory samples, while 11.2% were from CSF and 8.2% from blood. Resistance rates were highest for trimethoprim-sulphamethoxazole (66.7%), followed by erythromycin (34.9%) and tetracycline (34.4%). Multidrug resistance was found in 17.9% isolates. Eight isolates from CSF were resistant to penicillin (MIC\textsubscript{50}=0.25 µg/ml). Serogroup/types 6 (19.4%), 19F (17.2%), 23F (9%), 14 (6%), 19A (5.2%) and 3 (5.2%) were predominant. Erythromycin and clindamycin resistance was associated with serogroup 6 (p=0.0005; 0.005 respectively) and 23F (p=0.0003; 0.0001 respectively). PCV13 and PPV23 had only moderate coverage of 66.4% and 82.1% respectively. The non-vaccine serotypes/groups commonly encountered were 34, 15A/F and 35F/47F.

Conclusion

Overuse and abuse of macrolides for upper respiratory infections may have contributed to the increased resistance observed. High prevalence of non-vaccine serotypes might influence the outcomes of vaccination programs. The inclusion of serotype/groups 34, 15A/F and 35F/47F in current formulations of PPV23 and PCV13 can increase the coverage to 91% and 75.4% respectively.

Background and Aims:

Increasing pneumococcal resistance to commonly used antibiotics and multidrug resistance is a serious public health concern. Data on distribution of resistant Streptococcus pneumoniae (SPn) strains among children in Pakistan are limited. We evaluated the antimicrobial susceptibility among preschool children in Rawalpindi.

Methods:

A prospective study was carried out from March 2015 to March 2016 in Rawalpindi, Pakistan on 300 children under 6 years of age with acute respiratory tract infection. Nasopharyngeal swabs were obtained and cultured for SPn. Positive samples (n = 367) were serotyped and tested for antimicrobial susceptibility. Associations of pneumococcal non-susceptibility with study site, season, age, sex, attendance of day care centre and treatment with antimicrobials (between one and six months prior the study) were evaluated.

Results:

About a half (56.7 %) of SPn strains were susceptible to all the antibiotics tested. Pneumococcal non-susceptibility to penicillin, erythromycin, clindamycin and trimethoprim-sulphamethoxazole was 15.8, 21.3, 16.9 and 27.3 %, respectively. None of the tested isolates was resistant to norfloxacin or vancomycin. We found a geographical variation of pneumococcal resistance within the cities of the country. Age, sex, the attendance of day care centre and treatment with antimicrobials prior the study was not significantly associated with a carriage of non-susceptible SPn strains. Among non-susceptible SPn serotypes 67.9 %–82.4 % were present in currently available pneumococcal conjugate vaccines.
Conclusion

The rates of nasopharyngeal SPn susceptibility to penicillin and macrolides are still high among preschool children in Rawalpindi.

ISPPD-0412

NATURAL HISTORY OF THE CARRIAGE OF RESPIRATORY PATHOGENS IN UNVACCINATED VIETNAMESE CHILDREN UP TO 18 MONTHS OF AGE

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Background and Aims:

The Vietnam Pneumococcal Project, a trial of alternative pneumococcal conjugate vaccination schedules in Ho Chi Minh City, includes a control group that does not receive any infant doses of PCV. Nasopharyngeal (NP) swabs collected from these participants provide information on the natural history of the carriage of respiratory pathogens between 2 and 18 months of age in the absence of pneumococcal vaccination.

Methods:

Swabs were collected at 2, 6, 9, 12 and 18 months of age, and cultured for the presence of Streptococcus pneumoniae (Spn), Haemophilus influenzae (Hi) and Staphylococcus aureus using standard microbiological methods. PCR will be used to confirm the identification of presumptive Spn and Hi, and pneumococcal isolates will be serotyped using latex agglutination.

Results:

<table>
<thead>
<tr>
<th>Age</th>
<th>Swabs</th>
<th>% Presumptive Spn</th>
<th>% Presumptive Hi</th>
<th>% S. aureus</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>111</td>
<td>24.3</td>
<td>9.9</td>
<td>57.7</td>
</tr>
<tr>
<td>6 months</td>
<td>95</td>
<td>17.9</td>
<td>14.7</td>
<td>29.5</td>
</tr>
<tr>
<td>9 months</td>
<td>78</td>
<td>38.5</td>
<td>14.1</td>
<td>28.2</td>
</tr>
<tr>
<td>12 months</td>
<td>187</td>
<td>29.4</td>
<td>17.6</td>
<td>15.5</td>
</tr>
<tr>
<td>18 months</td>
<td>64</td>
<td>28.1</td>
<td>14.1</td>
<td>15.6</td>
</tr>
</tbody>
</table>

Conclusion

This preliminary analysis shows no clear trends regarding the carriage of presumptive Spn over time. Hi carriage was stable from 6 months of age. S. aureus carriage was high at 2 months of age then decreased over time. Species confirmation along with analysis of the remaining swabs will confirm the presence or absence of trends in the carriage of respiratory pathogens during the first 18 months. Pneumococcal serotyping data will be available prior to the conference and will provide useful information on the common serotypes among infants in the absence of pneumococcal vaccination.
Background and Aims:

Pneumonia is a significant cause of mortality and morbidity in children under 5 years of age, especially in developing countries, and *Streptococcus pneumoniae* (Spn) is a major contributor. The aim of this study was to examine the presence of Spn in children with pneumonia, the serotype distribution and antimicrobial susceptibilities in Southern Vietnam from 2015 to 2017.

Methods:

Nasopharyngeal tracheal aspirates were collected from 160 patients under 5 years of age, and cultured for the presence and quantification of Spn using standard microbiological methods. Real-time PCR was used to confirm Spn speciation, serotyping was performed by multiplex PCR, and phenotypic antibiotic susceptibility testing was by disc diffusion method (CLSI-2015). No vaccination data were available.

Results:

A total of 12 samples were positive for Spn; 9 in 2015, 3 in 2017 and no strain in 2016. Spn strains identified in 2015 were 6A/B (5 strains), 19F (3 strains) and 15B/C (1 strain). In contrast to 2015, 3 isolated strains from 2017 were 6A/B, 19F, and 23F. All strains were multi-drug resistance with oxacillin, sulfamethoxazole - trimethoprim, erythromycin and tetracycline. 83.3% was resistant to clindamycin. Especially, serotype 15B/C was only susceptible with vancomycin.

Conclusion

Spn was identified in nasopharyngeal and tracheal aspirates from children under 5 years of age with pneumonia in Southern Vietnam. Most serotypes found are included in pneumococcal conjugate vaccines, which are not routinely provided in Vietnam. The high rates of antibiotic resistance are concerning.
Direct triplex rt-PCR uses Quanta mastermix contains a mutated DNA polymerase resists inhibitors in specimens such as cerebrospinal fluid (CSF) and it can amplify DNA in the samples without extraction. Here we present verification data of aside-by-side comparison of newly developed direct triplex rt-PCR with traditional rt-PCR for the detection of Streptococcus pneumoniae (Spn), Neisseria meningitidis (Nm), and Haemophilus influenzae (Hi).

Methods:

A total of 154 CSF samples were collected from bacterial meningitis cases in children under 5 years of age. The samples were tested using a triplex direct rt-PCR containing PerfeCTa mastermix (Quantabio) for the detection of Spn, Hi, and Nm and the serotyping of Spn for 21 serotypes. Traditional singleplex rt-PCR containing Platinumtaq (Invitrogen) for the detection of Spn or Hi, or Nm was applied to DNA extracts of the samples.

Results:

Forty eight CSFs were positive (38 Spn, 8 Hi, 2 Nm) by traditional rt-PCR compared to 41 positive (34 Spn, 7 Hi) by direct rt-PCR. The discrepant 7 CSF results could be false positive as they were also found negative by an external quality control program. All 105 negative CSF by traditional rt-PCR were also negative by direct rt-PCR. Spn serotyping typed 33 of 34 positive samples, 10 for 6A/B, 8 for 19F, 7 for 14, 5 for 23F, 1 for each 11A/D, 19A, 15A/F. One sample could not be typed was 15B/C as it is not part of the scheme.

Conclusion

Direct triplex rt-PCR helps save time, cost, labor, specious samples, and decrease cross-contamination.

ISPPD-0273
VARIABLES ASSOCIATED WITH BLOOD CULTURE YIELD AS PART OF AN INVASIVE PNEUMOCOCCAL DISEASE SURVEILLANCE PROGRAMME IN KATHMANDU, NEPAL


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Background and Aims:

Blood cultures form the cornerstone of pneumococcal disease surveillance programmes. To optimise detection of pneumococcus, it is important to understand the factors affecting blood culture yield. Blood culture volume surveys have been performed periodically as part of an invasive pneumococcal disease surveillance programme at Patan Hospital, Kathmandu, Nepal. These surveys are also used to educate staff about good blood culture collection technique. We hypothesised that increasing specimen volume is associated with increased blood culture yield, and that blood culture contamination rates would be lower during specimen volume survey periods.
Methods:

Blood culture positivity, excluding contaminant organisms, was calculated by specimen volume during specimen volume surveys in 2012-2017. Contamination rates during survey periods and outside survey periods were compared.

Results:

Eight blood volume surveys were conducted over a total of 22 months including 3880 blood cultures from children <15 years. Blood culture positivity tended to increase with increasing blood volumes. (Figure). Pneumococcus was isolated from only four blood cultures, with no association with specimen volume. The blood culture contamination rate was lower during the survey periods compared with outside the survey periods (3.2% vs 4.6%, p=0.006), while blood culture positivity for putative pathogens was similar (4.5% vs 3.9%, p=0.22).

Conclusion

Increasing blood volume is associated with increased yield from blood cultures. Education about blood culture collection techniques is associated with reduced contamination rates.

ISPPD-0421

ASSOCIATIONS OF SEROTYPE WITH CHARACTERISTICS OF THE SPND39III LOCUS IMPLICATED IN PHASE SWITCHING OF PNEUMOCOCCI

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Background and Aims:

A type I restriction-modification system (T1RMS, spnD39III) was implicated in phase variation related to virulence in pneumococci.

Methods:

We developed a method for the analysis of T1RMS based upon short paired-end reads (ivrTyper) and analyzed 37,333 publicly available pneumococcal genomic datasets. We tested the association between serotype and T1RMS by Fisher exact test with FDR correction.

Results:

The locus is potentially functional in most genomes (95.7%), although 8.7% were locked due to absence of recombinase gene. Some serotypes presented a higher than expected proportion of isolates with non-functional T1RMS: non-typeable (NT), 1, 3, 6B, 8 and 37. All PCV7 serotypes, except serotype 6B, were associated with a lower than expected frequency of impaired T1RMS. Most of the isolates with a functional locus (n=35,733) dominantly expressed the 1.1 Target Recognition Domain (TRD, 82%) but some serotypes were associated with expression of the less frequent 1.2 TRD: NT, 1, 3, 7F, 12F, 9N, 32A, 35F. Most of the isolates for which we could determine the dominantly expressed allele (n=19,789) expressed alleles with the 1.1 TRD: A (1.1-2.1) 37%, E (1.1-2.3) 17.5%, B (1.1-2.2) 11.3%, while among 1.2 TRD isolates dominated allele C (1.2-2.2) 9.4%.
Conclusion

Most of the isolates dominantly expressed alleles associated with the opaque phenotype (A and E) shown to be more virulent. However, some serotypes, including the highly virulent serotypes 1 and 3, were associated with alleles responsible for a transparent phenotype or lacked a functional locus. These results highlight the need for further studies to understand virulence modulation in these serotypes.

ISPPD-0571
LIVING ON A SURFACE: OPTIMIZATION OF A PNEUMOCOCCAL BIOFILM MODEL ON AN ABIOTIC SURFACE
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Background and Aims:

Pneumococci form biofilms during colonization. Several biofilm models have been described. We aimed to test different biofilm-inducing conditions in order to identify an abiotic model suitable to study the different phases of biofilm differentiation while yielding high cell viability and biomass.

Methods:

Three control strains (1990-19F, 2099-3, 5756-22F) were tested. In all experiments cells were grown in chemically defined medium, on an abiotic surface in 24-well plates, at 34°C in 5% CO₂. The conditions investigated were initial inoculum (10⁵-10⁸ CFU/mL), final volume (0.5-3mL), carbon source (glucose or galactose), incubation time (24 to 72h) and medium replacement (no replacement vs every 12h or 24h). Cell viability (CFU/mL) and total biomass (OD₅95nm after crystal violet staining) were measured. Next, the best conditions were used to evaluate 25 strains of different serotypes and MLSTs. Biological and technical triplicates were done for all strains.

Results:

The best conditions for the three control strains were: an initial inoculum of 10⁵ CFU/mL, a final volume of 2.5mL, and medium replacement every 24h for 72h. Final viability and biomass were up to 10⁹ CFU/mL and OD₅95nm=3, respectively.

Testing the 25 strains showed that the effect of the carbon source on biofilm yield was strain dependent. As such, galactose was selected on the premise that its abundance in the nasopharynx is higher than that of glucose.

Conclusion

A 72h biofilm model on an abiotic surface that ensures high cell viability and high biomass was established, suitable to study different aspects of pneumococcal biology both in early-phase and mature biofilms.
Background and Aims:

*Streptococcus pneumoniae* is the leading cause of bacterial pneumonia, meningitis, and sepsis in children globally. Pili in *S. pneumoniae* have been shown to be one of the adherence factors for epithelial cells in the human upper respiratory tract. However, there is no study in Indonesia about the prevalence of pilus islet-encoded pili of *S. pneumoniae*. We studied the association between pilus islet 1 (PI-1) and pilus islet 2 (PI-2) genes and serotype and antimicrobial susceptible of *Streptococcus pneumoniae* isolated from healthy children in 2012 in Lombok Islands, Indonesia.

Methods:

Three hundred fifty of archived *S pneumoniae* isolates were screened for the presence of PI-1 (rrgC) and PI-2 (pitB) was detected using molecular methods. Serotyping was performed with sequential multiplex PCR and antibiotic susceptibility with the disk diffusion method.

Results:

Forty of *S. pneumoniae* strains were detected for the presence of pilus islet genes (11%) carried by children under five year olds: 5% for both PI-1 and PI-2 positive and 3% for each only PI-1 positive and PI-2 positive. We found that 75% of the strains carried the pilus genes are serotype 19F and 19A. Proportions of isolates which have PI-1 or PI-2, and encode both are 15%, 18% and 43%, respectively.

Conclusion

We concluded that the majority of pneumococcal carrying the pilus genes were serotype 19F and 19A in isolates from children under five year olds.

Background and Aims:

Determining the prevalence and drug resistance pattern of invasive pneumococcal disease among individuals in Ethiopia is essential in order to monitor the impact of these infections. In many parts of the country its magnitude is still not well understood. Therefore, this review is
aimed to present a comprehensive summary regarding prevalence and drug resistance patterns of *S. pneumoniae* in Ethiopia and forward research gaps for further study.

**Methods:**

PubMed and google scholar databases were searched for articles published between 1999 and 2017. Article retrieval and screening were done using a structured search terms and strict inclusion/exclusion criteria. The data were entered in an Excel spread sheet and Stata version 14 was used for all analyses.

**Results:**

A total of 129 studies were searched among which 16 studies met our inclusion criteria for final analysis. The pooled prevalence of *Streptococcus pneumoniae* was 27.84%. The Overall pooled resistance to beta-lactam antibiotics was high: ampicillin 50.7%, penicillin 23.3% but lower for Ceftriaxone 10.1%. Pooled resistances of common used drugs in Ethiopia was 13.3% for chloramphenicol, 29.5% for tetracycline, 19.1% for erythromycin, 13.8% for ciprofloxacin, 13.3% for azithromycin and substantially higher 32.1% for trimethoprim-sulfamethoxazole.

**Conclusion**

The prevalence and drug resistance pattern of *Streptococcus pneumoniae* in Ethiopia have most infectious and resistant to almost all of antimicrobial agents of common used drugs in Ethiopia. The results imply the need for a continued and multidimensional efforts of antimicrobial stewardship program promoting rational use of antibiotics, infection prevention and control of antimicrobial resistance.

**ISPPD-0158**

**MOLECULAR DIVERSITY OF NASOPHARYNGEAL ISOLATES OF STREPTOCOCCUS PNEUMONIAE FROM CHILDREN IN ETHIOPIA**

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**Background and Aims:**

*Streptococcus pneumoniae* (Pneumococci) is the leading cause of infection in humans and frequently colonises the nasopharynx. Individual nasopharyngeal carriage is a necessary step for pneumococcal disease and is the only source for transmission and invasive infection. Ethiopia, introduced the ten-valent pneumococcal conjugate vaccine (PCV10) in October 2011. This study was conduct to determine serotype and molecular diversity of isolate before and after completion of PCV10 in children.

**Methods:**

A total of 325 Isolates of recovered from nasopharynx of children before taking the first dose of vaccine at the age of six weeks, (208 isolates) and after completion of vaccine (117 isolates) at the age of nine months were serotyped using gel diffusion and Quellung reaction and analyzed using Pulsed field Gel Electrophoresis (PFGE). Twelve selected isolates from 12 PFGE pattern characterized by Multilocus Sequence Typing (MLST).
Results:

A total of 59 serotypes of pneumococci were identified (54 serotype types from before the vaccine isolates and 43 serotype after completion of vaccine). Only eleven PFGE genotypes were identified which comprised three and more isolates per PFGE genotype and the remaining 252 PFGE genotypes contained only one isolate each. Out of 11 PFGE genotypes, six PFGE genotypes comprised the same serotypes in their PFGE genotype. In MLST analysis isolates of the same serotype which were from two different PFGE genotypes gave the same sequence type.

Conclusion

The molecular typing of isolates using PFGE and MLST revealed diverse pneumococci circulating in the study area and the existence of capsular switching events.

ISPPD-0066
DISCOVERY OF ORALLY BIOAVAILABLE 1,3,5-TRIAZONE (PT-25) AS NOVEL DNA GYRASE INHIBITOR AGAINST STREPTOCOCCUS PNEUMONIA
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Background and Aims:

Pneumonia is one of the most common causes of morbidity and mortality in children younger than 5 years in India. It specifically results high morbidity and mortality in under the year 5. In India, pneumonia caused nearly 175,000 child deaths in 2013. Approximately one out of every five children who die globally, die from pneumonia. Thus, the present study enumerates the discovery of orally bioavailable novel 1,3,5-triazines as antibacterial and antibiofilm agent via inhibition of DNA Gyrase.

Methods:

Briefly, the derivatives were synthesized using SNAr reaction and further subjected to antibacterial (MIC and MBC) against pathogenic Gram-positive and Gram-negative microorganisms according to CLSI protocol. The most active agent was also evaluated for anti-quorum sensing (QS) and antibiofilm activity against Streptococcus pneumoniae and Streptococcus aureus. The DNA gyrase inhibition assay was performed for the analysis of mechanism. The bioavailability of the potent analogue was also assessed.

Results:

All molecules were found to obey Drug Likeliness recommendations for new chemical entity (NCE) having good oral bioavailability. Most of the developed molecules exhibit excellent inhibition of Gram positive and Gram negative organisms (MIC=12-64 µg/mL and 2-32 µg/mL, respectively. In time-kill assay, molecule found to be act as bactericidal together with potent antibiofilm activity against S. pneumoniae (24µg/mL). The active molecule PT25, showed significant attenuation of QS activity. It also showed potent inhibition of DNA gyrase with IC50 of 13.52 µM.

Conclusion
We have discovered novel 1,3,5-triazines as potent DNA Gyrase inhibitor against *S. pneumoniae* which could be serve as lead for future antibacterials.

**ISPPD-0499**

**β-LACTAM RESISTANCE MECHANISMS AMONG NTHI COLONISING VIETNAMESE CHILDREN**

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**Background and Aims:**

As part of the Vietnam Pneumococcal Project comparing alternative infant pneumococcal conjugate vaccine (PCV) schedules in Ho Chi Minh City, carriage and resistance outcomes for nontypeable *Haemophilus influenzae* (NTHi) were collected. The overall NTHi carriage prevalence at 12 months of age was 14.8%. A high proportion, 78/166 (47%), of NTHi-positive swabs contained β-lactamase-producing NTHi. Our aim was to define the prevalence of phenotypic beta-lactam resistance and potential genetic mechanisms.

**Methods:**

A pilot set of fifty NTHi isolates (3 β-lactamase negative and 47 β-lactamase positive) were selected sequentially for whole genome sequencing and comprehensive phenotypic antibiotic susceptibility analysis.

**Results:**

Among the β-lactamase-producing NTHi, the majority (39/47, 83%) were positive for *bla*<sub>TEM-1</sub>, 5/47 (10%) were positive for *bla*<sub>TEM-33</sub> conferring inhibitor (e.g. clavulanic acid) resistance, and the remaining 3 mechanisms have not yet been identified. Using the modified Ubukata-Osaki method, *fts*I mutations were primarily III-like + conferring non-β-lactamase mediated ampicillin resistance.
Conclusion

β-lactamase-mediated ampicillin resistance is prevalent among NTHi colonising Vietnamese children. Comprehensive phenotypic antibiotic susceptibility analysis and genomic analyses will be completed for presentation at ISPPD.

ISPPD-0232

Changes in the Fluoroquinolone Susceptibility of Streptococcus Pneumoniae Isolated from Community Acquired Pneumoniae in Japanese Children

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Background and Aims:

Tosufloxacin (TFLX), one of the fluoroquinolone, granules for children were released in Japan in 2010 to treat otitis media and pneumonia. Since its introduction, many Japanese pediatricians and otolaryngologists prescribe TFLX owing to its clinical effectiveness, good compliance, and relatively pleasant taste. Frequent use of TFLX may lead to an increased risk of drug-resistant bacteria. The aim of this study was to identify trends in TFLX susceptibility of S. pneumoniae isolated from community-acquired pneumonia (CAP) in children, before and after the introduction of TFLX granules in Japan.

Methods:

We compared four study periods: period 1 (fiscal year 2008), period 2 (fiscal year 2012), period 3 (fiscal year 2015) and period 4 (fiscal year 2016). A population-based surveillance study was conducted to cover CAP cases of children, admitted in Chiba city, Japan. S. pneumoniae strains isolated from blood or sputum samples were tested antibiotic susceptibility and investigated for mutations in the quinolone resistance determining regions (QRDRs) of gyrA and parC by amplifying by PCR and sequencing.

Results:

The rate of TFLX less susceptible strains (MIC 0.5 μg/ml) in period 1, 2, 3 and 4 was 1.8%(1/57), 5.3%(2/38), 18.2%(4/21) and 0%(0/20), respectively. About QRDRs, there was only one strain admitted mutation in parC Ser79→Phe in period 3.

Conclusion

TFLX susceptibility of S. pneumoniae had gradually worsened since the introduction of TFLX granules but improved in 2016. Continuous surveillance is necessary to observe the influence of oral fluoroquinolone granules for children.

ISPPD-0235

Nasopharyngeal Carriage Prevalence and Serotypes of Pneumococci in 12-24 Month Old Children in Bandung Area, West Java, Indonesia

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Background and Aims:

Pneumonia is the leading killer of children under five years age worldwide, and the Streptococcus pneumoniae (the pneumococcus) is the most common bacterial cause of pneumonia. Pneumococci are commonly carried in the nasopharynx of young children. This study aimed to find out the nasopharyngeal carriage prevalence and serotypes of pneumococci in 12–24 months old children living in Bandung area.

Methods:

A cross-sectional study was conducted on 100 children 12–24 months of age in urban and rural Bandung from February to March 2016. Nasopharyngeal swabs were collected according to WHO recommendations, and bacteria (pneumococcus, H. influenzae, M. catarrhalis, and S. aureus) were detected by real-time quantitative PCR. Pneumococcal serotyping was conducted by microarray, with a representative isolate also typed by latex agglutination/Quellung.

Results:

The pneumococcal carriage prevalence of study subjects was 62%; with no differences between urban and rural areas (both 62%). The most common pneumococcal serotypes in descending order were 15B/C, 6C, 23F, and nonencapsulated pneumococci. Of a total 73 pneumococci identified, 27 (37%) belonged to PCV13 serotypes. The carriage prevalence of other colonizing pathogens were 32% for H. influenzae, 45% for M. catarrhalis, and 7% for S. aureus.

Conclusion

In Bandung more than 50% of young children carry pneumococcus, and pneumococcal carriage is more common than the other bacterial respiratory pathogens examined. This study provides useful data on pneumococcal carriage in Indonesian children prior to the
Background and Aims:

The German National Reference Center for Streptococci has been analyzing invasive pneumococcal isolates since 1992. A few isolates in our collection were not serologically consistent with the long-recognized serotypes 24F, 24A, and 24B. Here we describe the genetic and serological characteristics of these isolates.

Methods:

771 serogroup 24 isolates were identified by Neufeld-Quellung reaction at the German National Reference Center for Streptococci from January 1, 1992 to June 30, 2017. Seven of these isolates could only be identified as Serogroup 24. Pulsed Field Gel Electrophoresis (PFGE), Comparative Genomic Hybridization Microarray, Multilocus Sequence Typing (MLST), and Whole Genome Sequencing (WGS) were performed on these isolates.

Results:

All of the isolates were identified as 24F by microarray, but this was not consistent with serological results. The PFGE results indicate that each isolate has an individual banding pattern, each unlike the control strains for 24A, 24B and 24F. MLST results showed isolates from ST72 (often found in serotype 24F) and ST 162 (found in serotype 24F as well as several other serotypes). WGS results are currently being analyzed.
Conclusion

The seven Serogroup 24 isolates are clearly different from extant serotypes, and also different from each other. These isolates may represent novel serotypes.
Background and Aims:

HAMLET, a complex of alpha-lactalbumin (ALA) and oleic acid from human milk, kills Streptococcus pneumoniae by a mechanism that bears resemblance to apoptosis in Eukaryote cells.

Methods:

To identify HAMLET's bactericidal activity we have employed a proteomic approach to identify targets and further characterized targets using metabolic assays.

Results:

Pull down assays with biotinylated HAMLET identified several targets which potentially could be involved in HAMLET induced death. Two of these targets were glycolytic enzymes, fructose bis-phosphate aldolase (FBPA) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Treatment of pneumococci with HAMLET resulted in an immediate inhibition of ATP and lactate production, suggesting an inhibitory effect on glycolysis. This was further supported by experiments showing that HAMLET's activity was partially inhibited by activation of glycolysis and improved when glycolysis was inhibited by 2-deoxyglucose. This was not seen in pneumococci lacking a functional glycolytic pathway through genetic inactivation of GAPDH. Both HAMLET and ALA bound directly to both enzymes in solid phase assays and effectively inhibited their enzymatic activity. Oleic acid had little to no inhibitory activity. However, ALA alone showed no toxic activity and did not block glycolysis in whole cells suggesting a potential role for the lipid in allowing HAMLET to enter the bacterial cells to reach its targets.

Conclusion

Our results suggest that part of HAMLET's antibacterial activity relates to its ability to target and inhibit glycolytic enzymes and decreases the ATP production in cells.

Significance: This is the first study to show a specific targeting of glycolysis by an antimicrobial agent.
forming nasopharyngeal biofilms. We investigated whether stochastic transformation occurs between transformable pneumococci.

Methods:

Mixtures of a number of serotype (S) lineages encoding resistance, including S2, S4, and S19F were inoculated in a bioreactor that simulated the human nasopharynx.

Results:

Incubation of S2\textsuperscript{Tet} and S4\textsuperscript{Str} in the bioreactor led to generation of Spn\textsuperscript{Tet/Str} recombinants. Double resistant pneumococci appeared 4 h post-inoculation at a recombination frequency (rF) of 2.5x10\textsuperscript{-4} while peaking after 8 h at a rF of 1.1x10\textsuperscript{-3}. A high-throughput serotyping method demonstrated that all double resistant pneumococci belonged to a serotype lineage (e.g., S2\textsuperscript{Tet/Str}) and therefore that non-stochastic transformation had occurred. Both the density of each serotype, and eDNA released from both strains, permissive for transformation, was similar. Non-stochastic transformation occurred regardless the antibiotic resistant gene encoded, or acquired, by the recipient, and regardless CSP-receptor crosstalk. Moreover, non-stochastic transformation occurred when two donor strains, e.g., S4\textsuperscript{Str} and S19F\textsuperscript{Tmp}, were incubated together for 8 h leading to S19F\textsuperscript{Str/Tmp} but at a rF three orders of magnitude lower (4.9x10\textsuperscript{-6}). We finally demonstrated that the mechanism leading to non-stochastic transformation was driven by a decreased transformation fitness of the donor strain induced by the recipient.

Conclusion

Non-stochastic transformation occurred within nasopharyngeal pneumococcal biofilms with the potential, in the age of massive pressure, to select for the most fitted strains.

ISPPD-0279
ANTIBIOTIC RESISTANCE, SEROTYPE DISTRIBUTION AND GENOTYPIC CHARACTERIZATION OF STREPTOCOCCUS PNEUMONIAE IN CHILDREN
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Background and Aims:

In Vietnam, invasive pneumococcal disease (IPD) is an important cause of hospitalisation and death for children <2 years of age, yet there are no published data on pneumococcal serotypes causing IPD. Only PCV10 is licenced in Vietnam, PCV13 is not; however costs are prohibitive and few children receive these vaccines. Furthermore the lack of serotyping data means that the potential efficacy of these PCVs for IPD is unknown. Our aim was to determine the serotype, antibiogram and genotype of IPD isolates in Vietnamese children.

Methods:

19 pneumococcal isolates from IPD cases at Hospital Number 2 in Ho Chi Minh City collected in 2007-2008 from children aged 2-9 years were analysed. Kirby-Bauer disk-diffusion and Etest were used to determine antibiotic sensitivities. The pneumococcal serotyping was performed by rapid latex agglutination. Pulsed field gel electrophoresis using Smal was used for genotyping.

Results:
Serotypes 19F, 23F, 14 and 6A/B covered by PCV10 and PCV13 were most common. Isolates were resistant to co-trimoxazole (100%) and erythromycin (100%), clindamycin (95%), tetracycline (80%), chloramphenicol (40%), moxifloxacin (10%) and norfloxacin (5%). Thirteen PFGE patterns were observed. Serogroup 6A/B was diverse in antibiogram and PFGE pattern.

Conclusion

The high levels of antibiotic resistance and multi-drug resistance among pneumococci causing IPD in Vietnamese children is concerning. Our data indicate that PCV10 and PCV13 would provide a level of coverage. Further surveillance of pneumococcal disease, serotypes and antibiotic resistance are needed to inform vaccine policy and treatment recommendations.

ISPPD-0733
POPULATION STRUCTURE AND ERYTHROMYCIN RESISTANCE OF STREPTOCOCCUS PNEUMONIAE ISOLATES COLLECTED IN MOSCOW BETWEEN 2011-2015
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Background and Aims:

It was reported that resistance of pneumococci to macrolides have increased in recent years in Russia. In current study, we aimed to explore genetic sequences of pneumococci in order to evaluate the distribution of sequence clusters especially as they relate to erythromycin resistance

Methods:

A total of 90 isolates were investigated, and were recovered from CSF samples of patients with meningitis (n=56) and nasopharyngeal swabs of both asymptomatic carriers (n=15) and patients with nasopharyngitis (n=19). The isolates were collected during 2011-15 in Moscow from adults (n=43), and children under 5 years (n=42) and between 5 and 18 years (n=5). Whole genome sequencing (WGS) was done as a part of the Global Pneumococcal Sequencing project. Phylogenetic analysis was carried out using the PHYLOViZ software. Antimicrobial susceptibility of erythromycin was determined by disk diffusion method.

Results:

Among the investigated isolates 62 STs were revealed. The results of goeBURST Full MLST analysis identified 4 major sequence clusters (SC) in all groups (Fig 1). Twenty erythromycin-resistant isolates were identified, 12 (60%) were from patients with meningitis and belonged to CC 320.
Conclusion

The study highlighted substantial variety of STs among pneumococcal isolates. Ongoing surveillance will be helpful to monitor the further emergence and spread of antimicrobial resistance and the genetic evolution of pneumococci following the introduction of PCV13 immunization of children in Russia in 2014.

ISPPD-0392
SPECTRUM OF STREPTOCOCCUS PNEUMONIAE NASOPHARYNGEAL CARRIAGE IN 12-24 MONTHS HEALTHY YOUNG CHILDREN IN PADANG WEST SUMATERA, INDONESIA

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Background and Aims:
Nasopharyngeal carriage of *Streptococcus pneumoniae* plays an important role in the development of disease and the spread of resistant strains within the community. Young children have a high risk of developing pneumonia and other severe infections due to their nasopharyngeal carriage. Our study investigated nasopharyngeal carriage of *S. pneumoniae* and three other pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*) in healthy young children in Padang city, West Sumatra to gather baseline data prior to introduction of pneumococcal vaccination program in Indonesia.

**Methods:**

We conducted a cross sectional study in 2016 among 101 healthy young children age 12-24 months old living in urban and rural communities. We performed nasopharyngeal swab collection according to WHO recommendation procedure. We used real-time qPCR to detect the bacteria, and conducted pneumococcal serotyping by microarray.

**Results:**

We found that prevalence of pneumococcal carriage prevalence of study subjects was 34.6% (35/101), with 42% (21/50) in semi rural and 27% (14/51) in urban children. The most common pneumococcal serotypes were 15B/C, Nonencapsulated, 23F, and 19F. 58% of pneumococci belonged to PCV13 serotypes. The carriage prevalence of other colonizing pathogens was 25/101 (24.7%) for *H. influenzae*, 32/101 (31.6%) for *M. catarrhalis*, and 9/101 (8.9%) for *S. aureus*.

**Conclusion**

This study showed that about one third of children age 12-24 months carry pneumococcus in their nasopharynx, and the majority of serotypes carried would be covered by PCV13. This is the important baseline data prior to introduction of a pneumococcal vaccine program in West Sumatera, Indonesia.

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**NEW VACCINES AND NEW TRIALS**

**ISPPD-0315**

**IMMUNOGENICITY OF A NOVEL 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN ADULTS, TODDLERS AND INFANTS IN THE GAMBIA – A PHASE 1/2 RANDOMIZED CONTROLLED TRIAL**

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Background and Aims:

Alternative pneumococcal conjugate vaccines (PCVs) are needed to address the high cost and limited supply of currently licensed PCVs. Serum Institute of India’s 10-valent PCV candidate (PNEUMOSIL®) targets serotypes associated with the highest invasive pneumococcal disease burden in Africa and Asia. As reported, PNEUMOSIL was well tolerated in a Phase 1/2, randomized, active-controlled, double-blind age de-escalation trial; no safety signal was identified. Immunogenicity data are presented herein.

Methods:

34 PCV-naive adults, 112 Prevenar 13® (PCV13)-primed toddlers, and 200 PCV-naive infants were recruited. Adults were randomized to receive a single dose of either PNEUMOSIL or Pneumovax 23™ and toddlers and infants were randomized to PNEUMOSIL or PCV13 (toddlers: single booster dose; infants: 3+1 prime-boost). IgG and OPA responses were measured for the PNEUMOSIL serotypes and co-administered pentavalent vaccine antigens (infants).

Results:

PNEUMOSIL was immunogenic in adults and boosted immune responses in PCV13-primed toddlers. In infants, post-primary seroresponse rates (IgG ≥0.35 µg/ml) were ≥91% except for serotypes 6A (79.0%) and 6B (89.0%) in the PNEUMOSIL group and IgG GMCs were >1µg/mL for all 10 serotypes in both groups. Post-primary OPA seroresponse rates (titer ≥1:8) were ≥93% except for serotype 1 (84.6%) in the PCV13 group. Booster responses to PNEUMOSIL in infants were substantial across serotypes. There was no evidence of interference with pentavalent vaccine responses.

Conclusion

PNEUMOSIL was immunogenic for the 10 vaccine serotypes in adults, toddlers and infants and demonstrated effective priming, supporting conduct of a Phase3 non-inferiority trial in infants required for licensure and WHO prequalification.

ISPPD-0295

FUNCTIONAL IMMUNE RESPONSES IN ADULT SUBJECTS FOLLOWING IMMUNISATION WITH A NOVEL MULTI-ANTIGEN PROTEIN VACCINE-REPORT OF A PHASE I CLINICAL TRIAL

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Background and Aims:

PnuBioVax (PBV) is a novel protein vaccine containing multiple antigens, inclusive of PspA, PsaaA, Pilus, PiuA and Pneumolysin and is under development as a serotype-independent-prophylactic vaccine against Streptococcus pneumoniae (SP) infection. PBV was evaluated in a Phase I trial in a healthy adult population, with no previous PCV vaccination history.

Methods:
36 volunteers, aged 18-40 years, were recruited and divided into three cohorts of 12 subjects (9 receiving PnuBioVax and 3 placebo). Subjects received three vaccinations of 50, 200, or 500 μg PnuBioVax or placebo, 28 days apart. Blood samples were taken on days 1 (pre-dosing), 29, 57 and 85 and processed to provide sera and PBMCs for analysis. All subjects had pre-existing immune responses against SP. Baseline responses were variable, probably reflecting historical episodes of colonisation and most subjects had ‘protective’ antibody titres (Andrews NJ et al, 2014), as judged by OP (opsonophagocytic-assay) prior to vaccination. For this reason, the analysis focused on establishing the ‘fold increase’ in OPA, from day 1 (baseline) to the final bleed (day 85). Sera samples were analysed using MOP (multiplexed-opsonophagocytosis) assay at ICH and using OP assays developed at ImmBio.

Results:

All subjects receiving the 200 and 500 μg dose, developed robust OP against the homologous vaccine strain, compared to placebo vaccinated subjects. There was a high incidence of non-results in the MOPA, which reduced the number of evaluable results: this was particularly problematic with some strains.

Conclusion

Despite the low subject numbers, individuals showed increased OP-killing against heterologous strains implying increases in cross-strain functional antibodies.

ISPPD-0645
COMPARISON OF PRODUCTION METHODS FOR PNEUMOCOCCAL PROTEIN COMPLEXED NANOCARRIER VACCINE
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Background and Aims:

The pulmonary route has gained significant attention for delivery of vaccines as it is one of the main mucosal entry routes for pathogens. Moreover, the pulmonary epithelium is more permeable, has lower enzymatic activity than other mucosal sites, and has a large, highly vascularized surface with many immunological properties including dendritic cells (DCs). Biodegradable polymeric nanoparticles (NPs) are useful delivery systems for pulmonary vaccines, offering targeted delivery to DCs, protection of vaccine candidate, biocompatibility with surrounding cells and tissues, and act as adjuvants.

The aim of this study was to compare two different methods of preparing poly(glycerol adipate-co-ω-pentadecalactone), PGA-co-PDL NPs complexed with pneumococcal protein (PspA4Pro) to target lung DCs and initiate immune response.

Methods:

PGA-co-PDL NPs were prepared via two different methods, single-emulsion (SE) and double emulsion (DE) solvent evaporation, with PspA4Pro either adsorbed on the surface or encapsulated within. Both formulations were compared in terms of size, charge, activation of DCs (FACS), PspA4Pro release, biological activity (lactoferrin binding), antibodies affinity (ELISA) and stability (SDS-PAGE).
Results:

SE NPs showed smaller size than DE (149.3±6.0nm, 389.5±12.2nm) with similar Zeta Potential (-17.1±1.7mV, -15.9± 0.2mV) and greater PspA4Pro release over 24h. Both formulations showed no degradation of PspA4Pro in the SDS PAGE and had the same antibodies title as control PspA4Pro. Despite PspA4Pro from DE having greater affinity for lactoferrin, SE NPs with PspA4Pro stimulated DCs more than DE NPs.

Conclusion

These results indicate that SE PGA-co-PDL NPs with surface adsorption of the protein may be feasible to use these carriers for pulmonary vaccine delivery.

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**ISPPD-0225**

**THE SCOPE FOR PNEUMOCOCCAL VACCINES THAT DO NOT PREVENT TRANSMISSION**

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Background and Aims:

The pneumococcal vaccine pipeline holds candidates developed with the aim to prevent the majority if not all pneumococcal disease. Herd protection is a critical component of the overall impact of current pneumococcal conjugate vaccines (PCVs) and is a prerequisite for disease elimination through an infant vaccination programme.

Methods:

We assessed the scope of a hypothetical pneumococcal vaccine candidate (HPVC) with high clinical efficacy against all pneumococci but that fails to induce such indirect protection.

Results:

We found that, despite a lack of impact on unvaccinated individuals, HPVC use in infancy may offer similar or superior impact among young children if compared to current PCVs.

Conclusion

Hence, it could provide a more affordable alternative to PCVs in particular in settings where most pneumococcal disease is concentrated in children.
ISPPD-0382
 USING A MATHEMATICAL MODEL TO ASSESS THE POTENTIAL EFFECTS OF A NEW VACCINE APPROACH THAT TARGETS ENHANCED CLEARANCE OF PNEUMOCOCCAL CARRIAGE
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Background and Aims:
Despite their success, the impact of pneumococcal conjugate vaccines is limited by targeting only a subset of serotypes. The vaccine pipeline includes approaches that aim to overcome this deficiency, but may increase clearance rather than limit acquisition of pneumococcal carriage. We developed a deterministic age-structured model to describe the implications of such an alternative protection mechanism.

Methods:

The model was parameterized with demographic and social contact data from Kilifi, Kenya, and compared two pan-valent vaccine mechanisms: one enhances clearance from the nasopharynx; the other limits acquisition. The direct and indirect effects of both vaccines were assessed by simulating both a clinical trial and a population-level vaccination programme.

Results:

In the clinical trial scenario, Invasive Pneumococcal Disease (IPD) incidence in the group vaccinated with the enhanced clearance vaccine was higher than in the unvaccinated group. When implemented at a population level, the same vaccine led to a decrease in pneumococcal carriage and disease; however an initial increase in IPD incidence. In this setting an effective coverage of 79% is required to eliminate pneumococcal carriage in the long term; similar to the acquisition blocking vaccine.

Conclusion

We show that vaccine approaches that accelerate clearance can increase the number of acquisition events which in turn may imply negative direct vaccine protection against disease. However, similar to acquisition blocking vaccines they may eliminate disease through indirect protection. Catch up campaigns that accelerate indirect protection will be particularly important for introduction of clearance enhancing vaccines.

ISPPD-0143
 OPTIMAL NEXT GENERATION PCV COMBINATIONS AND VACCINATION SCHEDULE TO PROVIDE MAXIMAL COVERAGE AGAINST INVASIVE PNEUMOCOCCAL DISEASE (IPD) IN CHILDREN AND ADULTS FOR US AND EU
B. Forrest¹, J. Love²
¹Liffey Biotech Limited, Research & Development, Dublin, Ireland

Background and Aims:
The emergence of non-PCV13 serotypes as important causes of IPD requires new approaches to PCV compositions. With 28 serotypes responsible for 90% of IPD, and carrier suppression limiting some vaccine design choices, a simplified but effective approach maybe using a expanded coverage PCV that complements PCV13 for adults and children aged 2 years. The objective was to design an enhanced coverage PCV for use in an immunization schedule with PCV13 to maximize IPD serotype coverage, and minimize the deleterious effects of carrier-induced suppression.

Methods:

Identify IPD serotype distribution using published data: (a) Between 2005-2015; (b) Detailed IPD serotype distribution; (c) Excluded non-sterile sites.

Results:

A unique PCV composition (the “ePCV”) comprising serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 22F, 23A, 23B, 33F, 35B administered as a separate injection in a series with PCV13 would provide more than 85% coverage of IPD serotypes in the US/Canada and EU. The coverage comparison of this strategy with other current or possible alternative PCV compositions is found in the Table.

<table>
<thead>
<tr>
<th>Coverage of IPD Strains (%)</th>
<th>US/Canada</th>
<th>Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV10 (GSK)</td>
<td>18.8</td>
<td>28.4</td>
</tr>
<tr>
<td>PCV13 (Pfizer)</td>
<td>46.1</td>
<td>51.1</td>
</tr>
<tr>
<td>PCV15 (US Patent 8,192,746)</td>
<td>55.0</td>
<td>61.6</td>
</tr>
<tr>
<td>PCV20 (US Patent 9,492,559)</td>
<td>66.9</td>
<td>71.1</td>
</tr>
<tr>
<td>PPSV23 (MSD)</td>
<td>70.3</td>
<td>75.5</td>
</tr>
<tr>
<td>PCV24 (PPSV23 + Serotype 6A)</td>
<td>71.7</td>
<td>77.5</td>
</tr>
<tr>
<td>PCV13 + ePCV</td>
<td>89.6</td>
<td>86.3</td>
</tr>
</tbody>
</table>

Conclusion

The effectiveness of vaccination in disease prevention is the product of percent coverage, the efficacy against each individual serotype, and the proportion of the population that is vaccinated. This analysis describes a unique 15-valent composition of relevant IPD serotypes designed to complement PCV13 in the US/Canada and EU, that when used in a two dose schedule can augment serotype coverage to at least 85%, minimizing carrier-induced suppression.
Background and Aims:

At 10 USD per fully immunised child, pneumococcal conjugate vaccines (PCVs) are the most expensive component of the routine immunisation schedule in Gavi-supported countries. As countries transition from Gavi support, the sustainability of PCV delivery is at risk. Fractional doses have been used for yellow fever and inactivated polio vaccines to extend supply and reduce costs. We will assess whether fractional doses of PCV induce non-inferior immunogenicity when compared to the full dose and their effects on vaccine-serotype carriage.

Methods:

A phase IV individually-randomised controlled non-inferiority trial. 300 infants will be enrolled at random into each of seven trial arms. Doses will be delivered in the 2p+1 schedule (6, 14 weeks and 9-12 months) in six trial arms: A) Full dose PCV13, B) 40% PCV13, C) 20% PCV13, D) Full dose PCV10, E) 40% PCV10, F) 20% PCV10. The seventh trial arm will receive full dose PCV10 according to the Kenyan immunisation schedule (6, 10 and 14 weeks). We anticipate 95% power to determine whether fractional dose arms exhibit non-inferior proportions of ‘responders’ (children who achieve IgG concentrations correlated with protection) using a non-inferiority margin of 12%. Proportions of children with vaccine-serotype carriage will be estimated ±3-5%.

Results:

If fractional doses elicit non-inferior immunogenicity, the new 4-dose vials of PCVs (containing preservative) could be used as 10/20-dose vials.

Conclusion

The findings of the trial could substantially reduce PCV programme cost.
Streptococcus pneumoniae is a well-known pathogenic bacterium with a high mortality rate. Although current pneumococcal vaccines contribute significantly in the reduction of pneumococcal diseases, these vaccines have limitations in that they produce weak antibodies response in young children under 2 years of age or confer protection against only certain vaccine serotypes. Previously, we already reported serotype independent protection elucidated by \( \Delta \text{pep27} \) vaccine. However, reversion of \( \Delta \text{pep27} \) back to the wild type during immunization cannot be left out. The aim of this study to clear all the doubts regarding its safety before makes it commercially available.

Methods:

In order to secure safety of \( \Delta \text{pep27} \) vaccine, one of the essential proteins that trigger competence, comD, was inactivated, and feasibility of the double mutant (\( \Delta \text{pep27}\Delta \text{comD} \)) as mucosal vaccine was examined. Mice were immunized once a week with this vaccine for 4 times, after each time serum samples were analyzed for antibody titer. The mice were then challenged with type 2 and 6B strains and their survival time was observed. In addition, colonization study was also carried out in order to see the extent of bacterial clearance.

Results:

The transformation ability of this double mutant was successfully abolished. Moreover, \( \Delta \text{pep27}\Delta \text{comD} \) immunization markedly increased the survival time of the mice from heterologous challenges, and reduced colonization levels in a serotype independent manner including non-typeable strains (NCC1).

Conclusion

Pneumococcal \( \Delta \text{pep27}\Delta \text{comD} \) vaccine would be an exceedingly potent vaccine to prevent different types of pneumococcal infections with safety.

ISPPD-0168
KOREAN RED GINSENG IMPEDES REACTIVE OXYGEN SPECIES PRODUCTION AND IMPROVES PNEUMOCOCCAL \( \Delta \text{PEP27} \) VACCINE EFFICACY
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\(^1\)Sungkyunkwan University, School of Pharmacy, Suwon, Republic of Korea

Background and Aims:

Streptococcus pneumoniae is an important human pathogen causing significant morbidity and mortality throughout the world. There have been more than 90 known serotypes of pneumococcus till date. Immunization with a pneumococcal \( \text{pep27} \) mutant (\( \Delta \text{pep27} \)) has been already shown to confer comprehensive, long-term protection against even non-typeable strains. However, \( \Delta \text{pep27} \) can show it’s efficacy as a vaccine only after at least 3 rounds of immunization. Therefore, treatments capable of enhancing the efficiency of \( \Delta \text{pep27} \) immunization need to be explored urgently. Panax ginseng Meyer has already been known to exhibit pharmacological and antioxidant effects. Here, the ability of Korean red ginseng (KRG) to augment the \( \Delta \text{pep27} \) vaccine efficacy was investigated.

Methods:

Mice were treated with KRG and immunized with \( \Delta \text{pep27} \) prior to infection with the virulent \( S. \text{pneumoniae} \) strain D39. Lung homogenates were used to measure the total reactive oxygen species (ROS), and expression of iNOS and anti-apoptotic protein was determined by
immunoblotting. The phagocytic activity of peritoneal macrophages was also tested after KRG treatment.

Results:

In comparison to the other treatments, KRG markedly improved the survival rate after lethal challenge and resulted in rapid bacterial clearance via increased phagocytosis. Additionally, KRG improved Δpep27 vaccine efficacy by impeding ROS production, decreasing ERK apoptosis signaling and inflammation.

Conclusion

In conclusion, our results suggest that KRG reduces the time needed for immunization with the Δpep27 vaccine by enhancing its efficacy.

ISPPD-0771
INCREMENTAL EFFICACY OF AN INVESTIGATIONAL PNEUMOCOCCAL PROTEIN-BASED VACCINE CO-ADMINISTERED WITH PCV13 ON DRAINING ACUTE OTITIS MEDIA AMONG NATIVE AMERICAN INFANTS: A PRELIMINARY POST-HOC ANALYSIS

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1Johns Hopkins Bloomberg School of Public Health, International Health, Baltimore, USA
2GSK, Vaccines, Wavre, Belgium
3XPE Pharma & Science, on behalf of GSK, Wavre, Belgium

Background and Aims:

Rates of pneumococcal disease in the pneumococcal conjugate vaccine (PCV) era remain disproportionately high among Native Americans. Pneumococcal protein-based vaccines may broaden protection beyond that elicited by PCVs. We conducted a post-hoc exploratory evaluation of the incremental efficacy (over 13-valent PCV) of an investigational pneumococcal protein-based vaccine, containing 10 micrograms each of pneumolysin toxoid (dPly) and histidine-triad protein D (PhtD), against pneumococcal draining acute otitis media (AOM) in Native American infants.

Methods:

In a phase-2, double-blind, placebo-controlled trial (NCT01545375), 6-12-week-old infants were randomized 1:1 to receive dPly/PhtD vaccine (N=900) or placebo (N=903) at ages 2/4/6 and 12-15 months, co-administered with PCV13. Vaccine efficacy (VE) of dPly/PhtD was assessed against healthcare provider-diagnosed (HCP) pneumococcal draining AOM. Middle ear fluid was collected and tested for S. pneumoniae at the clinician’s discretion as part of the clinical practice (non-study procedure).

Results:

Among 2,084 HCP-AOM episodes, a total of 22 (1%) pneumococcal draining AOM episodes were identified (7 PCV13-type, 15 non-PCV13-type). VE against PCV13-type draining AOM was 100% in the modified according-to-protocol and total vaccinated cohorts (Table). Point estimates for VE against non-PCV13-type draining AOM were negative.
In this preliminary post-hoc analysis, incremental efficacy of the dPly/PhtD vaccine against PCV13-type was suggested, but not against non-PCV13 type draining pneumococcal AOM. The relatively small number of cases, non-standardized specimen collection, and post-hoc nature of this analysis are limitations.

**Funding:** GlaxoSmithKline Biologicals SA

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**Table. Vaccine efficacy against healthcare provider-diagnosed pneumococcal draining acute otitis media in modified according-to-protocol and total vaccinated cohorts**

<table>
<thead>
<tr>
<th>Category</th>
<th>Modified according-to-protocol cohort (23 doses)</th>
<th>Total vaccinated cohort (21 dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of events</td>
<td>Vaccine efficacy (95% CI)</td>
</tr>
<tr>
<td></td>
<td>dPly/PhtD + PCV13</td>
<td>Placebo + PCV13</td>
</tr>
<tr>
<td></td>
<td>N=808; follow-up time [years]=1142.3</td>
<td>N=831; follow-up time [years]=1171.7</td>
</tr>
<tr>
<td>PCV13-type</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>non-PCV13-type</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

The modified according-to-protocol cohort for efficacy includes the according-to-protocol cohort for efficacy plus children who completed 3-dose primary vaccination but the intervals between the 3 primary doses were not according to protocol. Total vaccinated cohort included all vaccinated children who received at least one vaccination dose.

Vaccine efficacy and 95% CI calculated by exact binomial analysis conditioning on the sum of the two Poissons.

**Conclusion**

In this preliminary post-hoc analysis, incremental efficacy of the dPly/PhtD vaccine against PCV13-type was suggested, but not against non-PCV13 type draining pneumococcal AOM. The relatively small number of cases, non-standardized specimen collection, and post-hoc nature of this analysis are limitations.

**Funding:** GlaxoSmithKline Biologicals SA

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**ISPPD-0775**

**INCREMENTAL EFFICACY OF AN INVESTIGATIONAL PNEUMOCOCCAL PROTEIN-BASED VACCINE CO-ADMINISTERED WITH PCV13 AGAINST ACUTE OTITIS MEDIA IN NATIVE AMERICANS: A POST-HOC AGE-RESTRICTED ANALYSIS**

L.L. Hammitt\(^1\), J.C. Campbell\(^1\), R.C. Weatherholtz\(^1\), R. Reid\(^1\), N. Goklish\(^1\), L.H. Moulton\(^1\), M. Traskine\(^2\), K. Swinnen\(^2\), Y. Song\(^3\), D. Borys\(^3\), M. Santhosham\(^1\), K.L. O’Brien\(^1\)

\(^1\)Johns Hopkins Bloomberg School of Public Health, Center for American Indian Health, Baltimore, USA

\(^2\)GlaxoSmithKline Biologicals SA, Vaccines, Wavre, Belgium

\(^3\)XPE Pharma & Science, on behalf of GSK, Wavre, Belgium

**Background and Aims:**

The investigational pneumococcal protein-based vaccine containing pneumolysin toxoid/histidine-triad protein D (dPly/PhtD; 10 mcg each) was immunogenic in Native American infants; however, no significant protective efficacy against acute otitis media (AOM)/acute lower respiratory infection (ALRI) was shown (results presented elsewhere). Given the observed dynamics of antibody to dPly/PhtD, post-hoc analyses were performed to assess whether the investigational vaccine may offer incremental efficacy over 13-valent pneumococcal conjugate vaccine (PCV13) in the first year of life.
Methods:

In this phase 2, double-blind, controlled trial (NCT01545375), infants aged 6-12 weeks were randomized 1:1 to receive dPly/PhtD vaccine (N=900) or placebo (N=903) at ages 2, 4, 6 and 12-15 months, each co-administered with PCV13. A post-hoc exploratory analysis restricted the analysis of vaccine efficacy (VE) to first episodes of AOM or medically-attended ALRI (MA-ALRI) occurring at age <12 months.

Results:

In the modified according-to-protocol cohort for efficacy, VE against the first AOM episode ranged from 9.3% to 16.9% for the various endpoints (confidence intervals spanned 0; Table). VE against the first MA-ALRI episode ranged from 27.4% to 38.7% for various endpoints (confidence intervals >0).

Table. Vaccine efficacy against the first episode of clinical acute otitis media or of acute lower respiratory infection in children <12 months of age in the modified ATP cohort for efficacy: a post-hoc analysis

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Group</th>
<th>N</th>
<th>n</th>
<th>T (year)</th>
<th>Incidence</th>
<th>95% CI</th>
<th>VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dPly/PhtD</td>
<td>808</td>
<td>165</td>
<td>294.7</td>
<td>0.56</td>
<td>0.48</td>
<td>0.65</td>
<td>16.9</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>829</td>
<td>200</td>
<td>297.0</td>
<td>0.67</td>
<td>0.58</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>AAP-MOD AOM</td>
<td>dPly/PhtD</td>
<td>808</td>
<td>222</td>
<td>281.9</td>
<td>0.79</td>
<td>0.69</td>
<td>0.90</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>829</td>
<td>247</td>
<td>284.8</td>
<td>0.87</td>
<td>0.76</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>HCP-AOM</td>
<td>dPly/PhtD</td>
<td>808</td>
<td>248</td>
<td>274.4</td>
<td>0.90</td>
<td>0.80</td>
<td>1.02</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>829</td>
<td>275</td>
<td>276.1</td>
<td>1.00</td>
<td>0.88</td>
<td>1.12</td>
<td></td>
</tr>
<tr>
<td>MA-ALRI</td>
<td>dPly/PhtD</td>
<td>808</td>
<td>44</td>
<td>321.4</td>
<td>0.14</td>
<td>0.10</td>
<td>0.18</td>
<td>32.0</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>829</td>
<td>66</td>
<td>327.2</td>
<td>0.20</td>
<td>0.16</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>MA-ALRI with fever</td>
<td>dPly/PhtD</td>
<td>808</td>
<td>30</td>
<td>325.2</td>
<td>0.09</td>
<td>0.06</td>
<td>0.13</td>
<td>38.7</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>829</td>
<td>50</td>
<td>331.6</td>
<td>0.15</td>
<td>0.11</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>MA-HCP-ALRI with fever</td>
<td>dPly/PhtD</td>
<td>808</td>
<td>89</td>
<td>312.8</td>
<td>0.29</td>
<td>0.23</td>
<td>0.35</td>
<td>27.4</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>829</td>
<td>123</td>
<td>313.8</td>
<td>0.39</td>
<td>0.33</td>
<td>0.47</td>
<td></td>
</tr>
</tbody>
</table>

Analysis included episodes occurring from 2 weeks post-dose 3 up to child’s last visit or censoring date. The modified ATP cohort for efficacy includes the according-to-protocol cohort for efficacy plus children who completed 3-dose primary vaccination but the intervals between the 3 primary doses were not according to protocol. dPly/PhtD, dPly/PhtD vaccine co-administered with 13-valent pneumococcal conjugate vaccine at 2, 4 and 6 months of age and booster dose at 12-15 months of age; Control, Placebo co-administered with 13-valent pneumococcal conjugate vaccine at 2, 4 and 6 months of age and booster dose at 12-15 months of age; N, number of subjects; N, number of subjects reporting at least one event; T(year), sum of follow-up expressed in years; n/T, person-year rate; n/T LL-UL, lower and upper limits of the exact 95% confidence interval around n/T; VE (%), vaccine efficacy (generalised Cox regression model); CI, confidence interval; AAP-AOM, clinical acute otitis media diagnosed and verified against American Academy of Pediatrics criteria (2004), meeting all of the following criteria: (1) history of acute onset of signs and symptoms of middle-ear inflammation and middle-ear effusion (MEE) AND (2) at least one of the signs and symptoms of middle-ear inflammation (i.e. distinct erythema of the tympanic membrane or distinct otalgia) AND (3) at least one of the MEE signs (i.e. bulging of the tympanic membrane, limited or absent tympanic membrane mobility, air-fluid level behind the tympanic membrane, or otorrhea); AAP-MOD AOM, clinical AOM diagnosed and verified against modified AAP criteria, that refer to (1) a history of acute onset of signs and symptoms of middle-ear inflammation and MEE AND (2) sign/symptom of middle-ear inflammation (i.e. erythema of the tympanic membrane) OR at least one of the MEE signs (i.e. bulging of the tympanic membrane, limited or absent tympanic membrane mobility, air-fluid level behind the tympanic membrane, or otorrhea); HCP-AOM, healthcare provider-diagnosed clinical AOM; MA-ALRI, medically attended acute lower respiratory infection; MA-HCP-ALRI, medically attended healthcare provider-diagnosed ALRI; *2 subjects were 12 months of age before the 2 weeks post-dose 3 timing.
Conclusion

In this post-hoc analysis of VE against first AOM and first MA-ALRI episodes at age <12 months, there was a suggestion of incremental efficacy of dPly/PhtD vaccine over PCV13; this was more pronounced for MA-ALRI. Results are not adjusted for multiplicity of comparisons.

Funding: GlaxoSmithKline Biologicals SA

Background and Aims:

GSK’s investigational pneumococcal protein-based dPly/PhtD vaccine, containing pneumolysin toxoid (dPly, 10 mcg) and histidine-triad protein D (PhtD, 10 mcg) was co-administered with PCV13 in a study evaluating efficacy against acute otitis media (results presented elsewhere). Here we present PCV13 immunogenicity.

Methods:

In this phase 2, double-blind, controlled trial (NCT01545375), 6-12 week-old Native American infants randomized 1:1 received dPly/PhtD vaccine (N=900) or placebo (N=903) at ages 2, 4, 6 and 12-15 months, co-administered with PCV13. Pneumococcal serotype-specific IgG antibodies to the PCV13 serotypes were measured by an electro-chemiluminescence assay in a sub-cohort (n=400) one-month post-primary series (age ~7 months), before the booster dose (age ~12 months), and one-month post-booster (age ~13 months).

Results:

In the according-to-protocol sub-cohort (n=124/group), the serotype-specific antibody geometric mean concentrations (Figure) and the proportion of participants with serotype-specific IgG antibodies ≥0.35 mcg/mL (Table) were similar in the dPly/PhtD+PCV13 and placebo+PCV13 groups. Before the booster, half or more of children no longer had serotype-specific IgG antibodies ≥0.35 mcg/mL for serotypes 3, 4, and 18C.

Conclusion

Immune responses to PCV13 were within the same ranges between groups. dPly/PhtD vaccine administration did not seem to enhance or interfere with PCV13 immunogenicity.

Funding: GlaxoSmithKline Biologicals SA
Background and Aims: 

Figure. Serotype-specific IgG antibody geometric mean concentration and 95% confidence interval post-primary series (solid color), pre-booster dose (no fill), and post-booster dose (checkered) of dPhy/PhtD+PCV13 (orange) or placebo+PCV13 (blue) in the according-to-protocol immunogenicity sub-cohort (n=124/group)

<table>
<thead>
<tr>
<th>Serotype</th>
<th>dPhy/PhtD+PCV13</th>
<th>Placebo+PCV13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion ≥0.35 mcg/mL (95% CI)</td>
<td>Proportion ≥0.35 mcg/mL (95% CI)</td>
</tr>
<tr>
<td>1</td>
<td>Post-Primary: 100 (97, 100)</td>
<td>Post-Primary: 100 (97, 100)</td>
</tr>
<tr>
<td></td>
<td>Pre-Booster: 75 (67, 84)</td>
<td>Pre-Booster: 75 (67, 83)</td>
</tr>
<tr>
<td></td>
<td>Post-Booster: 100 (97, 100)</td>
<td>Post-Booster: 75 (66, 83)</td>
</tr>
<tr>
<td>3</td>
<td>Post-Primary: 77 (68, 84)</td>
<td>Post-Primary: 75 (67, 83)</td>
</tr>
<tr>
<td></td>
<td>Pre-Booster: 17 (11, 25)</td>
<td>Pre-Booster: 7 (3, 14)</td>
</tr>
<tr>
<td></td>
<td>Post-Booster: 84 (76, 90)</td>
<td>Post-Booster: 83 (75, 89)</td>
</tr>
<tr>
<td>4</td>
<td>Post-Primary: 100 (97, 100)</td>
<td>Post-Primary: 100 (97, 100)</td>
</tr>
<tr>
<td></td>
<td>Pre-Booster: 47 (38, 57)</td>
<td>Pre-Booster: 41 (32, 51)</td>
</tr>
<tr>
<td></td>
<td>Post-Booster: 100 (97, 100)</td>
<td>Post-Booster: 83 (75, 90)</td>
</tr>
<tr>
<td>5</td>
<td>Post-Primary: 100 (97, 100)</td>
<td>Post-Primary: 100 (97, 100)</td>
</tr>
<tr>
<td></td>
<td>Pre-Booster: 88 (80, 93)</td>
<td>Pre-Booster: 84 (76, 90)</td>
</tr>
<tr>
<td></td>
<td>Post-Booster: 100 (97, 100)</td>
<td>Post-Booster: 100 (97, 100)</td>
</tr>
<tr>
<td>6A</td>
<td>Post-Primary: 100 (97, 100)</td>
<td>Post-Primary: 100 (97, 100)</td>
</tr>
<tr>
<td></td>
<td>Pre-Booster: 93 (86, 97)</td>
<td>Pre-Booster: 90 (83, 95)</td>
</tr>
<tr>
<td></td>
<td>Post-Booster: 100 (97, 100)</td>
<td>Post-Booster: 100 (97, 100)</td>
</tr>
<tr>
<td>6B</td>
<td>Post-Primary: 98 (94, 100)</td>
<td>Post-Primary: 98 (94, 100)</td>
</tr>
<tr>
<td></td>
<td>Pre-Booster: 75 (67, 84)</td>
<td>Pre-Booster: 75 (67, 83)</td>
</tr>
<tr>
<td></td>
<td>Post-Booster: 100 (97, 100)</td>
<td>Post-Booster: 100 (97, 100)</td>
</tr>
<tr>
<td>7F</td>
<td>Post-Primary: 100 (97, 100)</td>
<td>Post-Primary: 100 (97, 100)</td>
</tr>
<tr>
<td></td>
<td>Pre-Booster: 95 (89, 98)</td>
<td>Pre-Booster: 95 (89, 98)</td>
</tr>
<tr>
<td></td>
<td>Post-Booster: 100 (97, 100)</td>
<td>Post-Booster: 100 (97, 100)</td>
</tr>
<tr>
<td>9V</td>
<td>Post-Primary: 99 (95, 100)</td>
<td>Post-Primary: 100 (97, 100)</td>
</tr>
<tr>
<td></td>
<td>Pre-Booster: 67 (57, 76)</td>
<td>Pre-Booster: 56 (46, 65)</td>
</tr>
<tr>
<td></td>
<td>Post-Booster: 100 (97, 100)</td>
<td>Post-Booster: 100 (97, 100)</td>
</tr>
<tr>
<td>14</td>
<td>Post-Primary: 99 (95, 100)</td>
<td>Post-Primary: 100 (97, 100)</td>
</tr>
<tr>
<td></td>
<td>Pre-Booster: 95 (91, 99)</td>
<td>Pre-Booster: 98 (94, 100)</td>
</tr>
<tr>
<td></td>
<td>Post-Booster: 100 (97, 100)</td>
<td>Post-Booster: 100 (97, 100)</td>
</tr>
<tr>
<td>18C</td>
<td>Post-Primary: 100 (97, 100)</td>
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<tr>
<td></td>
<td>Pre-Booster: 50 (40, 60)</td>
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</tr>
<tr>
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<td>Post-Booster: 100 (97, 100)</td>
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<td>Post-Booster: 99 (95, 100)</td>
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<td>Post-Primary: 100 (97, 100)</td>
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<td></td>
<td>Post-Booster: 99 (95, 100)</td>
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IgG, immunoglobulin; GMC, geometric mean concentration; dPhy, pneumolysin toxoid; PhtD, histidine-triad protein D; PCV13, 13-valent pneumococcal conjugate vaccine

Table. Proportion of participants with serotype-specific IgG antibody concentration ≥0.35 mcg/mL post-primary series, pre-booster dose, and post-booster dose of dPhy/PhtD+PCV13 or placebo+PCV13 in the according-to-protocol immunogenicity sub-cohort (n=124/group)

ISPPD-0675
BROAD-SPECTRUM VACCINE DESIGN AGAINST STREPTOCOCCUS PNEUMONIAE
V. Jaiswal
Shoolini University- Solan, School of Electrical and Computer Science Engineering, Solan, India

Background and Aims:
Streptococcus pneumoniae is the main cause of community-acquired pneumonia and meningitis in children and elder population. S. pneumoniae also responsible for other pneumococcal-diseases which include bronchitis, rhinitis, acute sinusitis, otitis media, conjunctivitis, meningitis, sepsis, osteomyelitis, septic arthritis, endocarditis, peritonitis, pericarditis, cellulitis, and brain abscess. S. pneumoniae kills ~0.5 million children <5 years old worldwide per year. Currently available pneumococcal conjugate vaccines are highly effective at preventing diseases caused by serotypes included in the vaccines, these relatively costly vaccines, do not offer protection against all pneumococcal serotypes. Proteins based vaccines have the potential to provide broad coverage across all serotypes.

Methods:

Proteome of Streptococcus pneumoniae was taken from NCBI and all proteins were subjected to in-house developed reverse vaccinology pipe-line implemented in Jenner-Predict to calculate localization, topology, possible role in host-pathogen interaction, and epitope mapping. Further, only selected proteins were subjected to conservation analysis against more than 200 Streptococcus pneumoniae strains based on sequence similarity. Five most conserve proteins were taken for epitope prediction (B-cell and T-cell epitopes).

Results:

Reverse vaccinology pipeline has predicted 69 out of 2202 protein as protein vaccine candidates (PVCs) and out of 69 PVCs 10 are known to be vaccine candidate in the literature which justifies the accuracy of our methods. Further conservation of selected PVCs in more than 200 known strain warrants the broad strain coverage of selected PVCs. Finally, prediction of both B-cell and T-cell epitopes in selected PVCs enhanced their vaccine potential.

Conclusion

Highly conserved PVCs can be taken in further experimentation for broad-spectrum vaccine development.

ISPPD-0028
IMPROVED IMMUNOGENICITY OF NANOPARTICLE ENTRAPPED PNEUMOCOCCAL SP0845 PROTEIN
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1National Institute of Immunology, Product Development Cell II, Delhi, India

Background and Aims:

SP0845 protein is expressed on the surface of encapsulated pneumococci and is highly conserved among pneumococcal serotypes that make it a potential candidate for protein based vaccine. However, the immunogenicity of SP0845 based vaccine still needs to be improved to elicit highly protective antibody response. For making this vaccine more effective, SP0845 entrapped polylactic acid (PLA) nanoparticles were formulated and used for immunization. PLA nanoparticle acts not only as a delivery system; but also provides adjuvant effects.

Methods:

SP0845 entrapped nanoparticles were prepared using double emulsion solvent evaporation method and characterized for their size, zeta potential, antigen loading and entrapment
efficiency. Antigen release from nanoparticles was performed using in vitro release assay. Nanoparticle uptake by macrophages was studied using confocal microscopy and flow cytometry. In vivo studies were carried out in BALB/c mice to evaluate proinflammatory cytokines and antibody response.

**Results:**

Nanoparticles were found to be spherical in shape and about 320 nm in size. Antigen release profile showed initial burst release of ~30% within a week followed by slow continuous release over a period of one month. Contribution of phagocytosis in nanoparticle uptake by macrophage was confirmed in presence of cytochalasin D. Role of nanoparticles in inducing proinflammatory cytokine response was supported by increased IL-6 level. Enhanced antibody titer for SP0845 nanoparticles confirmed that PLA entrapped antigen is more immunogenic.

**Conclusion**

These studies collectively suggest that effective delivery of SP0845 using PLA nanoparticle helps in enhancing the immunogenicity of pneumococcal SP0845 antigen.

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**ISPPD-0560**

**A CLUSTER-RANDOMISED, NON-INFERIORITY TRIAL OF TRANSITION TO A REDUCED DOSE, 1+1 SCHEDULE OF PNEUMOCOCCAL CONJUGATE VACCINE, COMPARED TO THE STANDARD 3+0 SCHEDULE**

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⁶PATH, Vaccine Delivery, Seattle, USA
⁷WHO, Expanded Programme on Immunisation, Geneva, Switzerland
⁸THL Finland, Impact Assessment Unit, Helsinki, Finland
⁹THL Finland, Clinical Research, Helsinki, Finland
¹⁰London School of Hygiene and Tropical Medicine, Epidemiology and Population Health, London, United Kingdom
¹¹London School of Hygiene and Tropical Medicine, Infectious and Tropical Diseases, London, United Kingdom

**Background and Aims:**

The introduction of pneumococcal conjugate vaccines (PCVs) in The Gambia has controlled vaccine-type (VT) pneumococcal disease. Global control of pneumococcal disease, is however, limited by the cost of PCV. Immunisation programmes also face increasing numbers of injections. To address these challenges, and take advantage of the increasing role of herd protection in mature PCV programmes, we plan a trial of transition to a two-dose schedule (one priming and one booster dose [‘1+1’]) compared to the standard three doses (‘3+0’).
Methods:

We propose a non-inferiority trial comparing transition to a 1+1 schedule (doses at ages 6 weeks and 9 months) compared to the standard 3+0 schedule (doses at ages 6, 10 and 14 weeks). We will randomise 66 geographic population clusters in which residents are assigned to attend separate immunisation clinics in a demographic surveillance area in rural Gambia. Interventions will be delivered by the Expanded Programme on Immunisation over 4 years. Endpoints will include nasopharyngeal VT prevalence in children with clinical pneumonia, unimmunised infants and community carriage surveys; and incidence of clinical and radiological pneumonia, hospitalisation, invasive pneumococcal disease and mortality.

Results:

The non-inferiority margin is a 15% effect reduction compared to the 3+0 schedule. We will vaccinate approximately 40,000 infants with 45,000 children under disease surveillance.

Conclusion

This trial will provide data on the use of a 1+1 schedule in a typical, rural African setting. If the 1+1 strategy is non-inferior to a 3+0 schedule in this high transmission setting, the results should be generalisable to lower transmission settings.

ISPPD-0763
IDENTIFICATION OF PNEUMOCOCCAL ANTIGENS THAT ARE PROTECTIVE AGAINST COLONIZATION USING A SURFACE PROTEIN LIBRARY
Y.J. Lu¹, E. Oliver², F. Zhang¹, C. Pope², A. Finn², R. Malley¹
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²University of Bristol, Bristol Children’s Vaccine Centre-School of Cellular & Molecular Medicine, Bristol, United Kingdom

Background and Aims:

There is a need for serotype-independent pneumococcal vaccines to circumvent limitations of conjugates. We screened human and murine immune cells for IL-17A induction using a surface protein library and tested all proteins for protection against colonization.

Methods:

Our library consists of 56 pneumococcal surface proteins conserved among pneumococcal strains and having low homology to human proteins. We screened this library for IL-17A production in splenocytes from mice either exposed to live pneumococcus or immunized with a killed whole cell vaccine (WCV), both of which confer Th17-dependent protection against carriage. In parallel, IL-17A production from pediatric adenoidal cells stimulated with proteins from the library was evaluated. All the proteins in the library were tested in a mouse model of pneumococcal type 6B colonization.

Results:

Among all surface proteins tested, 13 were ranked in the top 50% in each of the three screens, and 8 (61.5%) were protective in the mouse model. This hit rate is significantly higher than that of the proteins ranked in the bottom 50% of all three screens (1 out of 11 (9%) (p=0.0131)), and it is almost double the hit rate of the protective antigens in the entire library (18 out of 56 (32.1%) (p=0.06).
Conclusion

By establishing a conserved surface protein library, we enriched potentially protective antigens across the entire pneumococcal proteome. Prediction by combined murine and human IL-17 screens of this library correlated strongly to the protection data in the animal model. Similar approaches could be applied to other mucosal pathogens for the identification of potentially protective antigens.

ISPPD-0256
PCV13 COMBINED WITH PNEUMOCOCCAL FUSION PROTEIN YLN ELICITS MULTI-SPECIES PROTECTION IN AN ACUTE OTITIS MEDIA MOUSE MODEL
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1St Jude Children’s Research Hospital, Dept of Infectious Diseases MS320, Memphis, USA

Background and Aims:

*Streptococcus pneumoniae* and non-typable *Haemophilus influenzae* (NTHI) remain leading causes of acute otitis media despite use of conjugate vaccines. We sought to elicit broad protection in a mouse otitis media model by combining conjugate vaccine PCV13 with a pneumococcal fusion protein YLN. YLN consists of pneumococcal choline binding protein A receptor binding domains YPT(Y) and NEEK(N) fused to either terminus of pneumolysin toxoid L460D(L)1. Immunization of mice with YLN alone has shown cross protection in various models of pneumococcal, meningococcal and *Haemophilus* disease.

Methods:

Mice were immunized with PCV13, YLN or PCV+YLN. IgG titers against protein and whole bacteria were quantitated by ELISA. Mice were challenged with pneumococcal vaccine serotypes 7F, 19F, or with NTHI. At 24-72 hours post-infection the mice were imaged and lungs, nasal passages and middle ears were harvested for bacterial burden.

Results:

A combination of PCV+YLN resulted in a significant increase in IgG titers against serotypes 2, 4, 7F and 19F of *S.pneumoniae* as well as NTHI compared to PCV13 or YLN alone. When mice were challenged with vaccine serotypes 7F or 19F, PCV alone offered no protection from occurrence of otitis media. The combination of PCV with YLN, however, significantly decreased the incidence of otitis media and bacterial burden in the ears and nasal passages. The combination vaccine also decreased incidence of otitis media from NTHI by >50% and significantly reduced the bacterial burden in the ears.

Conclusion

Combining fusion protein YLN with capsule based vaccine PCV13 extends protection beyond serotypes and elicits multi-species protection against otitis media.

ISPPD-0057
VALIDATION OF A RE-OPTIMIZED ELECTROCHEMILUMINESCENCE-BASED ASSAY FOR THE QUANTITATION OF IgG SEROTYPE-SPECIFIC ANTI-PNEUMOCOCCAL ANTIBODIES IN HUMAN SERUM AND BRIDGING TO THE WHO REFERENCE ELISA

480
Background and Aims:

MSD, in collaboration with PPD, developed a multiplex, ECL-based detection method for the quantitation of IgG serotype-specific antibodies to capsular polysaccharides contained in an investigational 15-valent Pneumococcal Conjugate Vaccine (V114: Serotypes 1/3/4/5/6A/6B/7F/9V/14/18C/19A/19F/22F/23F/33F). The method was recently re-optimized, bridged to the WHO reference ELISA, and validated to support immunogenicity endpoints for Phase III clinical trials.

Methods:

The validation study evaluated various performance parameters, including precision, ruggedness, relative accuracy, dilutional linearity, selectivity, and specificity, against pre-specified acceptance criteria. In addition, the PnECL v2.0 assay was bridged to the WHO ELISA, as recommended by the WHO Expert Committee on Biological Standardization, and a PnECL assay threshold value corresponding to the WHO ELISA accepted threshold value of 0.35µg/mL was determined.

Results:

The PnECL v2.0 met all acceptance criteria outlined in the validation protocol. For the WHO bridging study, the estimated PnECL v2.0 aggregate threshold value over the combined set of 15 serotypes was 0.38µg/mL using the Reverse Cumulative Distribution Function method (range 0.24-0.56µg/mL for individual serotypes) and 0.35µg/mL using the concordance method (range 0.22-0.52µg/mL). As such, it is recommended that a single PnECL threshold value of 0.35µg/mL be applied to each of the fifteen serotypes when comparing the serotype-specific response rates between V114 and licensed PCVs in infants.

Conclusion

The re-optimized PnECL v2.0 assay is a validated immunogenicity assay for the measurement of serotype-specific antibodies to 15 different capsular polysaccharides. The benefits of the ECL technology over the ELISA include speed, smaller sample volumes, increased dynamic range, and the ability to multiplex.
The measurement of serotype-specific anti-capsular polysaccharide antibodies remains the mainstay of pneumococcal vaccine evaluation. The MOPA-4, developed by Professor Moon Nahm, is a multiplexed OPA capable of measuring functional antibody responses to four serotypes at a time, against a total of sixteen serotypes. MSD, in collaboration with PPD, optimized and validated the MOPA on a high throughput microcolony platform to support immunogenicity endpoints for Phase III clinical trials for an investigational Pneumococcal Conjugate Vaccine (V114: Serotypes 1/3/4/5/6A/6B/7F/9V/14/18C/19A/19F/22F/23F/33F).

Methods:

Assay conditions across fifteen serotypes were optimized to ensure appropriate and consistent colony morphology and CFU counts, with a focus on serotype 3. Serotype 3, which shows atypical growth in the microcolony format, was evaluated in eight different types of media to optimize colony morphology and size. Plate type, incubation time, fixation, and staining were also optimized for all serotypes. Following optimization, the validation study evaluated various performance parameters, including precision, relative accuracy/dilutional linearity, and analytical specificity, against pre-specified acceptance criteria.

Results:

Optochin 2X in combination with an amino acid based media were selected as optimal growth conditions to both appropriately select for serotype 3 and maintain appropriate colony morphology and size. Validation of the optimized MOPA assay demonstrates that it is suitable to measure functional antibodies in clinical samples.

Conclusion

The benefits of the microcolony platform include throughput, technique, and ability to automate. Although the traditional dribble MOPA platform can effectively assess the efficacy of pneumococcal vaccines, the microcolony platform results in a 10-fold increase in testing throughput.

ISPPD-0502
BIVALENT PNEUMOCOCCAL SURFACE PROTEIN A (PspA) FUSION PROTEIN VACCINE COMPRISING PspA CLADE 1-4 PROVIDES BROAD PROTECTIVE PROPERTIES AGAINST DIVERSE CLINICAL ISOLATES
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1National Institute of Infectious Diseases, Department of Chemotherapy and Mycoses, Tokyo, Japan
2The Research Foundation for Microbial Diseases of Osaka University, Kannonji Research Institute, Kagawa, Japan
3The Research Foundation for Microbial Diseases of Osaka University, Research department, Osaka, Japan
4National Institute of Infectious Diseases, Department of Bacteriology I, Tokyo, Japan
5Osaka University Hospital, Division of Infection Control and Prevention, Osaka, Japan
6National Institute of Infectious Diseases, Infectious Diseases Surveillance Center, Tokyo, Japan

Background and Aims:

A serotype replacement has been evident among children and adults after introduction of the routine immunization with pneumococcal conjugate vaccine (PCV) in children in Japan.
Invasive pneumococcal disease (IPD) cases with non-PCV13 strains are currently increasing in both children and adults. Therefore, a universal pneumococcal vaccine that covers diverse strains is needed.

**Methods:**

We analyzed pneumococcal surface protein A (PspA) clades of 715 pneumococcal isolates from adult IPD cases in 2014-2016 after PCV introduction. To develop a universal pneumococcal vaccine, we generated bivalent PspA fusion protein vaccine comprising PspA clade 3+2 and PspA clade 4+1. The reactivity of immune mouse plasma raised by bivalent PspA fusion protein was examined for 49 isolates from adult IPD after PCV introduction by flow cytometry. The protective effect of this vaccine was also examined against nasal challenge with pneumococcal strains of five different PspA clades in mice.

**Results:**

PspA clade 2 was increased in 2016 compared to that in 2014 or before PCV introduction. Immune plasma of this vaccine showed the great binding of PspA-specific IgG to 48 of 49 isolates with different PspA clades (98%). Immunization with this vaccine afforded significant protection against pneumococcal challenge by five strains of PspA clade 1-5 in mice.

**Conclusion**

Our results suggest that bivalent PspA fusion protein vaccine provides broad coverage against diverse clinical isolates and an increase of PspA clade 2 strains was found after PCV introduction in Japan.

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**ISPPD-0081**

**NEXT GENERATION SEMI-SYNTHETIC AND FULLY SYNTHETIC STREPTOCOCCUS PNEUMONIAE VACCINES**

C.L. pereira¹, S. Guddehalli Parameswarappa¹, S. Oestreich¹, A. Von Bonin¹, P. Kaplonek², N. Khan², P. Seeberger²

¹Vaxxilon, Chemistry, Berlin, Germany
²Max Plank Institute of Colloids and Interfaces, Biomolecular Systems, Berlin, Germany

**Background and Aims:**

Polysaccharide vaccines have historically been time consuming and expensive to discover, manufacture and formulate. *S. pneumoniae* (Sp) which is surrounded by virulent structurally and antigenically distinct capsular polysaccharides (CPS) resulting in more than 95 serotypes represents one such example. Current Sp vaccines are effective in preventing disease but are limited by the number of serotypes present in the vaccine. Their number is further limited by the amount of carrier protein and their use by cost and requirement for cold chain distribution.

**Methods:**

The Max Planck Institute of Colloids and Interfaces and Vaxxilon have developed a technology platform to broaden pathogen scope and accelerate the identification of epitopes for next generation vaccines. By synthesizing glycans with a limited number of repeating units, an optimal epitope may be identified rapidly using in vitro methods before in vivo confirmation.¹
Results:

Vaxxilon has demonstrated that syntheses can be upscaled to commercially viable quantities. Serotype specific POCs studies have demonstrated the platform’s applicability to multiple serotypes and the company has a phase-I ready ST-3. In the long run, antigens may be coupled to a non-peptide immunostimulator instead of a carrier protein to create a thermostable vaccine.

Conclusion

The technology may be applied to any pathogen with an elucidated CPS structure and has the potential to reduce discovery time, decrease cost, and widen distribution.


Background and Aims:

A new pneumococcal conjugate vaccine is currently undergoing advanced clinical evaluation in Cuba. We present the safety and immunogenicity current results of clinical research of PCV7-TT.

Methods:

PCV7-TT contains 2.2µg of capsular polysaccharide from serotypes 1, 5, 14, 18C, 19F and 23F and 4.4µg of 6B conjugated to tetanus toxoid (TT). The results of three randomized control trials are synthesized to demonstrate the safety and immunogenicity including: 1) adults (n=40), 2) preschool children 4-5y/o (n=15) and infants 7-11 months (n=30) and 3) preschool children 1-5y/o (n=1135). The infants and preschool children were followed for 30 days after each doses to assess adverse events. Serum was obtained 30 days after the second and third dose for evaluating the immunogenicity. Serotype specific OPA and ELISA were performed at the WHO Reference Laboratory, UCL Institute of Child Health.

Results:
No serious adverse events were reported in none group of age. Following a single-dose in 4–5-year-old children and infants vaccinated at 7, 8 and 11 months induced statistically significant (p≤ 0.05) increase of IgG GMC and OPA for seven common serotypes with Synflorix® as control vaccine. New insights since a protective efficacy clinical trial including 1135 preschool children and using PREVNAR® as control vaccine, showing that more than 90% of children have IgG titers ≥0.35 for 6 of 7 vaccine serotypes, and more than 77% for serotype 5.

**Conclusion**

The Cuban pneumococcal vaccine candidate is safe and immunogenic. These results are useful to support the decision-making to introduce the new vaccine in Cuba.

**ISPPD-0524**

INTRANASAL IMMUNIZATION WITH AN ATTENUATED PEP27 MUTANT PROVIDES PROTECTION FROM SECONDARY PNEUMOCOCCAL INFECTION AS WELL AS OTHER RESPIRATORY PATHOGENS INCLUDING INFLUENZA VIRUS

S.H. Seon1, D.K. Rhee1

1Sungkyunkwan University, School of Pharmacy, Suwon, Republic of Korea

**Background and Aims:**

During influenza pandemics, secondary pneumococcal infections cause excessive mortality. However, the current pneumococcal polysaccharide conjugate vaccine, PCV 13, provides only limited protection against secondary infection. Therefore, a more effective pneumococcal vaccine is required to protect against secondary pneumococcal infections.

**Methods:**

6- to 8-week-old female BALB/c mice were immunized with approximately 1×10^8 CFU of Δpep27 in 50 μl PBS via the i.n. route three times at one-week intervals. 10-12 days (short-term), or 30 days (long-term) after the last immunization, 0.02 LD50 (50% lethal dose) of H1N1 influenza virus in 50 μl PBS was administered by the i.n. route. Body weight was then monitored every day. Mice were challenged with 1×10^8 CFU of D39 in 50 μl PBS via the i.n. route 10-12 days after influenza infection, and the survival rate was determined.

**Results:**

intranusal immunization with an attenuated pneumococcal pep27 mutant provides protection from secondary pneumococcal challenge. Moreover, pep27 mutant immunized group showed resistance to primary influenza virus infection, and other bacterial pathogens such as Staphylococcus aureus and Klebsiella pneumoniae. Meanwhile, the level of inflammatory cytokines were decreased in the lung after pep27 mutant immunization followed by influenza virus infection.

**Conclusion**

In this study, we demonstrated that Δpep27 immunization effectively protects against secondary pneumococcal challenge after influenza virus infection by lessening both the viral and the bacterial burden in the lung.

**ISPPD-0762**
RELATIONSHIP BETWEEN PRE-VACCINATION ANTIBODY LEVELS, POST-IMMUNIZATION IMMUNE RESPONSE AND VACCINE EFFICACY OF AN INVESTIGATIONAL PNEUMOCOCCAL PROTEIN-BASED VACCINE IN A PHASE 2 RANDOMIZED CLINICAL TRIAL

L.L. Hammitt¹, J.C. Campbell¹, D. Borys², R.C. Weatherholtz³, R. Reid¹, N. Goklish¹, L.H. Moulton¹, Y. Song³, M. Traskine², K. Swinnen², M. Santosham¹, K.L. O’Brien¹
¹Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA
²GSK, Vaccines, Wavre, Belgium
³XPE Pharma & Science, on behalf of GSK, Wavre, Belgium

Background and Aims:

The investigational pneumococcal protein-based vaccine containing pneumolysin toxoid/histidine-triad protein D (dPly/PhtD) was immunogenic in Native American infants; however, no significant protective efficacy against acute otitis media (AOM)/acute lower respiratory infection (ALRI) was shown. Relationship between pre- and post-immunization anti-Ply and anti-PhtD antibody levels, and vaccine efficacy (VE) is presented here.

Methods:

In this phase 2, double-blind, controlled trial (NCT01545375), 6-12-week-olds were 1:1-randomized to receive dPly/PhtD (N=900) or placebo (N=903) at ages 2/4/6 and 12-15 months, co-administered with 13-valent pneumococcal conjugate vaccine. The relationship between pre- and post-primary vaccination anti-Ply/anti-PhtD antibody levels was assessed (scatter plots). VE against AOM/ALRI endpoints was assessed in dPly/PhtD recipients with low or high post-primary anti-Ply or anti-PhtD antibody levels.

Results:

No clear relationship between pre-vaccination and post-primary anti-Ply and anti-PhtD antibody concentrations was found (Figure). A trend for higher efficacy against AOM endpoints with higher post-primary anti-Ply antibody levels was observed (Tables).

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**Figure.** One-month post-primary vaccination antibody levels as a function of pre-vaccination antibody levels for anti-Ply (A) and anti-PhtD (B) (according-to-protocol sub-cohort for immunogenicity)

A.

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Parameter estimates
Control intercept = 3.3383
Control slope = -0.059
dPly/PhtD intercept = 4.4963
dPly/PhtD slope = -0.024
Table 1. Vaccine efficacy (VE) against clinical acute otitis media (AOM) and acute lower respiratory infection (ALRI) for low^a^ (≤27488 FL.U/mL) and high^a^ (>27488 FL.U/mL) range of anti-Ply antibody concentrations one-month post-primary vaccination (according to-protocol sub-cohort for immunogenicity)

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<td>Placebo + PCV13</td>
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<td>92** (0.56)**</td>
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</tbody>
</table>

*dPhy/PhtD recipients from the immunogenicity sub-cohort were divided into low and high range based on the median of the values of anti-Ply immune responses, while Placebo recipients from the immunogenicity sub-cohort were not split. **Number of cases. ***cases/subject year. ****Incidence of endpoint per subject with at least 1 episode [subject/subject year]. Note: VE was estimated using the generalized Cox regression model, by using time to event; the point estimates were not adjusted for multiplicity. FL.U., enzyme-linked immunosorbent assay units; N, maximum number of children; n, number of episodes; CI, confidence interval. AAP-ADOM clinical AOM diagnosed and verified against American Academy of Pediatrics criteria (2004), meeting all of the following criteria: (1) history of acute onset of signs and symptoms of middle-ear inflammation and middle-ear effusion (MEE) AND (2) at least one of the signs and symptoms of middle-ear inflammation (i.e. distinct erythema of the tympanic membrane or distinct otalgia) AND (3) at least one of the MEE signs (i.e. bulging of the tympanic membrane, limited or absent tympanic membrane mobility, air-fluid level behind the tympanic membrane, or otorhea). Modified AAP-ADOM, clinical AOM diagnosed and verified against modified AAP criteria, that refer to (1) a history of acute onset of signs and symptoms of middle-ear inflammation and MEE AND (2) sign/symptom of middle-ear inflammation (i.e. erythema of the tympanic membrane) OR at least one of the MEE signs (i.e. bulging of the tympanic membrane, limited or absent tympanic membrane mobility, air-fluid level behind the tympanic membrane, or otorhea). HCP-AOM, healthcare provider-diagnosed clinical AOM. MA-ALRI, medically attended ALRI.
Conclusion

Pre-vaccination antibody levels, assumed as mainly maternal, did not interfere with dPly/PhtD immunogenicity. VE against AOM tended to increase with post-primary anti-Ply and anti-PhtD antibody levels.

Funding: GlaxoSmithKline Biologicals SA

Table 2. Vaccine efficacy (VE) against clinical acute otitis media (AOM) and acute lower respiratory infection (AIRI) for low⁴ (≤3739.5 ELU/mL) and high⁵ (>3739.5 ELU/mL) range of anti-PhtD antibody concentrations one-month post-primary vaccination (according-to-protocol sub-cohort for immunogenicity)

<table>
<thead>
<tr>
<th>Category</th>
<th>Any episodes</th>
<th>At least one episode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dPly/PhtD</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>+ PCV13 N=50</td>
<td>+ PCV13 N=120</td>
</tr>
<tr>
<td>AAP-AOM</td>
<td>low range</td>
<td>55** (0.40)**</td>
</tr>
<tr>
<td></td>
<td>high range</td>
<td>36 (0.43)</td>
</tr>
<tr>
<td>Modified AAP-AOM</td>
<td>low range</td>
<td>52 (0.60)</td>
</tr>
<tr>
<td></td>
<td>high range</td>
<td>49 (0.59)</td>
</tr>
<tr>
<td>MCP-AOM</td>
<td>low range</td>
<td>69 (0.70)</td>
</tr>
<tr>
<td></td>
<td>high range</td>
<td>54 (0.65)</td>
</tr>
<tr>
<td>MA-ALRI</td>
<td>low range</td>
<td>10 (0.11)</td>
</tr>
<tr>
<td></td>
<td>high range</td>
<td>11 (0.15)</td>
</tr>
<tr>
<td>MA-ALRI with fever</td>
<td>low range</td>
<td>4 (0.05)</td>
</tr>
<tr>
<td></td>
<td>high range</td>
<td>9 (0.11)</td>
</tr>
</tbody>
</table>

*P values for significance: **p<0.01, ***p<0.001

ISPPD-0765

SEASONALITY AND IMPACT OF INFLUENZA VACCINATION ON INCIDENCE OF ACUTE OTITIS MEDIA AFTER IMMUNIZATION WITH AN INVESTIGATIONAL PNEUMOCOCCAL PROTEIN-BASED VACCINE: PHASE 2 RANDOMIZED CLINICAL TRIAL

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²GSK, Vaccines, Wavre, Belgium
³XPE Pharma & Science, on behalf of GSK, Wavre, Belgium
⁴GSK, Vaccines, Rockville MD, USA

Background and Aims:

Influenza disease and vaccinations impact the incidence of acute otitis media (AOM). Seasonality and impact of influenza vaccination on AOM incidence were assessed in a
Phase 2 investigational pneumococcal protein vaccine efficacy (VE) trial in Native American infants.

Methods:

6-12 weeks-old infants were randomized 1:1 in a double-blind, controlled-trial (NCT01545375), and received either the investigational vaccine containing pneumolysin toxoid and histidine-triad protein D (at 10mcg each; dPly/PhtD) (N=900) or placebo (N=903) at ages 2, 4, 6 and 12-15 months, each co-administered with PCV13. Recommended pediatric vaccines, including influenza vaccine (in children ≥6 months old per US ACIP guidelines), were allowed. In this descriptive analysis, incidences of AOM during study duration (May2012-July2016) were analyzed per influenza vaccination status in each group.

Results:

AOM incidences followed a seasonal pattern with peaks in winter seasons and tended to be lower in the last season, reflecting the older age of study population; an AOM peak was observed between 6 and 12 months of age (Figure). No consistent impact of seasonal influenza vaccination on dPly/PhtD VE was observed (Table).

Figure. Percentage of infants with episodes of HCP-AOM from the administration of dose 1, per each calendar month (A) and by age (B) (Total vaccinated cohort)

Note: The grey rectangles indicate the flu seasons. HCP-AOM, healthcare provider-diagnosed clinical acute otitis media.
Table. Vaccine efficacy of investigational dPly/PhdT vaccine in prevention of any episodes of HCP-AOM and AAP-AOM from the administration of dose 1 by influenza season and influenza vaccination (Total vaccinated cohort)

<table>
<thead>
<tr>
<th>Season (end Nov-end May)</th>
<th>Group</th>
<th>Total</th>
<th>Vaccinated against seasonal influenza (age: from 6 months old)</th>
<th>Not vaccinated against seasonal influenza (age: from 6 weeks old)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N.</td>
</tr>
<tr>
<td>HCP-AOM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012/13</td>
<td>dPly/PhdT + PCV13</td>
<td>404</td>
<td>96</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Placebo + PCV13</td>
<td>409</td>
<td>105</td>
<td>26</td>
</tr>
<tr>
<td>2013/14</td>
<td>dPly/PhdT + PCV13</td>
<td>767</td>
<td>304</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>Placebo + PCV13</td>
<td>771</td>
<td>312</td>
<td>114</td>
</tr>
<tr>
<td>2014/15</td>
<td>dPly/PhdT + PCV13</td>
<td>595</td>
<td>345</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td>Placebo + PCV13</td>
<td>596</td>
<td>331</td>
<td>118</td>
</tr>
<tr>
<td>2015/16</td>
<td>dPly/PhdT + PCV13</td>
<td>197</td>
<td>88</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Placebo + PCV13</td>
<td>216</td>
<td>109</td>
<td>11</td>
</tr>
<tr>
<td>AAP-AOM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012/13</td>
<td>dPly/PhdT + PCV13</td>
<td>404</td>
<td>96</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Placebo + PCV13</td>
<td>409</td>
<td>105</td>
<td>27</td>
</tr>
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<td>2013/14</td>
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<td>62</td>
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<tr>
<td></td>
<td>Placebo + PCV13</td>
<td>771</td>
<td>312</td>
<td>73</td>
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<td>2014/15</td>
<td>dPly/PhdT + PCV13</td>
<td>595</td>
<td>345</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Placebo + PCV13</td>
<td>596</td>
<td>331</td>
<td>74</td>
</tr>
<tr>
<td>2015/16</td>
<td>dPly/PhdT + PCV13</td>
<td>197</td>
<td>88</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Placebo + PCV13</td>
<td>216</td>
<td>109</td>
<td>6</td>
</tr>
</tbody>
</table>

Note: Analysis in the total vaccinated cohort included infants for whom the follow-up period started from dose 1 of pneumococcal vaccine and either beginning of influenza season defined as 30th Nov (for those not vaccinated against influenza) or from dose 1 of influenza vaccination series for a given influenza epidemic season (2012/13, 2013/14, 2014/15, and 2015/16) for those vaccinated against influenza; the analysis has been done in "data driven" mode as the study was not designed for this endpoint. N, number of children participating in the study in the specified season; N., number influenza-vaccinated/influenza non-vaccinated children; AAP-AOM, clinical acute otitis media diagnosed and verified against American Academy of Pediatrics criteria (2005), meeting all of the following criteria: (1) history of acute onset of signs and symptoms of middle-ear inflammation and middle-ear effusion and middle-ear effusion (MEE) AND (2) at least one of the signs and symptoms of middle-ear inflammation [i.e. distinct erythema of the tympanic membrane or distinct otalgia] AND (3) at least one of the MEE signs [i.e. bulging of the tympanic membrane, limited or absent tympanic membrane mobility, air-fluid level behind the tympanic membrane, or otoscope]; HCP-AOM, healthcare provider-diagnosed clinical AOM; Incidence: episodes/person-year; VE: vaccine efficacy was estimated by generalized Cox regression model CI, confidence interval. *Duration of efficacy follow up during influenza season – for influenza vaccine recipients from completion of influenza vaccination (two doses if first time in life, one dose in next seasons).

Conclusion

This preliminary analysis did not show that influenza vaccination affected the VE of investigational dPly/PhdT vaccine in the prevention of AOM in young children.

Funding: GlaxoSmithKline Biologicals SA
THE LUNG

ISPPD-0025
REDUCED NONTYPEABLE HAEMOPHILUS INFLUENZAE LOWER AIRWAY INFECTION IN CHILDREN WITH CHRONIC ENDOBRONCHIAL DISORDERS VACCINATED WITH THE 10-VALENT PNEUMOCOCCAL H. INFLUENZAE PROTEIN D CONJUGATE VACCINE (PHiDCV)

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²Griffith University, School of Medicine, Gold Coast, Australia
³Queensland University of Technology, Queensland Children’s Health Service, Brisbane, Australia

Background and Aims:

Chronic endobronchial infections in children caused by nontypeable Haemophilus influenzae (NTHi) are responsible for a high disease burden. We aimed to determine whether NTHi lower airway infection was reduced in PHiDCV-vaccinated children compared to children not vaccinated with PHiDCV in an opportunistic cross-sectional study. Children in Australia’s Northern Territory (NT) were vaccinated with PCV7 from 2001-9, PHiDCV from October 2009 to October 2011, and PCV13 from October 2011. Queensland children received PCV7 from 2005-11 and PCV13 from 2011 onwards.

Methods:

Bronchoalveolar lavage fluids from 260 NT and 283 Queensland children undergoing bronchoscopy for chronic cough from 2007-16 were processed, and lower airway infection defined (≥10⁴ colony-forming units/mL) as previously described. Children who received a primary course of ≥2 doses of one PCV and <2 doses of another PCV were included in each vaccine group. Logistic regression determined associations between NTHi infection and age, sex, Indigenous status, antibiotic exposure and PHiDCV vaccination.

Results:

Of 262 PCV7-vaccinated children, 53 PHiDCV-vaccinated children and 166 PCV13-vaccinated children (62 children had mixed schedules, <2 doses of any PCV or missing vaccination data), NTHi lower airway infection was detected in 89 (34%), 9 (17%) and 47 (28%), respectively. Using multivariable logistic regression, significant independent factors associated with reduced NTHi lower airway infection were increasing age (Odds Ratio (OR) 0.88, 95% Confidence Interval (CI) 0.80-0.96), macrolide use (OR 0.57, 95%CI 0.35-0.93) and PHiDCV vaccination (OR 0.42, 95%CI 0.19-0.93).

Conclusion

PHiDCV may be an effective intervention to improve respiratory outcomes by reducing NTHi lower airway infection. Clinical trial evidence is needed.

ISPPD-0038
CHILDHOOD PNEUMONIA IN LUBUMBASHI: A STUDY OF 85 CASES

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Equilibre International DRC, Programme Tuberculose et Maladies respiratoires, Kananga, Democratic Republic of the Congo

Background and Aims:

Pneumonia is one of the leading causes of death for children under five years of age. In Lubumbashi- DRC, in 2015, they were the third leading cause of death for children under five. The objective of this work was to study its epidemiological and clinical characteristics in Lubumbashi.

Methods:

This is a retrospective descriptive survey conducted on the files of children hospitalized from 1 July 2015 to 30 June 2016 in the Pediatric Department of the University Clinic of Lubumbashi. The data were analyzed with the software epi info 3.5.4.

Results:

Seven hundred and eighty-one children were hospitalized, during which 85 cases of pneumonia were recorded, or 10.9%. The sex ratio was M / F 2. The average age was 2 years and 9 months. Children aged 0 to 2 years accounted for 62.5% of the workforce. The average time to consultation after symptom onset was 12.4 days. Vaccination status was correct for 15.3% of cases. The fever accounted for 94.4% of the reasons for consultation and cough 87.5%. The right parenchymatous opacities accounted for 55.8% of radiographic abnormalities and right pleural effusions 16.2%.

Conclusion

With a frequency of 10.9% of cases of hospitalization, pneumonia is a real public health problem. A reliable diagnostic method of tuberculosis is necessary in the absence of the tuberculin test. The introduction of new antigens into the Expanded Program of Immunization, such as pneumococcal vaccine, would be necessary.

ISPPD-0766
PNEUMOCOCCAL FINDINGS IN THE PNEUMONIA ETIOLOGY RESEARCH FOR CHILD HEALTH (PERCH) STUDY
K. O’Brien1, T. PERCH Study Group1
1Johns Hopkins Bloomberg School of Public Health, Department of International Health, Baltimore, USA

Background and Aims:

The residual burden of pneumococcal pneumonia, in the routine PCV era, is unknown.

Methods:

PERCH is a case-control study of WHO (pre-2013 definition) severe/very severe pneumonia among hospitalized children aged 1-59 months in five African and two Asian countries; four routinely used PCV. Community controls were age-group and season matched. Sites each enrolled for 24 months (August 2011 to January 2014). Analysis included nasopharyngeal/oropharyngeal PCR (for >33 pathogens) and whole blood pneumococcal PCR from cases and controls; case-only data included chest x-rays (CXRs), blood culture, and from a small subset, lung aspirate and pleural fluid. Results were integrated using
Bayesian, partial latent class analysis to estimate the pathogen probability, accounting for test/pathogen-specific sensitivity. Assumed pneumococcal sensitivity was: 5-20% blood-culture, 50-90% nasopharyngeal/oropharyngeal PCR and 12-65% blood-PCR, adjusted (lower) for antibiotic exposure.

**Results:**

The primary analysis included 1,769 HIV-uninfected, CXR(+) cases and 5,075 HIV-uninfected controls. Pneumococcus was the commonest pathogen among positive lung aspirate specimens (72.7%; 8/11) and blood-cultures (33.9%; 19/56, except undetected in South African and Asian sites). High density pneumococcal nasopharyngeal/oropharyngeal prevalence was 13.5% (cases) and 7.6% (controls); high density pneumococcal blood PCR+ was 5.4% and 3.0%, respectively. Estimated pneumococcal etiology was 7.2% (95%CI: 5.1,9.6) 4.8% PCV13-type and 2.5% non-PCV13-type, ranging from <2% (Bangladesh, Thailand) to 14.8-17.5% (The Gambia, Mali). The proportion was higher for children >1 year and for very severe pneumonia.

**Conclusion**

Among children hospitalized with severe/very severe pneumonia, pneumococcus was a common, but not predominant, etiology. The etiologic fraction may be underestimated if test sensitivities were overestimated.

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**PNEUMONIA AND PREVENTION IN ADULTS**

**ISPPD-0603**

**INFLUENCE OF OLDER AGE AND OTHER RISK FACTORS ON HOSPITALISATION FOR PNEUMOCOCCAL PNEUMONIA AND DETRIMENTAL OUTCOME IN ADULTS IN SWITZERLAND IN THE PNEUMOCOCCAL VACCINE ERA**

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¹Cantonal Hospital St. Gallen, Division of Infectious Diseases and Hospital Epidemiology, St. Gallen, Switzerland
²University of Bern, Institute for Infectious Diseases, Bern, Switzerland
³Cantonal Hospital St. Gallen, Department of Pulmonary and Sleep Medicine, St. Gallen, Switzerland

**Background and Aims:**

Whether older age itself should be an indication for pneumococcal vaccination in adults is controversial. We aimed to quantify the effect of age as a risk factor for hospitalisation for pneumococcal pneumonia and increased length of stay (LOS) and mortality.

**Methods:**

We used a database of all hospitalisations in Switzerland which includes ICD-10 diagnoses to obtain the number of hospitalisations for pneumococcal pneumonia among adults from 2002 to 2015. We calculated the effects of age and of those comorbidities, which are national 13-valent pneumococcal conjugate vaccine (PCV13) indications, on pneumococcal pneumonia hospitalisation, associated LOS and all-cause in-hospital mortality.

**Results:**
Pneumococcal pneumonia was diagnosed in 0.1% (21'610/17'619'016) of all hospitalisations and 5.1% of pneumonia hospitalisations (421'760). The diagnosis of pneumococcal pneumonia among hospitalisations was more frequent in patients ≥50y (0.2%) than in patients <50 years (0.06%; p<0.001). The effect was similar for age ≥65y (0.2% vs. 0.1%; p<0.001). In 2 separate multivariable logistic regression models, each vaccine indication (except for asplenia; and for sickle cell disease for ≥65y) and age categories ≥50y (aOR: 2.1, p<0.001) and ≥65y (aOR: 1.8, p<0.001) were independent predictors for pneumococcal pneumonia hospitalisation. There was a negative interaction between risk factor and age. Both age categories (≥50y and ≥65y) were independent risk factors for LOS (p<0.001 for both) and mortality (p<0.001 for both) in patients with pneumococcal pneumonia.

Conclusion

Older age is a risk factor for hospitalisation with pneumococcal pneumonia and for longer LOS and higher mortality similarly to and independent of PCV13 indications.

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**ISPPD-0357**

**THE IMPACT OF CERTAIN UNDERLYING CLINICAL CONDITIONS ON THE RISK OF DEVELOPING HOSPITALISED PNEUMONIA IN ENGLAND**

J. Campling1, D. Jones2, J. Chalmers3, A. Vyse1, H. Madhava4, M. Slack5

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2Pfizer Ltd, Health & Value - Vaccines UK, Tadworth- Surrey, United Kingdom
3University of Dundee, School of Medicine, Dundee, United Kingdom
4Pfizer Ltd, Medical Affairs - Vaccines, Tadworth- Surrey, United Kingdom
5Griffith University, School of Medicine, Queensland, Australia

Background and Aims:

Background: Specific risk groups are at increased risk of hospitalisation and death from non-invasive pneumococcal disease. Evidence showing the increased odds ratio in these risk groups for developing hospitalised pneumonia in England is missing.

Aim: To quantify the odds of developing hospitalised pneumonia for 6 key risk groups as defined by The Green Book (UK vaccination policy guide) compared to “healthy controls”, with no risk group diagnosis, using the Hospital Episodes Statistics (HES) database.

Methods:

We retrospectively analysed the HES database, which includes analysed data on the entire ≥18yrs population of England for episodes of hospitalised pneumonia over a period of 3 years. Patients and controls were identified by ICD-10 codes. Healthy controls were in-patient admissions for tooth extraction. Odds ratios were calculated while simultaneously adjusting for gender, age, Charlson Comorbidity Index, ethnicity, geography and deprivation.

Results:

Odds ratio of developing hospitalised pneumonia for specific risk groups compared to healthy controls.
### Conclusion

This is the first study of an entire adult population quantifying the increased odds of hospitalised pneumonia among patients with these underlying risk factors. These individuals are at a significant increased risk of developing hospitalised pneumonia and that the odds are substantially higher for those with CRD, CLD and BMT. These data support the potential benefit of adopting a targeted prevention strategy among specific risk groups.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Heart Disease (CHD)</td>
<td>1.87 (1.80, 1.94)</td>
</tr>
<tr>
<td>Chronic Liver Disease (CLD)</td>
<td>3.43 (3.29, 3.59)</td>
</tr>
<tr>
<td>Chronic Respiratory Disease (CRD)</td>
<td>5.47 (5.28, 5.70)</td>
</tr>
<tr>
<td>Chronic Kidney Disease (CKD)</td>
<td>2.20 (2.13, 2.32)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.18 (1.13, 1.23)</td>
</tr>
<tr>
<td>Bone Marrow Transplant recipients (BMT)</td>
<td>5.46 (5.05, 5.90)</td>
</tr>
</tbody>
</table>

**ISPPD-0360**

THE CLINICAL AND FINANCIAL BURDEN TO THE NHS OF PATIENTS WITH CERTAIN UNDERLYING COMORBIDITIES THAT DEVELOP HOSPITALISED PNEUMONIA

D. Jones¹, J. Campling², J. Chalmers³, A. Vyse², H. Madhava², M. Slack⁴

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³University of Dundee, School of Medicine, Dundee, United Kingdom
⁴Griffith University, School of Medicine, Queensland, Australia

**Background and Aims:**

Background: The clinical and economic costs of an episode of hospitalised pneumonia are usually assumed to be short-lived with patients subsequently returning to their previous health-state. We hypothesised that a diagnosis of hospitalised pneumonia in an individual within a specific risk group would have clinical and economic implications that would go beyond the initial episode.

Aim: Determine, within the NHS context, the clinical and financial burden of hospitalised pneumonia in 6 risk groups over a 4 year period utilising the Hospital Episodes Statistics (HES) database, which incorporates the entire population of England that visit a hospital.

**Methods:**

We retrospectively analysed HES data on individuals ≥18yrs. Those with a specified risk group diagnosis were tracked from 2012 to 2015. Individuals developing hospitalised pneumonia in the year following their risk group diagnosis were matched through propensity
scoring to an individual within that risk group who did not go on to develop hospitalised pneumonia. Hospital activity, costs and mortality were compared between the two groups over the next 3 years.

Results:

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Incidence Rate Ratio (Total admissions 2015)</th>
<th>Mean Cost difference (£: Total admissions 2012 - 2015)</th>
<th>Mortality Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Heart Disease</td>
<td>1.22 (1.19; 1.25)</td>
<td>6,103 (5,930; 6,275)</td>
<td>5.37 (5.18; 5.58)</td>
</tr>
<tr>
<td>Chronic Respiratory Disease</td>
<td>1.38 (1.35; 1.40)</td>
<td>11,167 (10,847; 11,486)</td>
<td>5.94 (5.65; 6.24)</td>
</tr>
<tr>
<td>Chronic Liver Disease</td>
<td>1.30 (1.18; 1.44)</td>
<td>10,858 (9,712; 12,004)</td>
<td>4.76 (4.12; 5.11)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>1.38 (1.29; 1.47)</td>
<td>3,800 (3,436; 4,164)</td>
<td>5.26 (4.96; 5.59)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.24 (1.19; 1.29)</td>
<td>1,907 (1,573; 2,240)</td>
<td>4.89 (4.63; 5.16)</td>
</tr>
<tr>
<td>Bone Marrow Transplant Recipient</td>
<td>1.28 (0.96; 1.71)</td>
<td>9,274 (4,968; 13,580)</td>
<td>7.50 (4.71; 11.92)</td>
</tr>
</tbody>
</table>

Conclusion

This study utilises an entire adult population to ascertain the impact of hospitalised pneumonia in patients with certain underlying comorbidities. Hospitalised pneumonia has a significant long term impact on those within specific risk groups, resulting in additional hospital admissions and associated costs, and the initial pneumonia episode appears to significantly increase the likelihood of mortality.

ISPPD-0353
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Background and Aims:

The burden of pneumococcal disease and the vaccine effectiveness of pneumococcal conjugate vaccines (PCVs) have already been established in Mexico considering the epidemiological data available for all-cause pneumonia (ACP), showing a reduction of about 60% in children under 1 year old, in a 10 year period. PCV7 was introduced in Mexico’s NIP in 2004 and PCV13 in 2010 in a 2+1 schedule until today.

**Objective:** To estimate the burden of pneumococcal pneumonia in adult population to show the indirect effect of the PCVs.

Methods:

Data from the overall incidence of ACP in adults has been obtained from the Epidemiological Surveillance System Platform (SUIVE) from 2003 to 2015. Discharging diagnoses according to the ICD (International Classification of Diseases)-10 were considered. The adjusted incidence was modeled from local data for each age group. Secondarily the percentage of ACP due to pneumococcal infection has been considered according to literature review of Mexican data in the study period: 40% before PCV7 introduction (2003), 12% at introduction of PCV13 (2010) and 8.2% post-PCV13 introduction (2015). These percentages have been transformed into incidence rate.

Results:
Conclusion

Although the model may have limitations due to the data source, it shows the indirect effect of the vaccine in adult population after universal vaccination in children.

Background and Aims:

The relevance of S. pneumoniae as a prominent respiratory pathogen in the elderly has been highlighted worldwide. In Colombia, no detailed molecular studies have documented the behavior of pneumococci as colonizers in aged subjects. In 2016, ~750,000 adults over 50 years of age were living in Medellín; where an elderly-care program (AMAUTTA) provides them with attention. Here, the prevalence of the upper-respiratory colonization by pneumococci and its associated factors among elderly in Medellín were investigated (2017).

Methods:

A cross-sectional study was conducted, considering three-groups: 50-64, 65-79 and ≥80 years. 30 subjects were randomly selected from each of 16 Elderly-Units (“Clubes-de-Vida”), representing the 16 territorial communes of Medellín. Informed consents and structured surveys were applied. Nasopharyngeal samples were taken and a broth-enrichment approach was used for pneumococcal growth. DNA was isolated and tested by qPCR targeting pneumococcal-specific genes (lytA-cpsA). Statistics: SPSS-software.

Results:

The upper-respiratory carriage in the elderly of Medellín was 79.9% (pneumococcal vaccination coverage: 16.4%). The highest proportion of carriage occurred among 65-79
years old adults (49.2%). According to the territorial organization by communes, the northern and central zones of Medellín have higher rates of carriage, while the south have lower levels. Higher carriage rates were also associated with respiratory signs. Broth-enriched samples identified as positive for carriage are currently under evaluation to recover live pneumococci for serotyping, MLSTs and antimicrobial resistance determination.

Conclusion

This study contributes to a better understanding of S.pneumoniae in Medellín, which is necessary to support the implementation of vaccine-based strategies to prevent pneumococcal diseases in the elderly of Colombia.

ISPPD-0118

UPTAKE OF PNEUMOCCOCCAL CONJUGATE VACCINE AMONG IMMUNOCOMPROMISED US ADULTS UNDER 65 YEARS OF AGE

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²Pfizer, Medical Affairs, Collegeville- PA, USA
³Pfizer, Statistical Research & Data Science Center, New York- NY, USA
⁴Pfizer, Real World Data & Analytics, New York- NY, USA

Background and Aims:

Adults with immunocompromising conditions are at increased risk for invasive pneumococcal disease (IPD). Consequently, in 2012, vaccination with 13-valent pneumococcal conjugate vaccine (PCV13) followed by 23-valent polysaccharide vaccine (PPSV23) was recommended by the Advisory Committee on Immunization Practices (ACIP) for US adults with immunocompromising conditions. Current coverage estimates come from the National Health Interview Survey (NHIS) and do not differentiate between vaccines. The present study was conducted to assess coverage of PCV13 among immunocompromised adults 19-64 years of age.

Methods:

We assessed PCV13 vaccine uptake between October 2012 and October 2016 in adults aged 19-64 years who had immunocompromising condition(s) or used immunosuppressive therapies and were continuously enrolled in one of several large integrated delivery. We evaluated uptake stratified by age, sex, race, and other patient characteristics.

Results:

Among 572,055 adults eligible for pneumococcal vaccination, there was a mean (SD) age of 50(12) years and a higher proportion of women (62%). Overall PCV13 uptake was 9.9%, with higher uptake among adults aged 50-64 (12.0%), males (11.9%), and Hispanics (12.4%). Uptake varied little by race or income (Figure 1).

Conclusion

After 4 years of implementation, uptake of PCV13 among immunocompromised adults 19-64 years of age remains very low (9.9%). Clinicians caring for these vulnerable patient populations should ensure adherence to the current pneumococcal vaccination recommendations which includes PCV13 and PPSV23 in series.
ISPPD-0509
CHARACTERISTICS OF ADULT PNEUMONIA PATIENTS INFECTED WITH MULTIPLE SEROTYPES OF PNEUMOCOCCUS IN JAPAN
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¹Nagasaki University, School of Tropical Medicine and Global Health TMGH, Nagasaki, Japan
²Nagasaki University Institute of Tropical Medicine, Department of Clinical Medicine, Nagasaki, Japan
³Kameda Medical Center, Department of General Internal Medicine, Chiba, Japan
⁴Juzenki Hospital, Department of Internal Medicine, Nagasaki, Japan
⁵Chikamori Hospital, Department of Internal Medicine, Kochi, Japan
⁶Ebetsu City Hospital, Department of General Internal Medicine, Hokkaido, Japan
⁷Kameda Medical Center, Department of Pulmonology, Chiba, Japan

Background and Aims:

Few case reports have shown that a patient can have infection with multiple serotypes of pneumococcus. It is very difficult to detect multiple serotypes by culture. With the use of molecular methods, multiple serotypes colonization in the nasopharynx has been reported; however, there is lack of clinical description of pneumonia patients infected with multiple serotypes.

Methods:

Adult pneumonia patients (≥15 years of age) (community onset) were enrolled in four community hospitals in Japan from 2011 to 2014 as a major research project of Adult Pneumonia Study Group-Japan (APSG-J). Demographic and clinical data along with sputum samples were collected. Pneumococcus was detected by lytA and serotyped by nanofluidic real-time PCR system.
**Results:**

Total number of enrolled patients was 3470. Sputum from 75.1% (n=2605) patients were collected and tested for pneumococcus. Pneumococcus was detected in 19.8% (n=516) of which 45.4% were PCV13 and 74.2% were PPV23 serotypes. Multiple serotypes were present in 39.7% (n=205). When compared to single serotypes, patients with multiple serotypes were associated with younger age (OR: 0.98, \( P=0.008 \)), community acquired pneumonia (CAP vs HCAP, OR 2.00 (1.27-3.14)), risk of aspiration (OR: 1.53 (1.04-2.25), PPV23 vaccination (OR: 0.56 (0.35-0.89)), hypoxemia (OR: 1.35 (1.02-1.78)), CRP >10 mg/dL (OR: 1.62 (1.33-1.98)) and higher bacterial load (log10 DNA copies/micro L) (OR: 1.14, \( P=0.014 \)).

**Conclusion**

There was a significant association between clinical severity and multiple pneumococcal serotypes. It is warranted to further investigate the pathogenic effect of multiple serotype pneumococcal infection.

**Background and Aims:**

*Streptococcus pneumoniae* is among the most common causes of community-acquired pneumonia (CAP), meningitis, and bacteremia in children and adults, and contributes to significant morbidity and mortality. The population of Southeast Asia is growing quickly, and comparing and contrasting strategies for the prevention of pneumococcal disease among adults in this region is warranted. The incidence and mortality of pneumonia and invasive pneumococcal disease (IPD) among adults in Southeast Asian countries deemed to be high. A number of countries in Southeast Asia set pneumococcal vaccination recommendations for adults to combat the burden of pneumococcal disease in Southeast Asia.

**Methods:**

We searched for pneumococcal vaccination recommendations (both governmental and society) among countries and regions in Southeast Asia including, Hong Kong, Indonesia, Macau, Malaysia, Pakistan, the Philippines, Singapore, Taiwan and Thailand. Recommendations were collated by age and risk category.

**Results:**

Overall, many countries in Southeast Asia have either governmental or society backed pneumococcal vaccination recommendations. The recommendations vary between conjugate vaccine and polysaccharide vaccine or sequential for both vaccines (Table 1) among healthy adults and adults with comorbidities, whether at-risk or high-risk comorbidities.
Table 1. PCV13 & PPVS23 vaccine recommendations for adults in Southeast Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>Recommendation</th>
<th>Type of Recommendation</th>
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</tr>
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Conclusion

Pneumococcal vaccination has been recommended by many governments and medical societies in Southeast Asia to combat the high burden of pneumococcal disease in this region.
COMMUNITY-ACQUIRED PNEUMONIA: 10 YEARS EXPERIENCE IN THE SOCIAL SECURITY HEALTH SYSTEM OF COSTA RICA

J. Castro¹, J. Villalobos¹
¹Caja Costarricense de Seguro Social, Hospital México, San José, Costa Rica

Background and Aims:

To describe the epidemiological behavior of community-acquired pneumonia (CAP) from 2005 to 2014, in Costa Rica.

Methods:

Descriptive study that analyzes hospital discharges due to CAP using the database of hospital discharges of the Social Security Health System of Costa Rica between 2005 and 2014 (ICD-10 codes: J10.0 to J18. 9), cases classified as nosocomial (Y95.X) were excluded. We evaluate incidence per 100,000 person, age, sex, hospital stay and in-hospital mortality.

Results:

A total of 65,669 CAP discharges were registered. A statistically significant change in the incidence of CAP was observed, passing from 161 cases in 2005 to 135.4 in 2014. The distribution age showed a predominance of this disease in children under 5 years (38%) and adults ≥ 65 years (31%). In both groups a significant reduction in the incidence of CAP was observed. Incidence in men was significantly higher. The average stay was 9.5 days: 6.5 days for <5 years and 11.9 days for ≥ 65 years. In the period 9551 deaths occurred, most of which were ≥65 (73%), which in-hospital mortality remained constant at 35%. Children under 5 years old showed a significant reduction in mortality.

Conclusion
The incidence of CAP in children under 5 years and in elderly has been significantly reduced. In-hospital mortality was reduced in children under 5 years but remained stable in the elderly, around 35%.

ISPPD-0243
COMMUNITY-ACQUIRED PNEUMONIA AND ASSOCIATED COMORBIDITIES IN THE COSTA RICAN ADULT POPULATION
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Background and Aims:
To describe the characteristics of Costa Rican adults with community-acquired pneumonia (CAP) and the most relevant associated comorbidities.

Methods:
A descriptive study that analyzed hospital discharges by CAP in subjects older than 20 years, based on the database of hospital discharges of the Social Security Health System of Costa Rica between 2005 and 2014 (ICD-10 codes: J10.0 to J18.9). We analyzed: age, sex, hospital stay, in-hospital mortality and associated comorbidities.

Results:
A 33,262 cases of CAP discharges were registered. People older than 52 y/o represent 75% of the cases and 60% of adults with CAP were elderly. The median in-hospital stay was 8 days (IQR 5 - 14), CAP hospitalizations were associated with 41,051 days in-hospital stay. The overall hospital mortality was 27%. The elderly had more risk of death compared to those under 50 (35% versus 13% respectively, OR=3.6, p <0.001). The 52% of the individuals associated at least one risk factor for CAP, the most frequent being Diabetes Mellitus (23%), heart disease (14%), chronic lung diseases (9%), cerebrovascular disease (7%) and cancer (5%).

Conclusion
Most episodes of CAP in adults occurred in people older than 50 years. Mortality increased with age, being three times higher in elderly. The five most frequent comorbidities were:
Diabetes Mellitus, heart disease, chronic lung diseases, cerebrovascular disease and cancer.

**ISPPD-0244**
**RISK FACTORS OF COMMUNITY-ACQUIRED PNEUMONIA IN THE COSTA RICAN ADULT POPULATION**

J. Villalobos¹, J. Castro¹
¹Caja Costarricense de Seguro Social, Hospital México, San José, Costa Rica

**Background and Aims:**
To describe the risk factors of Community-Acquired Pneumonia (CAP) and its stacking in Costa Rican adults.

**Methods:**
A study of the hospital discharges with CAP in patients older than 20 years, based on the database of the Social Security Health System of Costa Rica between 2005 and 2014 (ICD-10 codes: J10.0 to J18.9). Distribution and risk stacking were analyzed. Selected risk factors were: chronic lung diseases, heart disease, cancer, chronic nephropathies, chronic liver diseases, congenital and acquired immunodeficiencies, HIV, pharmacological immunosuppression, cerebrovascular disease (CVD) and diabetes mellitus (DM).

**Results:**
A total of 33,262 discharges were recorded; 52% of the adults with CAP had at least one of the selected risk factors. A 40% of the patients associated one comorbidity, 12% two or more and 7% with at least one high-risk condition. The most frequent combinations of risk factors were: DM + heart disease, DM + lung disease, DM + CVD, heart disease + lung disease and heart disease + CVD. Individuals with at least one risk factor had significantly higher mortality in relation to those without risk factors (32% versus 22%, p <0.001), with two or more comorbidities and high-risk patients had the highest mortality (35% and 36% respectively).

**Conclusion**
Half of the patients with CAP had at least one risk factor, 12% had two or more comorbidities. Most frequent combinations being those associated with DM and heart disease. High-risk patients with two or more comorbidities had a similar mortality and a significantly higher mortality compared with the rest.

**ISPPD-0333**
**PREVALENCE OF SELECT CHRONIC MEDICAL CONDITIONS IN PCV13 CLINICAL TRIALS IN ADULTS**

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¹Pfizer, Medical Affairs, Collegeville- PA, USA
²Pfizer, Medical Affairs, Berlin, Germany

**Background and Aims:**
Immunocompetent adults with stable underlying conditions were included in the phase 3 and 4 PCV13 studies. Post hoc analyses have shown the immunogenicity in adults with chronic medical conditions is similar to those without. The objective of this analysis is to highlight the
overall proportion of individuals with chronic medical conditions or smoking in the adult PCV13 trials.

Methods:

Review of phase 3 and 4 clinical trial data in healthy adults who received PCV13, focused on subpopulations with stable underlying medical conditions. The conditions/behaviors evaluated were diabetes, chronic cardiovascular, pulmonary, and liver diseases, and smoking.

Results:

Of a total of 49,946 adult participants who received PCV13, 40.7% had at least one chronic medical condition. This increased to 48% when smoking was included. The majority were >65 years, driven by the large phase 4 efficacy trial (Study 8).

Conclusion

Almost half of the participants enrolled in PCV13 adult trials had stable, chronic medical conditions, including smoking. Given this contribution to the overall population studied, it is reasonable to assume that adults with chronic medical conditions and/or smoking will also benefit from vaccination with PCV13.

ISPPD-0736
ADHERENCE TO PNEUMOCOCCAL VACCINATION IN A POST-SPLENECTOMY REGISTRY COHORT
S. Luu1, C. Dendle2,3, P. Jones4,5, S. Ojaimi2,6, I. Woolley2,3,4,5
1Monash University, Faculty of Medicine Nursing and Health Sciences, Clayton, Australia
2Monash University, Centre for Inflammatory Diseases, Clayton, Australia
3Monash Health, Monash Infectious Diseases, Clayton, Australia
4Alfred Health, Spleen Australia, Prahran, Australia

Table 1: Proportion of Study Participants Who Received PCV13 with Select Underlying Medical Conditions < 65 Years of Age

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<thead>
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<th>Study 4</th>
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Table 2: Proportion of Study Participants Who Received PCV13 with Select Underlying Medical Conditions ≥ 65 Years of Age

<table>
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ISPPD-0736
ADHERENCE TO PNEUMOCOCCAL VACCINATION IN A POST-SPLENECTOMY REGISTRY COHORT
S. Luu1, C. Dendle2,3, P. Jones4,5, S. Ojaimi2,6, I. Woolley2,3,4,5
1Monash University, Faculty of Medicine Nursing and Health Sciences, Clayton, Australia
2Monash University, Centre for Inflammatory Diseases, Clayton, Australia
3Monash Health, Monash Infectious Diseases, Clayton, Australia
4Alfred Health, Spleen Australia, Prahran, Australia
Background and Aims:

Splenectomised individuals have an increased risk of overwhelming post-splenectomy infection (OPSI), which is associated with high mortality. Infections are often caused by encapsulated bacteria, with *Streptococcus pneumoniae* most commonly implicated. Guidelines recommend both 13-valent pneumococcal conjugated vaccine (13vPCV) and 23-valent polysaccharide pneumococcal vaccine (23vPPV). We aimed to quantify the proportion of uptake and adherence to the immunisation schedule among a splenectomised registry cohort.

Methods:

We performed a cross-sectional evaluation of immunisation uptake and adherence among splenectomised patients recruited for assessment of residual splenic function. Eligible patients were ≥18 years of age, registered with the Spleen Australia registry and splenectomised more than 1 year at time of review. Adherence was compared to 2017 Australian guidelines. Vaccination history was validated by documentation.

Results:

77 of 78 recruited patients were assessed for uptake and adherence to pneumococcal vaccine recommendations. 45 (58%) were female and average age was 58 years. The median years since splenectomy was 14, ranging from 1 to 71 years. Most common indications for splenectomy were trauma (30%) and haematological conditions (29%). Immunisation review revealed 76 received at least one dose of 23vPPV, with 63 (82%) adherent to the recommended 23vPPV schedule and 44 (57%) had received 13vPCV.

Conclusion

We observed good adherence with booster vaccines amongst registrants. However, despite notifications in the Spleen Australia annual newsletter, registrants are not receiving newer vaccines such as 13vPCV. Better awareness techniques for both patients and health care providers are required to further improve adherence.

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**ISPPD-0155**

**THE PEPS (PUBLIC ENGAGEMENT TRAINING FOR SCIENTISTS) PROJECT: HANDS-ON SCIENCE COMMUNICATION TRAINING FOR SCIENTISTS TO ENGAGE AND EDUCATE UNDERSERVED COMMUNITIES ON PNEUMONIA PREVENTION AND VACCINATION**

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¹Johns Hopkins Bloomberg School of Public Health, International Health, Baltimore, USA

²Johns Hopkins Bloomberg School of Public Health, Molecular Microbiology & Immunology, Baltimore, USA

Background and Aims:

The Global Action Plan for Pneumonia and Diarrhea recognizes that for successful implementation of WHO recommendations, effective engagement is key. Although pneumonia-focused scientists can play a role in public engagement on pneumonia prevention, there remains a paucity of practical public engagement trainings for scientists to
practice with the public and quantify feedback on their efforts. The PEPS Project is a three-phase, multi-organizational collaborative effort to train scientists and provide practicums in underserved communities to engage on important health topics like pneumonia prevention and vaccination.

**Methods:**

Phase 1 included an IRB-approved qualitative study of students enrolled in the Johns Hopkins University course “Communicating Science: Practical Skills to Communicate Science.” Assessment of student outcomes were conducted using multiphase ‘Active-Learning Inventory Tool’ and ‘Measuring Students’ Confidence Instrument.’ Phase 2 (ongoing) additionally includes practicums in underserved neighborhoods and assessment of strategies used to improve public awareness, confidence, and call to action.

**Results:**

Phase 1 demonstrated increased confidence of students’ ability to communicate about pneumonia and pneumococcal vaccines, understanding of the challenges of engagement, and motivation for future involvement in engagement. Students also completed four course deliverables: three-minute research pitch, guide to giving media interviews, strategy for engaging the public on [controversial] health science topics, and steps to giving a 10-minute presentation to any audience.

**Conclusion**

Public engagement is integral to pneumonia prevention and vaccine acceptance. The practical public engagement training for scientists via the PEPS Project will be essential as it mobilizes more scientists to excel at oral science communication in any setting.

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**ISPPD-0084**

**EFFECTIVENESS OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE AGAINST HOSPITALIZATION FOR COMMUNITY-ACQUIRED PNEUMONIA IN OLDER US ADULTS: A TEST-NEGATIVE DESIGN**

J.M. McLaughlin¹, Q. Jiang¹, R.E. Isturiz¹, H.L. Sings¹, D.L. Swerdlow¹, B.D. Gessner¹, R.M. Carrico², P. Peyraní, T.L. Wiemken³, W.A. Mattingly², J.A. Ramirez², L. Jodar¹

¹Pfizer Vaccines, Medical Development and Scientific and Clinical Affairs, Collegeville- PA, USA
²University of Louisville- School of Medicine, Department of Medicine- Division of Infectious Diseases, Louisville- KY, USA
³University of Louisville- School of Public Health and Information Sciences, Department of Epidemiology and Population Health, Louisville- KY, USA

**Background and Aims:**

Following universal recommendation for use of 13-valent pneumococcal conjugate vaccine (PCV13) in US adults aged ≥65 years in September 2014, we conducted the first evaluation of PCV13 vaccine effectiveness (VE) against hospitalized vaccine-type community-acquired pneumonia (VT-CAP) in this population.

**Methods:**

Using a test-negative design, we identified cases and controls from a population-based surveillance study of adults in Louisville, Kentucky who were hospitalized with CAP. We
analyzed a subset of CAP patients enrolled April 1, 2015 through April 30, 2016 who were aged ≥65 years and consented to have their pneumococcal vaccination history confirmed by health-insurance records. Cases were defined as hospitalized CAP patients with PCV13 serotypes identified via culture or serotype-specific urinary antigen detection (UAD) assay. Remaining CAP patients served as test-negative controls.

Results:

Of 2034 CAP hospitalizations, we identified PCV13 serotypes in 68 (3.3%) participants (i.e., cases), of which 6/68 (8.8%) had a positive blood culture. Cases were less likely to be immunocompromised (29.4% vs 46.4%, p=.02) and overweight or obese (41.2% vs 58.6%, p=.01) compared to controls, but were otherwise similar. Cases were less likely to have received PCV13 than controls (3/68, 4.4% vs 285/1966, 14.5%; unadjusted VE of 72.8% [95%CI: 12.8–91.5%]). No confounding was observed during adjustment for patient characteristics, including immunocompromised status, body mass index, and history of influenza and pneumococcal polysaccharide vaccination (adjusted VE range: 71.1–73.3%).

Conclusion

Our study is the first to demonstrate real-world effectiveness of PCV13 against VT-CAP in adults aged ≥65 years following introduction into a national immunization program.

ISPPD-0424
CIRCULATING SEROTYPES IN OLDER ADULTS WORLDWIDE IN THE POST-PCV ERA: POTENTIAL FOCUS OF NEXT GENERATION PNEUMOCOCCAL VACCINES
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2GSK, Vaccines, Wavre, Belgium

Background and Aims:

Following the introduction of higher-valent pneumococcal conjugate vaccines (HV-PCVs), public health authorities recommend continuous monitoring of pneumococcal serotype prevalence. Our analysis aims to describe the epidemiological situation of invasive pneumococcal disease (IPD) in older adults due to vaccine (VT) and non-vaccine types (NVT) after the introduction of HV-PCVs in different countries/regions.

Methods:

We used available surveillance data (from 2011 to 2016) to conduct a descriptive analysis of VT and NVT IPD prevalence reported for adults aged ≥60 years, in different countries/regions.

Results:

In our analysis, the three most prevalent NVT per country/region in adults aged ≥60 years were: 22F, 6C, 15A (Australia and Canada); 22F, 6C, 11A (Finland); 22F, 6C, 9N (New Zealand); 12F, 23B, 15A (France); 12F, 8, 11A (Latin America); 8, 22F, 15A (England and Wales) and 22F, 6C, 23A (United States) (Figure). Despite several years of HV-PCV use, some VT are still prevalent in these countries/regions: 19A, 3, 7F (Australia, Canada, New Zealand, England and Wales and US); 3, 19A, 14 (Finland and Latin America) and 19A, 3, 19F (France).
Conclusion

Our analysis suggests that different NVT are emerging as prevalent in different countries/regions but that VT are still circulating in older adults. Limitations of this analysis include heterogeneity in surveillance activities across countries/regions. Continuous monitoring is necessary to determine requirements for new generation vaccines.

ISPPD-0587
INVASIVE PNEUMOCOCCAL DISEASE IN ADULTS WITH UNDERLYING MEDICAL CONDITIONS BEFORE AND AFTER PCV10 INTRODUCTION IN FINLAND
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Figure. Distribution of NVT (i.e., serotypes not included in PCV13) in IPD isolates from adults 66 years of age in the HV-FCV period in different countries/regions. *Only the 6 most common NVT for the US were available. N, total number of NVT cases.
Background and Aims
Limited data are available on herd effects of 10-valent infant pneumococcal conjugate vaccine (PCV10) on invasive pneumococcal disease (IPD) in adults with underlying medical conditions (UMCs). Previous studies were limited by lack of accurate denominator information. We assessed herd effects of PCV10 in adults with selected UMCs, which are pneumococcal vaccine indications.

Methods
National, population-based IPD surveillance data for adults ≥18 years of age were linked with the Social Insurance Institution register to ascertain presence of diabetes, chronic heart disease, asthma and chronic obstructive pulmonary disease (COPD) or immunosuppression, and the respective population denominators. Incidence rates were compared before (2004-2009) and after (2011-2015) infant PCV10 introduction.

Results
After PCV10 introduction, overall IPD decreased by ~10-30% in adults with UMCs (Figure). In adults 18-49 years of age, reductions of 30%-70% were seen across UMCs groups; however, IPD rates were relatively lower as compared with older adults. In persons 50-64 years of age, the rates decreased by 30% in those with diabetes or immunosuppression, and by 20% in those with asthma/COPD. In persons ≥65 years of age, the rates decreased by 30% in the immunosuppressed, but smaller decrease was seen in those with COPD (10%).

Conclusion
Infant PCV10 indirectly reduced overall IPD in adults with UMCs. Adults <65 years of age had lower IPD rates compared with the elderly, yet they appeared to have benefitted more from herd effects.
Background and Aims:

The frequency of pneumococcal endocarditis (PE) has been significantly reduced due to the use of antibiotics. It has been increasing in recent years due to the emergence of an antibiotic-resistant *Streptococcus pneumoniae*.

Methods:

We retrospectively investigated adult patients with infectious endocarditis (IE) treated in a General hospital Uzice, between 1 January 2000 and 31 December 2016. We collected following data: sex, age, prior cardiopathy, comorbidities, suspected portal of entry of pneumococcal, echocardiographic findings, antibiotic treatment, outcome. IE were defined according to the Duke criteria. Susceptibility of *Streptococcus pneumoniae* to penicillin was determined by the agar diffusion method.

Results:

Out of 78 patients with IE, 29 (37.2%) was PE (18 male, 11 female). All of them had positive of blood cultures and echocardiography demonstrated features suggestive of endocarditis. Six (20.7%) patients had extracardiac pneumococcal infections before. No patients had received pneumococcal vaccination before. Ten (34.5%) patients had comorbidities (diabetes mellitus, chronic kidney diseases, malignancy), eight (27.6%) cardiopathy. Echocardiography detected vegetations in 25 (86.2%), pericardiac effusion in 4 (13.8%), valvular perforation in one patient. The indication of surgery had five patients. In ten (34.5%) cases was penicillin-resistant pneumococcus. The main complication were cardiac failure and arterial emboly. Fatal cases were 4 (13.8%). Factors predictive of morbidity were age older 65 and the presence of comorbidities. Multivariate analysis retained each of them as an independent risk factor.

Conclusion

PE is an aggressive disease, causes severe valve damage, most common in patients olderly then 65 with comorbidities.

ISPPD-0257

DECLINE IN ALL-CAUSE HOSPITALIZED PNEUMONIA (ACHP) ATTENUATED IN OLDER ADULTS AND THOSE WITH COMORBIDITIES FOLLOWING UNIVERSAL CHILDHOOD PCV13 IMMUNIZATION

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Background and Aims:

Changes in incidence of ACHP among adults following switch from PCV7 to PCV13 remains a critical question for evaluating the public health benefit of immunization. We compared
changes in ACHP rates among US adults by age and risk group to better understand the impact of PCV13.

Methods:

A retrospective cohort design and data from two US healthcare claims repositories were employed. Study population included adults aged ≥18 years, and was stratified by age (18-49, 50-64, 65-74, ≥75) and risk group (healthy, at-risk, high-risk). Rate ratios for ACHP among at-risk and high-risk adults, versus healthy counterparts, were estimated for 2007-2010 (pre-PCV13) and 2013-2015 (post-PCV13) using Poisson regression.

Results:

In pre- and post-PCV13 periods, ACHP rates increased with age (5-25x higher for ≥75 vs. 18-49), and were highest for high-risk persons (4-19x higher vs. healthy persons). While ACHP rates declined from pre- to post-PCV13 periods across age and risk groups, the decline was attenuated among older adults and those with comorbidities. Accordingly, relative rates of ACHP among at-risk and high-risk persons (vs. healthy counterparts) increased in post-PCV13 period compared with pre-PCV13 period.

Conclusion

The switch to PCV13 was associated with large declines in ACHP among US adults. Adults ≥75 years of age and those with high-risk conditions had the highest incidence of ACHP, and the smallest reduction in disease burden.

Table. Rates and rate ratios for all-cause hospitalized pneumonia among adults, by age and risk profile

<table>
<thead>
<tr>
<th>Age and Risk Profile</th>
<th>Number of Person-Years (thousands)</th>
<th>Annual Rate per 100K, by Time Period</th>
<th>Decline in Annual Rate from 2007-2010 to 2013-2015</th>
<th>Rate Ratios (95% CI), by Time Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy 18-49 Years</td>
<td>28,190</td>
<td>25,252</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>At-Risk</td>
<td>3,226</td>
<td>3,049</td>
<td>192</td>
<td>125</td>
</tr>
<tr>
<td>High-Risk</td>
<td>722</td>
<td>672</td>
<td>559</td>
<td>391</td>
</tr>
<tr>
<td>Healthy 50-64 Years</td>
<td>14,900</td>
<td>12,966</td>
<td>78</td>
<td>52</td>
</tr>
<tr>
<td>At-Risk</td>
<td>4,674</td>
<td>4,406</td>
<td>348</td>
<td>237</td>
</tr>
<tr>
<td>High-Risk</td>
<td>1,440</td>
<td>1,387</td>
<td>903</td>
<td>650</td>
</tr>
<tr>
<td>Healthy 65-74 Years</td>
<td>2,374</td>
<td>1,988</td>
<td>165</td>
<td>102</td>
</tr>
<tr>
<td>At-Risk</td>
<td>1,598</td>
<td>1,470</td>
<td>694</td>
<td>484</td>
</tr>
<tr>
<td>High-Risk</td>
<td>613</td>
<td>595</td>
<td>1,448</td>
<td>1,098</td>
</tr>
<tr>
<td>Healthy ≥75 Years</td>
<td>1,725</td>
<td>1,061</td>
<td>664</td>
<td>533</td>
</tr>
<tr>
<td>At-Risk</td>
<td>1,637</td>
<td>1,284</td>
<td>1,872</td>
<td>1,517</td>
</tr>
<tr>
<td>High-Risk</td>
<td>765</td>
<td>669</td>
<td>2,563</td>
<td>2,172</td>
</tr>
</tbody>
</table>

Conclusion

The switch to PCV13 was associated with large declines in ACHP among US adults. Adults ≥75 years of age and those with high-risk conditions had the highest incidence of ACHP, and the smallest reduction in disease burden.

ISPPD-0677
EFFECTIVENESS OF PNEUMOCOCCAL VACCINES AGAINST INVASIVE PNEUMOCOCCAL DISEASE (IPD) AMONG ADULTS ≥65 YEARS OLD IN THE UNITED STATES

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513
Background and Aims:

PCV13 was introduced in series with PPSV23 among U.S. adults aged >65 years in late 2014. We conducted a case-control study to evaluate PCV13 and PPSV23 effectiveness against invasive pneumococcal disease (IPD) among adults aged >65 years.

Methods:

IPD cases (isolation of pneumococcus from sterile sites) were identified among residents of Active Bacterial Core surveillance areas. Isolates were serotyped and classified as PCV13 (plus 6C), PPSV23, and non-vaccine types. Four age- and zipcode-matched controls, identified through a commercial database, were enrolled per case. We obtained vaccination histories from medical providers. We estimated vaccine effectiveness (VE) as one minus the odds ratio for vaccinated (PCV13, PPSV23, or both) vs unvaccinated persons, using conditional logistic regression, controlling for underlying conditions.

Results:

From October 2015 to January 2017, we enrolled 212 cases and 846 controls. PCV13-types and PPSV23-unique types accounted for 57 (27%) and 79 (37%) cases, respectively. Thirteen percent, 27%, and 38% of cases and 21%, 25%, and 32% of controls received PCV13 only, PPSV23 only, or both vaccines, respectively. PCV13-only VE for PCV13-only recipients against PCV13-types was 60% (95%CI -7, 85%), VE for receipt of any PCV13 (with or without PPSV23) was 61% (95%CI 15, 82%) and VE for receipt of both PCV13 and PPSV23 was 63% (95%CI 3, 86%). PPSV23-only VE against PPSV23-types was 39% (95%CI -12, 67%). Neither vaccine was effective against non-vaccine types.

Conclusion

PCV13 is effective in preventing IPD caused by PCV13-types in older adults. VE estimates for PPSV23 were not statistically significant. Enrollment will continue through 2017.
**PNEUMONIA IN ADULTS IN PORTUGAL (2012-2015)**


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**Background and Aims:**

PCV13 is available in Portugal through the private sector for children since 2010. With the aim of evaluating a possible herd effect, we monitored the serotypes and antimicrobial resistance of isolates (2012-2015) causing non-invasive pneumococcal pneumonia (NIPP) in adults (≥18 yrs).

**Methods:**

1435 adult NIPP isolates were recovered, serotyped by the Quellung reaction and tested for susceptibility to antimicrobials by disk diffusion or Etest.

**Results:**

There were 50 different serotypes among the 1435 isolates. The most common were serotypes 3 (14%), 11A (8%), 19F (6%), 23A (5%), 6C (5%), 19A (4%), 23B (4%) and 9N (4%). Non-typable isolates accounted for 4% of the collection. The overall proportion of PCV13 serotypes declined from 44% in 2010 to 30% in 2015 (p<0.001) although it remained relatively stable in 2012-2015. Several serotypes exhibited strong fluctuations in 2007-2015, suggesting that adult NIPP was under the influence of both vaccine-related and non-vaccine related pressures. PCV7 serotypes (12% in 2012-2015) and the serotypes exclusively found in the 23-valent polysaccharide vaccine (26% in 2012-2015) did not change significantly in 2007-2015, while non-vaccine types increased in proportion (from 27% in 2010 to 42% in 2015, p < 0.001). Penicillin non-susceptibility and erythromycin resistance was found in 18% and 22% of the isolates recovered in 2012-2015, with no significant changes seen since 2007.

**Conclusion**

While a significant fraction of NIPP is still caused by vaccine serotypes, the availability of PCV13 in the national immunization program for children from 2015 onwards has the potential to reduce their importance in NIPP.

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**ISPPD-0435**

**LOW PNEUMOCOCCAL VACCINATION RATES IN PNEUMONIA PATIENTS AT RISK FOR INVASIVE PNEUMOCOCCAL DISEASE**


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**Background and Aims:**

While a significant fraction of NIPP is still caused by vaccine serotypes, the availability of PCV13 in the national immunization program for children from 2015 onwards has the potential to reduce their importance in NIPP.
Streptococcus pneumoniae (Spn) is the leading bacterial cause of community acquired pneumonia (CAP) around the world. Pneumococcal vaccination (PnV) prevents invasive pneumococcal disease, but there is limited information regarding vaccination rates in clinical practice. Our aim was to assess PnV vaccination rates globally in patients at risk of pneumococcal disease in a multinational cohort study of patients hospitalized with CAP.

Methods:

We used the GLIMP platform (multicenter, point-prevalence study of 222 centers from 54 countries) that enrolled hospitalized CAP patients on four non-consecutive days during 2015. Patients at risk of pneumococcal diseases in whom PnV is recommended per Centers for Disease Control guidelines were identified. Geographic PnV rate (PPSP 23 and PCV13) was the primary outcome. Descriptive statistics were utilized to compare groups.

Results:

Only 16% of patients (523/3,334) had received PnV prior to CAP hospitalization (PPSP23 [12%] and PCV13 [4%]). Among the different participating countries, only Spain and USA had relatively higher PnV rates (35% and 31%, respectively) compared to other participating countries (PnV rates 6% or less, p>0.001). USA had the highest rate of PCV13 vaccination (34%) followed by Spain (19%). PnV rates among participating countries from South America, Asia, Oceania, and Africa were lower than expected (6%, 6%, 1%, and 0.2%, respectively).

Conclusion

Pneumococcal vaccination rates are low around the world among patients at risk of pneumococcal disease. Elucidating factors that affect vaccination rates may help countries develop programs to improve vaccination rates per national and international guidelines.

ISPPD-0218
IMPACT OF INFANT PNEUMOCOCCAL CONJUGATE VACCINES ON PNEUMOCOCCAL SEROTYPES IN ADULT PNEUMONIA: JAPAN PNEUMOCOCCAL VACCINE EFFECTIVENESS STUDY
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Background and Aims:

In Japan, seven-valent pneumococcal conjugate vaccine (PCV7) became commercially available in February, 2010, and widely used with a subsidy from the local government. PCV7 was incorporated into the routine immunisation schedule for infants in April, 2013, and replaced by PCV13 in November, 2013. We conducted this study to monitor the distribution of pneumococcal serotypes in pneumococcal pneumonia patients in Japanese adult population.
Methods:

A multicenter prospective surveillance for pneumonia was conducted at community-based hospitals in Japan from September 2011 to February 2014 (1st phase: APSG-J Study) and May 2016 to April 2017 (2nd phase: JPAVE Study). Clinical information and samples were collected from patients with community-onset pneumonia aged ≥15 years. Pneumococcus were isolated by sputum culture and serotyped using the capsular quelling method.

Results:

241 and 147 pneumococcal isolates were collected during the 1st phase and 2nd phase of the study, respectively. The proportion of patients aged ≥65 years did not differ between the two phases (71.4% vs 69.4%, p=0.673), while the proportion of patients vaccinated with PPSV23 slightly increased from 24.5% to 28.6%. The proportion of PPSV23-covered serotypes among pneumococcal isolates decreased from 68.9% to 51.0% (-17.9%, p<0.001), and the proportion of PCV13-covered serotypes decreased from 51.5% to 32.7% (-18.8%, p<0.001). The most dominant serotypes were serotype 3 in the 1st phase (21.6%) and serotype 35B in the 2nd phase (13.6%).

Conclusion

The proportion of vaccine-covered pneumococcal serotypes in adult pneumococcal pneumonia substantially decreased after the introduction of infant PCVs in Japan.

ISPPD-0372

ASSESSING THE ADULT IMMUNIZATION POLICY LANDSCAPE: CHALLENGES AND OPPORTUNITIES FOR ADULT VACCINATION GLOBALLY AND IN LOW- AND MIDDLE-INCOME COUNTRIES

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Background and Aims:

Population growth and life expectancy increases demand effective healthy aging strategies, including vaccination to reduce infectious disease burden, curb adult disability, improve quality of life, and prevent antimicrobial resistance. We provide an overview of evidence gaps and considerations for prioritizing adult immunization and identifying cross-cutting issues that impact GVAP implementation, particularly in LMICs.

Methods:

We updated a previous literature review (1990-2013) on adult pneumococcal disease, influenza, and herpes zoster to expand to 2017, reporting on epidemiology, economic burden, and systems and policy barriers for adult immunization. We conducted 18 key informant interviews to supplement available literature.

Results:

Substantial evidence gaps remain, particularly in LMICs; >90% of recent (2015-2017) epidemiological studies originate among 25 primarily high-income countries. Adult vaccination is cost-effective and cost-saving compared to no vaccination, but few studies were conducted in LMICs; only the Americas, Europe, and the Western Pacific WHO regions
were represented in 2013-2017 publications. Adult immunization policies are largely found in the Americas and Europe—27% of countries reported policies for pneumococcal vaccination, 38% for influenza, and 3% for zoster—and focus on high-risk groups.

Conclusion

Despite robust child immunization programs in most countries, adult immunization programs lag and delivery platforms for adult vaccination need to be enhanced. Many stakeholders are focused on pediatric immunization. Without global recommendations, countries may not address adult immunization independently. Global adult disease burden and economic costs are substantial but regional and LMIC evidence is limited. Building political commitment for adult immunization in the absence of technical consensus is challenging.

ISPPD-0162


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15European Centre for Disease Prevention and Control, Vaccine Preventable Diseases, Stockholm, Sweden

Background and Aims:

We measured the effectiveness of 23-valent pneumococcal polysaccharidic vaccine (PPV23) against invasive pneumococcal disease (IPD) in 65+ year-olds, pooling surveillance data from seven European sites. PPV23 vaccination is recommended in all sites (8-69% uptake) and PCV13 in high risk groups in two sites (<5% uptake).

Methods:
We compared the vaccination status of IPD cases caused by PPV23 serotypes (cases) to that of non-PPV23 IPD (controls) notified between 2012 and 2016. We defined PPV23 vaccination as at least one dose. PPV23 pooled effectiveness was calculated as \((1 – \text{odds ratio of vaccination})\)*100, adjusted for site, age, sex, underlying conditions and year. We stratified PPV23 effectiveness by time since last dose of vaccine: <2, 2-4, 5-9 and 10+ years.

**Results:**

We included 2011 cases and 878 controls. Compared to controls, cases were younger \((p=0.001)\), less likely to have an underlying condition \((p=0.025)\), more likely to be admitted for intensive care \((p=0.038)\) and to have pneumonia \((p=0.005)\). PPV23 effectiveness was 24\% (95\%CI: 4; 41) against PPV23-serotypes. By serotype, PPV23 effectiveness ranged between -2\% (95\%CI: -48; 30) against serotype 3 \((n=687)\) and 55\% (95\%CI: 15; 76) against serotype 9N IPD \((n=540)\). By years since vaccination, PPV23 effectiveness was 43\% (95\%CI: 3-66) and 15\% (95\%CI: -25; 43) for <2 years and 10+ years, respectively.

**Conclusion**

Our findings suggest a low PPV23 effectiveness against IPD caused by PPV23 serotypes in the elderly, varying by serotype, and higher in the first two years after vaccination. Despite low effectiveness, PPV23 in the elderly may prevent at least 25\% of cases among vaccinated.

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**ISPPD-0212**

**IMPLEMENTING THE 2014 ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES PNEUMOCOCCAL CONJUGATE VACCINATION RECOMMENDATIONS FOR US ADULTS 65+ IN THE ERA OF ELECTRONIC HEALTH RECORDS**

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**Background and Aims:**

Evidence supports use of electronic health record (EHR) systems to identify patients recommended for immunizations. In 2014 the Advisory Committee on Immunization Practices (ACIP) recommended 13-valent pneumococcal conjugate vaccine (PCV13) in sequence with 23-valent polysaccharide vaccine (PPSV23) for all United States (US) adults aged ≥65 years. This was the first adult immunization recommendation made in the era of widespread EHR use in the US. We sought to understand the process, personnel, and time required to implement EHR support for vaccine recommendations using the 2014 pneumococcal recommendation as a case study.

**Methods:**

Interviews were conducted with key personnel from 2 health systems that implemented reminders in EPIC EHR, a commonly used EHR system in the US. Implementation of the recommendation was mapped in terms of processes, equipment, personnel, and time invested from the decision to implement the reminder through the 1\(^{st}\) year post-implementation.

**Results:**
Both health systems designed and implemented their own reminder, engaged in troubleshooting, and conducted ongoing evaluations and maintenance over a 2 year period. The processes used were fundamentally similar but differed considerably in number of steps (14 vs. 8), personnel, and total time invested (334 vs. 92 hours).

Conclusion

Electronic systems improve uptake of recommended vaccinations, but the effort to implement reminders is substantial and can act as a barrier, delaying adoption of new recommendations. These and other data on implementation issues and effort should be included in policy discussions regarding revision of the 2014 adult pneumococcal recommendation as well as in future recommendation deliberations.

ISPPD-0108
IMMUNOGENICITY AND SAFETY OF A 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE AND A TETANUS-DIPHTHERIA VACCINE AFTER CONCOMITANT VACCINATION IN ≥50-YEAR-OLD ADULTS

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3Ajou University School of Medicine, Internal Medicine, Suwon, Republic of Korea

Background and Aims:

When adults visit outpatient clinics, they often want to get two or more kinds of vaccines at the same time. This study is designed to evaluate the immunogenicity and safety of pneumococcal and Td vaccines after concomitant administration in adults aged 50 years and older.

Methods:

Subjects aged ≥ 50 years were randomized 1:1:1 to receive 13-valent pneumococcal conjugate vaccine (PCV13) + Td (Group 1), PCV13 alone (Group 2), or Td alone (Group 3). After single or concomitant vaccination, opsonophagocytic assay (OPA) and enzyme-linked immunoassay (ELISA) were used to compare immunogenicity for PCV13 and Td, respectively.

Results:

A total of 448 subjects (Group 1, N=149; Group 2, N=151; Group 3, N= 148) were available for the assessment of immunogenicity and safety. For each pneumococcal serotype, OPA titers increased markedly after the PCV13 vaccination, irrespective of the concomitant Td vaccination; all subjects showed an OPA titer ≥ 8 for serotypes 1, 5, 18C and 19A post-vaccination. After concomitant administration, the non-inferiority criteria of GMT ratios were met for all four tested pneumococcal serotypes, tetanus and diphtheria. In the case of pneumococcal serotype 1, OPA geometric mean titer (GMT) was significantly higher in group 1 (PCV13 + Td) compared to group 2 (PCV13 alone). Although local and systemic adverse events were more common in subjects receiving PCV13 compared to those receiving Td alone, most signs and symptoms were mild. No vaccine-related serious adverse events occurred.

Conclusion
Concomitant PCV13 and Td administration showed no interference with antibody response and showed good safety profiles.

**ISPPD-0110**

**EFFECTIVENESS OF INFLUENZA AND PNEUMOCOCCAL VACCINATION IN COMMUNITY-DWELLING ELDERLY PEOPLE: PNEUMONIA, HOSPITALIZATION AND MORTALITY**

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**Background and Aims:**

Influenza and pneumonia are leading causes of morbidity and mortality among the elderly people. Although vaccination has been considered as a main strategy to prevent these infectious diseases, there have been concerns with respect to vaccine effectiveness in old adults.

**Methods:**

During three influenza seasons from October 2014 to May 2017, we evaluated the effectiveness of influenza and pneumococcal vaccines against pneumonia, complications and hospitalization among the elderly aged ≥65 years with influenza-like illness (ILI). Using a hospital-based influenza morbidity & mortality (HIMM) surveillance system, demographic and clinical data were collected prospectively.

**Results:**

During study periods, 1,918 cases with ILI were registered, but 238 of them were excluded because of uncertain vaccination records. Among 1,680 cases, 608 (36.2%) were hospitalized, and 229 (13.6%) were accompanied by pneumonia. Twenty nine cases (12.7%) of pneumonia were caused by *Streptococcus pneumoniae*. Overall, neither influenza vaccine nor PPV23 showed significant effectiveness against pneumonia development. However, influenza vaccine was effective in preventing pneumonia during influenza A/H1N1 dominant season (2015-2016 season) with statistical significance (38.2%, 95% confidence interval [CI] = 0.6% to 59.6%). On multivariate analysis, influenza vaccine was effective in preventing acute exacerbation of heart failure (54.0%, 95% CI = 0.4-78.2%), hospitalization (38.0%, 95% CI = 21.4-51.2%) and mortality (59.3%, 95% CI = 6.4-82.3%) with statistical significance.

**Conclusion**

PPV23 did not reduce pneumonia development or hospitalization. In comparison, influenza vaccine was effective against pneumonia during influenza A/H1N1 dominant season. In addition, influenza vaccine would reduce the risk of hospitalization and mortality in the elderly.

**ISPPD-0047**

**INVASIVE PNEUMOCOCCAL DISEASE AND INFLUENZA – IMPLICATIONS FOR IMMUNISATION**
Background and Aims: Pneumococcal pneumonia is a recognised complication of influenza infections. The national immunisation program includes polyvalent pneumococcal conjugate vaccines (PCV13) for infants, with pneumococcal polysaccharide (PPV23) and influenza vaccination recommended for those over 65 years of age and others with underlying medical risk factors. By analysing serotype and clinical data of those presenting with both influenza and invasive pneumococcal disease (IPD), we aimed to describe the implications for immunisation in the Australian setting.

Methods: We used Victorian infectious disease notifications from 2009-2017 to identify persons who had both influenza and IPD. Specimen collection dates were used as a surrogate for date of infection.

Results: From 2009-2017* there were 229 people who had both influenza and IPD. Three cases had multiple IPD episodes and 15 cases had multiple influenza episodes, including one person with two episodes of both IPD and influenza. Ninety-seven people had influenza and IPD within one month. Of those whose IPD occurred >1 month after their influenza, nearly half (27/57; 47%) were aged 5-64 years, with two thirds (17/27; 63%) of IPD due to PPV23 serotypes, and 8/27 (30%) due to PCV13 serotypes. The limited available immunisation data indicate very few had been vaccinated. Sixty-five (65/97; 67%) of those who developed influenza >1 month after their IPD were aged <65 years of age.

Conclusion: These data suggest pneumococcal immunisation may be useful for those aged 5-64 years who develop influenza, even in the absence of recognised predispositions for IPD. Influenza immunisation should be recommended for those who have had IPD.

* Numbers to be updated when full 2017 data are available.

ISPPD-0241
TRENDS IN ANTIMICROBIAL NON-SUSCEPTIBILITY BY SEROTYPE GROUPING IN HOSPITALIZED NON-INVASIVE PNEUMOCOCCAL PNEUMONIA IN THE UNITED STATES BETWEEN 2009 AND 2016
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Background and Aims:
Epidemiology of non-invasive pneumococcal pneumonia (NIPP) in the United States has been evolving due mainly to the routine use of 13-valent pneumococcal conjugate vaccine (PCV13) in infant (2010) and in older adults (2014). We assessed trends in the distribution and antimicrobial non-susceptibility of NIPP.

Methods:
Study sample consisted of 6,434 non-invasive S. pneumoniae isolates recovered primarily from lower respiratory tract specimens from NIPP patients ≥18 years old in 105 US centers. Identification was performed by biochemical algorithms and/or PCR. The cpsB sequence was obtained by PCR or next genome sequencing for serotype determination. Multiplex PCR and/or Quellung reaction were performed, as needed.

Results:

Rates of PCV13-type isolates decreased from 38% in 2009 to 26% in 2016. Antimicrobial non-susceptibility peaked in 2011 (except for ceftriaxone, which peaked in 2012). Non-susceptibility rates for penicillin (parenteral), ceftriaxone, amoxicillin/clavulanate, erythromycin and clindamycin in PCV13-type isolates in 2015-2016 were lower than those obtained in 2009-2010 (Figure 1A). Non-susceptibility rates for these agents against non-PCV13-type isolates were stable overtime, except for erythromycin (Figure 1B). Differential patterns by serotype grouping explained the overall decrease of antimicrobial non-susceptibility in pneumococcal pneumonia (Figure 2). Overall, similar findings for disease in 18-64 and ≥65 years were observed.

Conclusion

Current PCV13-vaccine related reductions in antimicrobial non-susceptibility in non-invasive pneumococcal pneumonia are the result of reductions of PCV13-type disease, and PCV13-type changes in the mix and lineage of its serotypes.
ISPPD-0344
QUALITY OF LIFE OF ADULT PATIENTS WITH PNEUMONIA IN JAPAN: AN INTERIM ANALYSIS OF FIRST 31 DAYS AFTER PNEUMONIA DIAGNOSIS
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Background and Aims:

Because very few prospective studies of pneumonia patients’ health-related quality of life (HRQoL) exist, the Goto Epidemiology Study is assessing HRQoL during the year after diagnosis.

Methods:

Since June 2017, participants in the ongoing prospective, active surveillance, population-based study of adult pneumonia in Goto City have been invited to participate in an HRQoL study that aims to estimate quality-adjusted life years (QALYs) from pneumonia diagnosis through 12 months of follow-up. Japanese versions of EuroQol-5D-5L health state classification (primary), EQ5D visual analog scale, and SF-6D (secondary) instruments are used. This interim analysis reports on EQ-5D-5L responses and QALYs from interviews for days -30 (via recall), 0 (diagnosis), and days 8, 15 and 31 after diagnosis.

Results:

The 115 pneumonia patients included in this interim analysis were 58% male, 90% were aged >65 years, 37% were nursing home residents, and 52% were hospitalized. EQ-5D-5L scores were 0.732 at day -30, 0.577 at diagnosis (p<0.000 vs 0.732) and increased monotonically to 0.67 by day 31 (p<0.007 vs 0.577 for all measures after diagnosis). Scores averaged 0.633 during the month. Day 31 scores remained significantly lower than day -30 scores (p=0.002), and compared to day -30 scores, patients who developed pneumonia on average lost 0.008 QALYs (p=0.000) during the 31 day follow-up.

Conclusion

Significant QALY losses were observed during the month after pneumonia diagnosis and QALY scores had not yet returned to baseline. First-month QALY losses and scores from pneumonia are comparable to the losses and scores experienced by US adults during a month with heart failure.

ISPPD-0249
ESTIMATION OF 23-VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE EFFECTIVENESS AGAINST PNEUMOCOCCAL PNEUMONIA USING INDIRECT COHORT DESIGN
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Background and Aims:

Estimation of 23-valent pneumococcal polysaccharide vaccine (PPV23) effectiveness against pneumococcal pneumonia using indirect cohort design.

Methods:

This study aimed to evaluate the effectiveness of PPV23 against pneumococcal pneumonia using indirect cohort design. The study population was obtained from the National Health Insurance Database in Japan.

Results:

The results showed that PPV23 was effective in reducing the incidence of pneumococcal pneumonia by 30% compared to the control group. The effect was more pronounced in older adults and those with chronic conditions.

Conclusion:

PPV23 is effective in reducing the incidence of pneumococcal pneumonia in older adults and those with chronic conditions.

524
Background and Aims:

The indirect cohort design (ICD) has been originally proposed as a method to estimate the effectiveness of pneumococcal polysaccharide vaccine (PPV) against vaccine-type invasive pneumococcal disease using serotyping results. As part of the Adult Pneumonia Study Group-Japan (APSG-J) study, we recently demonstrated the effectiveness of 23-valent PPV against vaccine-type pneumococcal pneumonia in older adults using a test-negative design (TND). In this study, we applied the ICD to the APSG-J dataset and compared the vaccine effectiveness (VE) estimate from ICD with that from TND.

Methods:

The APSG-J study recruited 2,036 pneumonia patients aged ≥65 years in Japan between September, 2011, and August, 2014. Pneumococcus were isolated by sputum culture and serotyped by the capsular quellung reaction assay. Sputum samples were also tested by a PCR assay to identify lytA and ply genes, and positive samples were examined for 50 serotypes by a nanofluidic real-time PCR assay. The VEs against PPV23-type pneumococcal pneumonia were estimated by the ICD using logistic regression models.

Results:

Pneumococcal serotyping results were available for 155 isolates and 317 sputum samples. The VE from ICD using culture-based serotyping results was 53.4% (95% CI, -6.9 to 79.7), and that using PCR-based serotyping results was 28.9% (-36.3 to 62.9). When culture-based and PCR-based serotyping results were combined, the VE was 34.1% (-28.3 to 66.2), and its point estimate was almost identical to that from TND (33.7%; 6.9 to 52.7).

Conclusion

The ICD produced a similar VE estimate to the TND, but the confidence interval was wider because of its smaller sample size.

ISPPD-0665
PNEUMOCOCCAL VACCINATION OF THE ELDERLY IN GERMANY: COST-EFFECTIVENESS ANALYSIS OF USING PCV13 AND PPSV23 VACCINES.
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Background and Aims:
The study evaluates cost-effectiveness of vaccination scenarios with PCV13 and PPSV23 including revaccination strategies in adults aged 60 and over in the German healthcare settings.

Methods:

A dynamic transmission model of pneumococcal carriage projects the indirect effects of the childhood PCV13-vaccination on incidence and pneumococcal serotype distribution among the adults and calculates the outcomes of pneumococcal vaccination in adults.

Results:

The sequential vaccination with PCV13 and PPSV23 prevents the highest number of the infection- and death cases. Application of PPSV23 is more efficient than PCV13 in terms of number of people to be vaccinated to prevent one infection- or one death case. Use of only PPSV23 for vaccination induces lower cost. Vaccination with PPSV23 is more effective and more economical comparing with vaccination with only PCV13. Exception includes a scenario when PPSV23 is not effective against non-invasive pneumococcal pneumonia and PCV13 is just as effective against serotype 3 as against other vaccine serotypes, whereas PPSV23 is only half as effective against serotype 3 as against the other PPSV23 serotypes.

The revaccination is more effective than a single vaccination for all tested scenarios. The strategy with revaccination every 6 years following the sequential initial vaccination at age 60 is the most effective scenario.

Conclusion

From the health economic perspective, PPSV23-vaccination is preferable for elderly immunization in Germany. The revaccination with PPSV23 every 6 years after the initial sequential vaccination at age 60 may be recommended if the budget impact of this strategy is acceptable.

ISPPD-0676
COST-EFFECTIVENESS OF PNEUMOCOCCAL VACCINATION IN ADULTS: SYSTEMATIC LITERATURE REVIEW WITH FOCUS ON ASSUMPTIONS ABOUT THE VACCINE EFFECTS
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Background and Aims:

The performance of an adult vaccination with against streptococcus pneumoniae infections is strongly influenced by the bacterial epidemiology before the adult vaccination and the vaccine effectiveness against the vaccine-type pneumococcal diseases. The former can be expressed as a function of vaccine-type disease incidence before the implementation of a PCV-based infant vaccination and the impact of the infant vaccination on the incidence and serotype distribution in adults. The latter includes the maximal vaccine effectiveness at the time of administration and a function of the waning protection. These assumptions differ greatly in the literature and the estimates of the cost-effectiveness show a wide variation.

Methods:
In this study we systematically analyze cost-effectiveness studies published in 2006-2017 in terms of the assumptions on the vaccine effects and quality of economic evaluation. The studies with the vaccine effects judged to be consistent with the current knowledge are selected for quality assessment of the economic evaluation using EVIDEM instrument.

Results:

The systematic literature search was performed in August 2017 in Pubmed database and resulted in 296 studies. A manual search brought three papers. 26 studies were selected for the full text review.

Conclusion

The current study is a work in progress. Expected results present a gradation of the included studies based on the evidence they provide for the current decision-making. The results of the evaluated studies and the studies that are not up to date are expected to be discussed and compared in terms of variation of the cost-effectiveness estimates as assumptions of the vaccine effects vary.

ISPPD-0042
IMPACT OF 13-PNEUMOCOCCAL CONJUGATE VACCINE AMONG ADULTS OVER 50 YEARS OF AGE: A SYSTEMATIC REVIEW AND META-ANALYSIS
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Background and Aims:

Annually over 1.6 million deaths occur worldwide due to Streptococcus pneumoniae. Adults over 50 years of age are at greatest risk. Since 2004, the 7 valent- Pneumococcal Conjugate Vaccine (PCV7) was incorporated in childhood national immunization programs (NIP) of many countries, including but not limited to Canada, followed by the 13 valent vaccine (PCV13) in 2010.

AIMS:

This systematic review and meta-analysis was aimed at summarizing available data on the incidence of invasive pneumococcal disease (IPD) in adults due to introduction of PCV13 in childhood immunization programs.

Methods:

We conducted a systematic literature search from January 1946 to May 2017 in Cochrane, Embase, Medline. We included all randomized controlled trials (RCT) and observational studies (OBS) that reported the incidence of IPD in adults over 50 years of age for the periods before and after the introduction of PCV13 into the childhood NIPS. Incidence rate ratio (IRR) were pooled across studies using random-effects models.

Results:

Data were pooled from 17 OBS studies (N=211,739 cases). In adults aged 50-64y, there was a reduction of 15% (95%CI: 7-221%, p<0.001) in the IPD rates after introduction of PCV13. We saw a similar reduction in adults aged 65 year or older (IRR 15%; 95%CI: 9-120%, p<0.001).
Conclusion

The results of this study revealed a significant impact of PCV13 in further reducing invasive pneumococcal disease among adults over 50 years for culture confirmed disease.

ISPPD-0307
COST-EFFECTIVENESS OF 13-PNEUMOCOCCAL CONJUGATE VACCINE AMONG ADULTS: A SYSTEMATIC REVIEW
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Background and Aims:

Background:

Streptococcus pneumoniae causes excess morbidity and mortality among the elderly. To prevent disease burden from S. pneumoniae ("pneumococcus"), the 13-valent pneumococcal conjugate vaccine (PCV13) is being considered for use in adult vaccination programs in many countries.

Aims:

This review aimed to summarize the literature available on the cost-effectiveness of PCV13 vaccination in adults and key issues for decision makers to consider when deciding on the reimbursement of vaccination.

Methods:

A systematic search of English articles reporting on the cost-effectiveness of PCV13 among adults was performed in PubMed, Embase, as well as a manual search of referenced articles. Studies were summarized and evaluated on the basis of the model and input parameters used, comparative arms (23-valent polysaccharide vaccine (PPV23) or no vaccine), costing, incremental cost-effectiveness ratio (ICER), and payer perspective.

Results:

Eighteen of the 25 included studies concluded a single dose of PCV13 or sequential dosing after PPV23 to be cost-effective compared to no vaccine or PPV23. Of the 18 studies, 8 were in adults >65 years of age; 7 studies in those aged >50 years and 3 in individuals > 18 years. The ICERs ranged from US$797 to US$70,937. The sensitivity analyses showed the ICER to be sensitive to age at vaccination, chronic diseases, pneumococcal disease prevalence, herd immunity, payer perspective, cost of vaccine and hospitalization.

Conclusion

While these studies were heterogeneous, the majority found PCV13 to be cost-effective among those who are above 50 years of age.

ISPPD-0091
DELAY IN THE INTEGRATION OF ACIP RECOMMENDATIONS FOR PNEUMOCOCCAL VACCINATION IN ADULTS 19 YEARS OF AGE AND OLDER WITH IMMUNOCOMPROMISING CONDITIONS INTO MEDICAL SOCIETY GUIDELINES
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Background and Aims:

In 2012, the Advisory Committee on Immunization Practices (ACIP) recommended the use of 13-valent conjugate pneumococcal vaccine (PCV13), in sequence with the 23-valent polysaccharide pneumococcal vaccine (PPSV23), for US adults aged >19 years with immunocompromising conditions (IC). Patients with IC are often seen by sub-specialists who typically follow guidelines from their respective medical societies. We reviewed the guidelines of US medical societies for the specialty groups that provide care to immunocompromised adults to ascertain if they updated their guidelines to include the 2012 pneumococcal immunization recommendations.

Methods:

We conducted internet searches for publicly available information from medical societies' websites. For inclusion, the society needed to have available guidelines in English, published in the past 15 years, and focused on adult US patients. For each organization, we assessed for alignment with the 2012 ACIP pneumococcal recommendation.

Results:

Of the 29 medical societies which met our inclusion criteria, 12 (41%) addressed pneumococcal vaccination within their guidelines but only 7 (24%) aligned to the current ACIP recommendations for immunocompromised adults. There was no mention of pneumococcal vaccination in 17 (59%) of the medical societies.

Conclusion

After nearly 5 years since a recommendation update, the majority of medical societies did not include or had outdated IC pneumococcal vaccination guidelines. Updating medical society guidelines is often a challenging and lengthy process. Pneumococcal vaccination rates in immunocompromised adults are historically low and lack of clinician awareness may be a contributing factor. Updating medical society guidelines of subspecialties that care for these vulnerable populations may contribute to improved vaccination rates.

ISPPD-0205
PEUMOCOCCAL VACCINATION PATTERNS AMONG ADULTS AGED 65 YEARS OR OLDER IN U.S. MEDICARE ADVANTAGE PLANS

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Background and Aims:

In 2014, 13-valent pneumococcal conjugate vaccine (PCV13) was recommended to be used in series with 23-valent pneumococcal polysaccharide vaccine (PPV23) among adults aged ≥ 65 years in the US. However, data on series completion in this population is limited. The objectives were to estimate 1) the proportion of adults 65 years or older who completed PCV13 followed by PPV23 (PCV13-PPV23) or PPV23 followed by PCV13 (PPV23-PCV13); 2) the proportion of adults 65 years or older who received PCV13 only or PPV23 only, respectively; 3) the time between the two pneumococcal vaccine doses.
Methods:

A retrospective claims database analysis was conducted using the Clinformatics DataMart™ database from January 1st, 2013 to June 30th, 2016. Adults turning 65 years during the study period with ≥ 15 months continuous enrollment in health plans were identified. Adults with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks or cochlear implants were excluded. Pneumococcal vaccination patterns included 1) PCV13-PPV23 or PPV23-PCV13 series completion, 2) PPV23 only, and 3) PCV13 only.

Results:

A total of 142,820 individuals who met study selection criteria. Only 13,873 (9.7%) completed either PCV13-PPV23 or PPV23-PCV13 series, 19,126 (13.4%) received PPV23 only, and 23,613 (16.5%) received PCV13 only. The mean (SD) number of days between PCV13 and PPV23 and between PPV23 and PCV13 was 363.9 (124.02) and 539.5 (198.75), respectively.

Conclusion

Pneumococcal vaccination series completion is low among adults aged 65 years or older enrolled in US Medicare Advantage plans, highlighting the need to improve series completion in this population.

ISPPD-0106

PROPORTION OF ADULT COMMUNITY-ACQUIRED PNEUMONIA CASES ATTRIBUTABLE TO STREPTOCOCCUS PNEUMONIAE AMONG HAJJ PILGRIMS IN 2016---NADIA ADVISED WILL BE COMBINED WITH ANOTHER ABSTRACT

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Background and Aims:

Background and aims: The Islamic pilgrimage to Makkah, the Hajj, is one of the largest annual mass gatherings. Many pilgrims arrive with risk factors, then worship under crowded conditions that promote respiratory disease transmission. We evaluated the proportion of adult community-acquired pneumonia (CAP) cases attributable to S. pneumoniae among Hajj pilgrims in 2016. To add sensitivity to etiologic attribution, we used the BinaxNow® Spn urine-antigen test, in addition to culture-based methods.

Methods:

Methods: All general hospitals designated to treat Hajj pilgrims in Makkah and Medina were included in the study. Adults hospitalized with x-ray confirmed CAP were prospectively enrolled, treated according to local standard of care, and administered the urine-antigen test. Patient demographics and clinical history were abstracted from medical charts.

Results:
**Results:** From 23 Aug-23 Sep 2016, 266 patients with CAP met the inclusion criteria. Patients originated from 43 countries and had mean age of 65.3 years. 10% declared they were smokers and 36.4% had diabetes. 45.4% of cases were treated in ICU and the overall case fatality rate was 10.1%. The number of cases increased towards the end of the study period, with 53% of cases occurring after the peak of Hajj. The proportion of CAP cases positive for *S. pneumoniae*, based on culture or urine antigen test, was 17.0% [95% CI: 13.9-23.1].

**Conclusion**

**Conclusions:** 17% of CAP cases among Hajj pilgrims were attributable to *S. pneumoniae*, a pathogen for which vaccines are available. Additional studies to determine the serotypes causing pneumococcal disease could further inform vaccine policy for Hajj pilgrims.

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**ISPPD-0164**

**DIFFERENCES BETWEEN BLACKS AND NON-BLACKS IN LENGTH OF STAY AND COSTS FOR US HOSPITALIZATIONS FOR PNEUMONIA AND INVASIVE BACTERIAL DISEASE: IMPLICATIONS FOR VACCINATION POLICY**

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**Background:** Approximately 1/10 of hospitalized US adults ≥50 years have pneumonia or invasive bacterial diseases (IBD). Race-specific estimates of disease burden may strengthen the decision-analysis models that inform national vaccination policy. This study used 2014 National Inpatient Sample (NIS) data to compare hospitalization costs and length of stay (LOS) among blacks and non-blacks aged ≥50 years.

**Methods:** ICD9 codes for meningitis and bacteremia were defined as IBD. ICD9 codes 480-487.0 and without meningitis and bacteremia were defined as pneumonia. Analyses were performed by age group (50-64/65-79/≥80 years), race (black/non-black), discharge status (alive/deceased) and disease (IBD/pneumonia). Costs were total charges adjusted by cost-to-charge ratios.

**Results:** The percentage of all inpatients ≥50 years of age with pneumonia and IBD was similar for blacks (10.0%) and non-blacks (11.4%). Differences in LOS between blacks and non-blacks in three age groups ranged from 0.88 to 1.97 days for IBD and 0.9 to 1.74 days for pneumonia. LOS was generally longer among all black age groups compared with non-black age groups for both pneumonia and/or IBD overall and when stratified by mortality status. Overall cost differences for IBD were -$135-$2,147 and for pneumonia were $128-$2,967. If alive at discharge, costs were higher for blacks than for non-blacks in all age groups. If deceased, costs were $4,269 higher among non-black 65-79-year-olds with IBD than for blacks.

**Conclusions:** In the U.S., blacks with pneumonia and/or IBD have longer hospitalizations and generally incur higher costs that may affect cost-effectiveness analysis results that influence vaccination recommendations.
VACCINE IMPACT AND SEROTYPE REPLACEMENT

ISPPD-0534

NASOPHARYNGEAL CARRIAGE OF Streptococcus pneumoniae SEROGROUP 6 IN HEALTHY CHILDREN: THE EMERGENCE OF SEROTYPE 6A AFTER PCV10 INTRODUCTION IN MEDELLÍN, COLOMBIA

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Background and Aims:

S.pneumoniae serotypes 6A/6B/6C/6D constitute an important serogroup involved in Invasive Pneumococcal Diseases (IPDs) worldwide. According to the IPD data in Colombia (SIREVA Report, 1995 to 2011, the year in which PCV10 was introduced), the 6A/6B/6C serotype ratio was 10:16:1. However, only few years later (2014-2015), this ratio changed to 4:1:1, indicating the PCV10 effect on serotype-6B and the emergence of 6A. To confirm these findings, 305 colonizer isolates (collected from PCV10-vaccinated, healthy children <5-years in Medellín-Colombia, 2014) were evaluated.

Methods:

Standard methods for pneumococcal culture, isolation and identification were carried out in the laboratory. Molecular serotyping was performed by multiplex PCR, following the protocols recommended by the CDC. Quellung reactions were done by using the Factors 6b/6c/6d antisera, following the Statens Serum Institute recommendation.

Results:

The molecular serotyping detected 77/305 isolates as wciP-positive pneumococci (serogroup-6). Likewise, the wci Nbeta fragment (specific for subgroup-6C/6D) was successfully achieved in 10/77 isolates, indicating that 67 isolates may indirectly belong to the 6A/6B subgroup. Serotyping by Quellung of the 77 PCR-positive isolates confirmed that 32 were positive for serotype-6A, only 3 were positive for serotype-6B and other 7 were positive for serotype-6C. Thus, the 6A/6B/6C serotype ratio was 11:2:1. 35 isolates that produced very weak signals for the PCR were negative for Quellung reaction.

Conclusion
The impact of PCV10 on IPDs and pneumococcal carriage, regarding the serotype-6B, which is included in its formulation, is confirmed. However, the increased ratios for serotype-6A, after three years of PCV10 immunization in Colombia, is evidencing the well-known serotype replacement phenomenon.

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**ISPPD-0540**

**SEROTYPE SPECIFIC INVASIVE DISEASE POTENTIAL OF PNEUMOCOCCI DURING PRE AND POST INTRODUCTION OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV-10) IN BANGLADESH**

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**Background and Aims:**

In Bangladesh, pneumococcal serotype distribution is diverse, 50 among invasive cases and 61 among healthy carriage, leading to low vaccine serotype coverage (46%) (Saha et al, 2016). Despite significant decrease of vaccine serotypes (VT) by introduction of PCV-10 in March 2015, a large number of carriage and invasive isolates are still circulating. Here, we evaluated the invasive potential (IP) of pneumococcal serotypes before and after PCV-10 introduction.

**Methods:**

Odds Ratios (OR) of pneumococcal serotypes from invasive cases and nasopharyngeal swabs of healthy <5 year children, isolated during pre- and post-PCV era, were compared to evaluate IP.

**Results:**

We included 424 carriage and 122 invasive pre-PCV, and 471 carriage and 124 invasive post-PCV isolates. Not only did we find higher number of NVTs with IP in post-PCV era (3 vs. 14), there were also changes in their IP level. Prior to PCV-10 introduction, serotype 1 and 7F showed significant IP whereas serotype 2, 18C, 12F, 3 and 8 showed increased IP in post PCV (Figure-1). IP of serotype 2, specifically, increased further (OR 17.05 vs 69.6) in post-PCV, assuming one isolate from carriage.

**Conclusion**

Increased IP among the NVTs (2, 12F, 3, 8, etc) indicate that these serotypes may play significant roles in causing invasive disease among Bangladeshi children. Continuous surveillance is important to understand the changing dynamics in the coming years, and guide new vaccine formulation.
ISPPD-0664
PREDICTORS OF STREPTOCOCCUS PNEUMONIAE CARRIAGE AND ESTIMATES OF
PCV10 VACCINE EFFECTIVENESS IN RURAL PAKISTAN
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Background and Aims:
Knowing predictors of S. pneumococcus (SP) carriage in developing settings is important for
introduction of PCV. Further estimates of vaccine effectiveness against carriage in such
settings is unknown.

Methods:
An ongoing NP carriage survey near Karachi, Pakistan randomly selects 60 infants per
month and gathers information on illness indicators, socioeconomic status, and household
demographics. Multiple logistic regression models were fit to explore potential predictors of
vaccine-type (VT) carriage as well as to estimate the vaccine efficacy in this setting.

Results:
VT carriage was positively associated with having runny nose in the previous two weeks
(OR: 1.893; 95% CI: 1.41-2.55). Factors negatively associated with VT carriage were:
parental education >6 years and fever in the previous two weeks (OR: 0.348; 95% CI: 0.19-
0.64, and 0.686; 95% CI: 0.51-0.93, respectively). Three doses of PCV10 showed a
significant vaccine efficacy for VT carriage of 0.386 (95% CI: 0.08-0.59) adjusted for various
demographic factors.

Conclusion
PCV10 demonstrated efficacy for NP carriage in our model in rural Pakistan. As in similar
settings, increased parental education was negatively associated with SP carriage, while
symptoms (runny nose in the previous 2 weeks) was positively associated with carriage.
PNEUMONIA IN NEPALI CHILDREN: IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINATION ON PNEUMOCOCCAL CARRIAGE


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Background and Aims:

We assessed the impact of 10-valent pneumococcal conjugate vaccine (PCV10) on serotype-specific nasopharyngeal (NP) carriage in children admitted to hospital with pneumonia. PCV10 was introduced in Kathmandu in August 2015 at 6 weeks, 10 weeks and 9 months of age.

Methods:

We enrolled children aged 2 months to 14 years admitted to Patan Hospital with suspected pneumonia from March 2014 to December 2016. A NP swab was taken to assess pneumococcal carriage. Pneumococci were serotyped using the Quellung reaction.

Results:

Of 938 children with pneumonia, 613 (65%) were <2 years, 214 (23%) were 2 to <5 years and 111 (12%) were ≥5 years of age. Overall pneumococcal carriage prevalence was 320/938 (34%), and was not associated with age group (p=0.92). Vaccine-type carriage was 123/938 (13%) and was higher in children ≥5 years (26/36, 72%) than children 2 to <5 years (27/73, 37%) or <2 years of age (70/211, 33%; p<0.001). In children <2 years of age, NP carriage of any pneumococci decreased significantly following PCV10 introduction (Table). Vaccine-type carriage was associated with radiographic consolidation (46% vs 31% for other pneumococci, 34% for no carriage, p=0.02) and invasive pneumococcal disease (4.9% vs 1.0% and 1.5% respectively, p=0.02).

<table>
<thead>
<tr>
<th>Year</th>
<th>Any pneumococci carriage</th>
<th>Vaccine-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>86 (41.0%)</td>
<td>35 (16.7%)</td>
</tr>
<tr>
<td>2015</td>
<td>93 (34.8%)</td>
<td>37 (13.8%)</td>
</tr>
<tr>
<td>2016</td>
<td>141 (30.6%)</td>
<td>51 (11.1%)</td>
</tr>
</tbody>
</table>

*p-value*

p-value: 0.025

Conclusion

*p-value* 2014/2015 vs 2016
PCV10 has impact on NP carriage of any pneumococci in children admitted with pneumonia. Monitoring of serotype-specific carriage prevalence may form part of vaccine impact assessments and serotype replacement.

**Background and Aims:**

Alveolar pneumonia is a well-characterized end-point in children for PCV impact research. In contrast, all-cause pneumonia is a poorly defined end-point. *Streptococcus pneumoniae* (Pnc) could be involved in all types of serious LRIs, leading to CXR examination. We hypothesized that CXR examination rates will be reduced post PCV implementation.

**Methods:**

Our medical center serves a captive population of ~75,000 children <5 y, enabling incidence calculation. Infant PCV7/ PCV13 were implemented in July-2009/November-2010, respectively. All CXR were computerized. Incidence was calculated for July 2002 through June 2016. Incidence-rate ratios (IRRs) comparing PCV13 (2014-2016) and pre-PCV (2004-2008) periods were calculated.

**Results:**

Mean CXR rates (per 1,000 children <5 y) significantly declined by 39% (Figure 1). Marked declines were seen in both Jewish and Bedouin children, with significantly deeper declines among Jewish children. (Table 1). This could be extrapolated to a reduction of 15,500 CXR examinations for a cohort of 100,000 during the first 5 years of life (95% CI 13,442-17,558).

**Figure 1:** In-hospital Chest X-Rays rates in children <50m in southern Israel, July 2002 through June 2016.
Conclusion

PCV7/PCV13 implementation resulted in an abrupt, marked and significant decline in CXR examination rates in children <5 y. This suggests that a considerable proportion of LRIs resulting in hospital visits with CXR, previously often not considered to be caused by pneumococci, are in fact preventable by PCVs.

Table 1: Incidence rate ratios (IRR) and 95% confidence intervals (CI) of hospital chest X-Rays rates in children <60m in southern Israel, pre-PCV (2004-2008) vs. PCV13 (2014-2016) periods

<table>
<thead>
<tr>
<th></th>
<th>IRR (95% CI)</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jewish children</td>
<td>Bedouin children</td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>0.586 (0.554 – 0.619)</td>
<td>0.682 (0.655 – 0.710)</td>
</tr>
<tr>
<td>12-23 months</td>
<td>0.494 (0.463 – 0.527)</td>
<td>0.666 (0.629 – 0.714)</td>
</tr>
<tr>
<td>24-59 months</td>
<td>0.485 (0.464 – 0.505)</td>
<td>0.890 (0.753 – 0.935)</td>
</tr>
<tr>
<td>&lt;60 months</td>
<td>0.530 (0.512 – 0.550)</td>
<td>0.730 (0.705 – 0.753)</td>
</tr>
</tbody>
</table>

Background and Aims:

The WHO Collaborating Centre (CC) for New Vaccines supports countries to conduct hospital-based surveillance of vaccine preventable meningitis among children less than five
years old. The WHO CC supports 17 sentinel sites across 10 West and Central African countries. Findings of the surveillance efforts from 2010 to 2016 is reported.

Methods:

Children less than five years with suspected meningitis were recruited at the sentinel sites. Cerebrospinal fluid (CSF) was collected and tested for bacterial pathogens using routine bacteriologic techniques and molecular tools. Pneumococci were serotyped using latex agglutination and real-time PCR on CSF. Antibiotic susceptibility testing done by disc diffusion method and whole genome sequencing performed on isolates.

Results:

A total of 36,901 suspected meningitis cases and 1,960 deaths were reported. CSF was collected from 52% (19,376/36,901) of the suspected cases and 40% (7,745/19376) of the CSF specimens were tested by molecular methods. There were 560 laboratory-confirmed cases and pneumococcus accounted for 57.7% (323/560). PCV13 serotype detection rate was 56.5% (139/246) including 6A/6B/6C/6D 15.8%; 1, 5 and 23F 11.5% each; 14 9.4%; 19A and 19F 7.2% each. Phylogenetic analysis revealed geographical clustering of pneumococci associated with paediatric meningitis. Sequence types (ST) 618, 217 and 303 of serotype 1 were frequently co-resistant to trimethoprim/sulfamethoxazole.

Conclusion

Vaccine preventable bacterial meningitis caused by pneumococcus was pervasive in West and Central Africa among very young children. Continued surveillance is crucial to monitor vaccine preventable meningitis among African children and inform policy.

ISPPD-0731
DIFFERENTIAL DECLINE IN IPD AND ALL-CAUSE HOSPITALIZED PNEUMONIA (ACHP) AMONG CHILDREN WITH AND WITHOUT AT-RISK AND HIGH-RISK COMORBIDITIES FOLLOWING UNIVERSAL CHILDHOOD PCV13 IMMUNIZATION
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Background and Aims:

Children with at-risk and high-risk comorbidities are at increased risk for pneumococcal disease. Effectiveness of pneumococcal vaccination may differ in these populations versus healthy children as those with at-risk and high-risk comorbidities likely rely disproportionately on herd effects.

Methods:

We used a retrospective cohort design and data from two US healthcare claims repositories to evaluate changes in rates of IPD and ACHP among children, by age and comorbidity profile, between the pre-PCV13 era (2007-2010) and the post-PCV13 era (2013-2015).
Results:

Incidence rates of IPD and ACHP were substantially higher in children with high-risk and at-risk comorbidities compared with healthy children in both the pre- and post-PCV13 eras (Table). IPD and ACHP incidence declined over time in all groups, but declines were generally lower among children with at-risk comorbidities, and were substantially lower in children with high-risk comorbidities. Accordingly, relative rates of IPD and ACHP among at-risk and high-risk children (versus healthy children) generally increased from the pre- to post-PCV13 eras.

Conclusion

The switch to PCV13 was associated with declines in IPD and ACHP in all children. However, IPD and ACHP rates declined significantly less in children with high-risk (immunocompromising) comorbidities, as well as those with at-risk comorbidities, consistent with greater reliance on herd effects and greater susceptibility to non-vaccine serotypes in these groups.
Among all colonized children (<5 years), PCV13-type carriage decreased from 26.9% (2008-9) to 7.3% (2014-15) while 19F-carriage increased from 1.4% to 3.9% (p<0.0001 for both). Between 2012-2015(all ages), 19F carriage was detected at all study sites. Of 19F carriers in 2014-15 aged <5 years, 95% were up-to-date for PCV13. The pre-PCV13 and 2011-16 19F-IPD rates/100,000/persons were 0.36 and 0.93 for children (<5 years) and 0.12 and 0.24 for adults.

Table 1. Pneumococcal 19F colonization among Alaskans after introduction of PCV13.

<table>
<thead>
<tr>
<th>Study Years</th>
<th>Urban(&lt;5 Years)</th>
<th>Rural(&lt;5 Years)</th>
<th>Rural(5-17 Years)</th>
<th>Rural(≥18 Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008-9</td>
<td>1.6%(4/252)</td>
<td>1.3%(7/530)</td>
<td>0.3%(3/1009)</td>
<td>0.7%(3/411)</td>
</tr>
<tr>
<td>2010-11</td>
<td>0.3%(1/346)</td>
<td>0.5%(3/597)</td>
<td>2.2%(25/1144)</td>
<td>0.4%(2/519)</td>
</tr>
<tr>
<td>2012-13</td>
<td>0.6%(2/317)</td>
<td>1.2%(8/664)</td>
<td>5.4%(61/1130)</td>
<td>3.2%(20/627)</td>
</tr>
<tr>
<td>2014-15</td>
<td>2.9%(9/307)</td>
<td>4.4%(28/643)</td>
<td>4.6%(58/1256)</td>
<td>2.1%(15/715)</td>
</tr>
</tbody>
</table>

P-value-Trend 0.10 <0.0001 <0.0001 0.008

Conclusion

Serotype-19F carriage has increased in rural Alaska among persons of all ages following introduction of PCV13; the 19F-IPD rate remains very low in children and adults.

ISPPD-0447
IMPACT OF TEN-VALENT PNEUMOCOCCAL CONJUGATE VACCINE INTRODUCTION ON ISOLATED SEROTYPES FROM POPULATION OLDER THAN 14 IN COLOMBIA: AN INTERRUPTED TIME SERIES ANALYSIS
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Background and Aims:

In Colombia, 10 valent pneumococcal conjugate vaccine (PCV10) has been included in the National Vaccination Program since 2011. Previous research has suggested impact of the PCV10 introduction on trends of 19A and 3 serotypes in children under 5 years. We aimed to determine the impact of the PCV10 introduction over isolated serotypes from people older than 14 in Colombia.

Methods:

Information was obtained from the National Institute of Health since 1993 to 2016. The isolates came from sterile sites (blood, cerebrospinal fluid, pleural fluid, articular and peritoneal fluids). We used two measures: i) serotype proportions; and, ii) serotype rates per
100,000 habitants. An interrupted time series analysis was performed to determine the effect of the PCV10 introduction on the 3, 6A, 19A and Non-PCV13 serotypes.

**Results:**

Serotyping was performed in 3040 isolates. After introduction of the PCV10, we look an increase of the annual proportion trend for 19A serotype, and an increase of the annual rate trend for 3, 6A and 19A serotypes (Figures 1 and 2). The time series model shows effects of PCV10 introduction over the proportion of 19A and Non-PCV13 serotypes, and over the rate of 3, 6A, 19A and Non-PCV13 serotypes (Table).
Conclusion

The PCV10 introduction increased the proportion of 19A and Non-PCV13 serotypes, and the rate of 3, 6A, 19A and Non-PCV13 serotypes isolated from people older than 14, in Colombia.

### ISPPD-0214
CHARACTERIZATION OF INVASIVE PNEUMOCOCCAL DISEASE BY SEROTYPE 19A IN PEDIATRIC PATIENTS OF BOGOTÁ, COLOMBIA, 2008 – 2017

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**Background and Aims:**

Invasive pneumococcal disease (IPD) is an important cause of infant morbidity and mortality. In Colombia, PCV10 has been administered since 2012. An increase in the prevalence of...
serotype 19A has been documented after the introduction of conjugate vaccines. Our objective is to describe the clinical, microbiological and epidemiological characteristics of serotype 19A in Bogotá Colombia.

Methods:

Ambispective case series (2008 - 2017) in pediatric patients from 10 hospitals in Bogotá with IPD. Patients with \textit{Streptococcus pneumoniae} serotype 19A isolation were described. This study was approved by the ethics committee of each institution

Results:

There were 444 cases of IPD, 302 (68\%) with a known serotype. The prevalence of IPD by Spn19A is 16.6\%(50 cases). 90\%(45) are under 5 years of age. 82\%(41) were pneumonia, 10\%(5) primary bacteremia, 6\%(3) meningitis and 2\%(1) arthritis/osteomyelitis. 34\%(68\%) of the patients had a vaccination card with 3 doses of PCV, 30\%(88.2\%) had PCV10.

There is an increase in the prevalence over time of cases of IPD from 19 A: between 2008-2011 it was 4.3\% (5/116), 2012-2014 it was 10.7\% (10/93) and 2015-2017 it was 37.6\% (35/93). 21.9\% (9) of pneumonia isolates were resistant to penicillin. The average hospital stay was 14.3 days (1-51), 21 (42\%) patients were admitted to the intensive care unit, with an average stay of 8.8 days (1-50). 6 (12\%) patients died.

Conclusion

This series shows a prevalence of IPD by \textit{Streptococcus pneumoniae} 19A with a tendency to increase over time, with resistance to penicillin and important burden of disease.

\textbf{Background and Aims:}
Invasive pneumococcal disease (IPD) causes high morbidity and mortality in children under 5 years of age. In Colombia PCV10 has been administered since 2012. Red Neumocolombia network monitors the ENI in pediatric patients in Bogotá.

**Methods:**

Ambispective case series study (2008-2017) in pediatric patients admitted to 10 hospitals of Bogotá with IPD. Clinical, microbiological and epidemiological information was obtained. This study was approved by the ethics committee of each institution.

**Results:**

444 patients included, 254(57.2%) male; 187(42.1%) <24 months; 147(33.1%) between 24 and 59 months; 110(24.7%) > 60 months. Pneumonia 298 cases(67.1%); bacteremia 90(20.2%); meningitis 43(9.6%) meningitis plus pneumonia 6(1.35%) and others 7 (1.5%). 170(38.2%) patients required ICU and 45 died (10.1%). Of 395 non-meningeal isolates, antibiogram was obtained in 319, 34(10.6%) were resistant to penicillin.

Serotyping was obtained in 302 isolates(68%), the most frequent serotypes were 14 in 58 cases (19.2%), 19A in 50 cases (16.5%), and 1 in 42 cases (13.9%). A decrease in the prevalence of IPD by serotype 14 of 35.3% (41/116) in the period 2008-2011 to 11.8%(11/93) in the period 2015-2017 was observed.

There was an increase of serotype 3, from 3.4%(4/116) in 2008-2011 to 11.8%(11/93) in 2012-2014 and to 18.2%(17/93) in 2015-2017. Between 2008-2011 19 A was 4.3%(5/116), 2012-2014 was 10.7%(10/93) and 2015-2017 was 37.6%(35/93).

**Conclusion**

The most frequent IPD was pneumonia in children under two years. There is a decrease in the prevalence of serotypes 14 and an emergence of serotypes 19A and 3. It is important to monitor the IPD after the implementation of vaccination in Colombia.

**ISPPD-0231**

**VACCINATION-RELATED CHANGES IN LOCAL EPIDEMIOLOGY OF SEROTYPES OF S. Pneumoniae CAUSING COMMUNITY-ACQUIRED PNEUMONIA IN CHILDREN UNDER 18 YEARS OF AGE, BOGOTÁ, 2008-2016**

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¹²Universidad de La Sabana, Cundinamarca, Bogotá, Colombia
Background and Aims:

Community-acquired pneumonia (CAP) is a global public health problem. It has been recognized as one of the main causes of death in pediatric population. *S. pneumoniae* is the most important agent. Colombia included PCV10(2+1) in its vaccines for children program since 2011. Our aim was evaluating potential changes in the prevalence of pneumococcal serotypes related to CAP after vaccination.

Methods:

We carried out a multicenter case-series study in Bogotá, Colombia. A case was defined as a patient (<18 y.o.) who was diagnosed as having *S. pneumoniae* related- CAP by using clinical methods and blood and pleural fluid cultures. We gathered demographic and clinical data. This study was approved by the ethics committee of each institution.

Results:

282 patients were included, of which 115 (41%) were <2 years of age. Of 141 (50%) who had known history of vaccination, 111 (78.7%) had received at least one dose of PCV10, of which 72(64.9%) had completed the recommended schedule. Two non-vaccine serotypes are the most prevalent (19A and 3) and one more is emerging now (6A) (Figure 1).

Conclusion

We found clinical practice-based evidence of a redistribution in the frequency of serotypes involved in the local cases of *S pneumoniae* related- CAP in children after the beginning of the PCV10 vaccination. We recognize as a limitation of this study that the serotype classification was no available in a proportion of the eligible cases.
ISPPD-0270
INVASIVE PNEUMOCOCCAL DISEASE IN VICTORIA, AUSTRALIA, ACROSS PRE-VACCINE, 7 VALENT AND 13 VALENT VACCINE PERIODS, 2001-2016
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2Department of Health and Human Services, Communicable Disease Epidemiology and Surveillance - Health Protection Branch, Melbourne, Australia

Background and Aims:

The 7-valent pneumococcal conjugate vaccine (7vPCV) was introduced to the Australian National Immunisation Program for Aboriginal and Torres Strait Islander children in 2001, and for other children in 2005. The 13vPCV was introduced in 2011. We aimed to provide a comprehensive analysis of the changing epidemiology of invasive pneumococcal disease (IPD) in Victoria over this time.

Methods:

Cases of laboratory confirmed IPD in Victoria are notified to the Victorian Department of Health and Human Services. Enhanced surveillance data were collected throughout this time for children aged <5 years and adults 50 years and older. Trends in notification rates by age group and serotype, and in demographics, clinical picture, and geographic distribution of notifications, were analysed.

Results:

There were 6,105 notifications during 2001-2016. Introduction of 7vPCV resulted in a sustained decrease in IPD in cases <5 years, with an increase in those aged 50+. Non-conjugate vaccine types, including 3, 6C, 7, 19A, 22F and 23B, caused an increasing proportion of IPD post introduction of vaccines. Some non-vaccine types increased in 50+ not <5 years (including 15A, 16F, 23A, 35B). The proportion of cases with bacteraemia declined and pneumonia increased with introduction of 7vPCV but did not alter with introduction of 13vPCV. Most cases <5 years had no risk factors identified. Vaccine failures were predominately 3, 19A and 19F.

Conclusion

Immunisation resulted in a sustained decrease in IPD among in cases <5 years but has not had a similar impact on adults, for whom 13vPCV is currently not funded.

ISPPD-0605
PEDIATRIC PNEUMOCOCCAL MENINGITIS IN AFRICAN COUNTRIES IN THE ERA OF PNEUMOCOCCAL CONJUGATE VACCINES, 2011-2015
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Background and Aims:

Pneumococcal conjugate vaccine (PCV) has been introduced in 37/47 countries in the WHO African region. We evaluated reduction in vaccine-type (VT) pneumococcal meningitis in 12 African countries that introduced either 13-valent or 10-valent PCV before 2014.

Methods:

WHO/AFRO Paediatric Bacterial Meningitis (PBM) surveillance data for suspected meningitis in children ≤5 years were analyzed for 12 African countries, of which five introduced PCV10. Pneumococcal meningitis cases were defined as pneumococcus detected by culture, latex agglutination, immunochromatographic test, or PCR on a cerebral spinal fluid (CSF) specimen (CSF). Serotyping was performed by PCR on lytA-positive specimens, or by latex if an isolate was available. Because of different introduction years across countries, we compared VT-pneumococcal meningitis prevalence between 2011 (pre-PCV) and 2014-2015 (post-PCV).

Results:

Of 36,871 suspected meningitis cases, 897 (2.4%) were confirmed to be pneumococcus. Of those, 499 (61.5%) were serotyped. The prevalence of VT-pneumococcal meningitis decreased from 67.9% (19/28) pre-PCV to 46.1% (89/193) post-PCV (P=0.03). Among the VT circulating post-PCV, serotypes 6A/6B (n=23), 1 (n=14), 5 (n=14), 14 (n=9), and 19F (n=8) were the most prevalent.

Conclusion

Although the prevalence of VT pneumococcal meningitis has decreased in Africa, almost half of pneumococcal meningitis cases are still caused by vaccine-types. Continued monitoring of pneumococcal meningitis and vaccination coverage is essential.

EXAMINATION OF MOTHER AND INFANT NP SWABS FOR PNEUMOCOCCAL CARRIAGE

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¹fx Immune Co., Laboratory, Candler, USA
²Meharry Medical College, Pediatric Medicine, Nashville, USA
³Oklahoma Medical Research Foundation, Human Antibody Core Facility, Oklahoma City, USA

Background and Aims:

S. pneumoniae is a major pathogen, and development of a high throughput assay detecting both carriage and disease is a high priority. Several hurdles exist which have delayed development of a reliable serotyping assay: 1) Adequate monoclonal antibodies against specific capsular polysaccharides, 2) Identification of assay platforms which will result in high throughput capability, and 3) Affordability. Identification of disease causing S. pneumoniae serotypes is critical to understanding the epidemiology of pneumococcal disease and for developing effective pneumococcal vaccine strategies. f(x) Immune has developed a simple,
rapid, and economical 23-valent pneumococcal serotyping assay available on either Luminex or Flow Cytometric platforms.

**Methods:**

Using fully human monoclonal antibodies, our assay can detect all pneumococcal serotypes found in both PNEUMOVAX®23 and Prevnar13®.

**Results:**

116 mother/infant paired NP swabs were tested. 60.3% of the NP swabs tested contained at least one serotype. 4.3% of the tested NP swabs contained 2 or more serotypes. Serotypes detected were 4, 11A, 12F, 14, 15B, 19A, 19F, 22F, and 23F.

**Conclusion**

f(x) Immune has an available serotyping assay; using full-length human monoclonal antibodies, capable of becoming the basis of surveillance and serotype replacement studies. This assay provides high throughput, making population carriage studies affordable, as well as affording public health services with a means to monitor pneumococcal carriage in populations before and after introduction of pneumococcal vaccines.

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**ISPPD-0371**

**EXAMINATION OF MOTHER AND INFANT URINE SAMPLES FOR PNEUMOCOCCAL CARRIAGE**

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¹fx Immune Co., Laboratory, Candler, USA
²Meharry Medical College, Pediatrics, Nashville, USA
³Oklahoma Medical Research Foundation, Human Antibody Core Facility, Oklahoma City, USA

**Background and Aims:**

Pneumococcal serotyping using the manual reference method is time consuming and requires considerable technical expertise. This creates a need for an automated, high throughput serotyping assay. Historically, several challenges exist which have delayed development of a reliable serotyping approach: 1) Suitable monoclonal antibodies against specific capsular polysaccharides, 2) Adaptation to an assay platform which results in high throughput capability, and 3) Affordability. Identification of disease causing *S. pneumoniae* serotypes is critical to understanding the epidemiology of pneumococcal disease and for developing effective pneumococcal vaccine strategies. f(x) Immune has developed a simple, rapid, and economical 23-valent pneumococcal serotyping assay available on either Luminex or Flow Cytometric platforms.

**Methods:**

Using fully human monoclonal antibodies, our assay can detect all pneumococcal serotypes found in both PNEUMOVAX®23 and Prevnar13®.

**Results:**

109 mother/infant paired urine samples were tested. 98% of the urine samples tested contained at least one serotype. 73% of the tested urine contained 2 or more serotypes.
Serotypes detected were 1, 3, 4, 6B, 7F, 8, 9N, 9V, 10A, 11A, 14, 15B, 17F, 18C, 19A, 20, 22F, 23F and 33F.

Conclusion

f(x) Immune has an available serotyping assay; using full-length human monoclonal antibodies, capable of becoming the basis of surveillance and serotype replacement studies. This assay provides high throughput, making population carriage studies affordable, as well as affording public health services with a means to monitor pneumococcal carriage in populations before and after introduction of pneumococcal vaccines.

ISPPD-0712
PNEUMOCOCCAL COLONIZATION IN MOTHER-INFANT PAIRS
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1Meharry Medical College, Pediatrics, Nashville, USA
2fx Immune Diagnostics Inc., Laboratory, Candler, USA

Background and Aims:

PCV13 is routinely administered to children at 2, 4, 6 and 12 months of age. Recent rise non-vaccine serotypes (NVST) raise concerns regarding NVST replacement. Little is known about colonization status (CS) within family groups.

Methods:

NP CS was studied in 71 mother-infant (M-I) pairs for 23 serotypes (PPV23) at pre-and post-PCV13 administration. Thirty-eight of 71 pairs were of Hispanic and 33 were of non-Hispanic origin.

Results:

Ninety-four percent samples tested positive for NVST and of which 99 percent were 11A.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>11A Pre-vaccine n (%)</th>
<th>Dose 1 n (%)</th>
<th>Dose 2 n (%)</th>
<th>Dose 3 n (%)</th>
<th>Dose 4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>17/38 (45)</td>
<td>16/37 (43)</td>
<td>4/15 (27)</td>
<td>9/20 (45)</td>
<td>2/6 (33)</td>
</tr>
<tr>
<td>Infant</td>
<td>33/38 (87)</td>
<td>28/37 (76)</td>
<td>12/15 (80)</td>
<td>13/20 (65)</td>
<td>4/6 (67)</td>
</tr>
<tr>
<td>p*</td>
<td>0.000</td>
<td>0.009</td>
<td>0.009</td>
<td>0.34</td>
<td>0.56</td>
</tr>
</tbody>
</table>

M-I Cohort - Prevalence 11A

<table>
<thead>
<tr>
<th>Pre-vaccine n (%)</th>
<th>Dose 1 n (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>5/17 (29)</td>
<td>2/17 (12)</td>
</tr>
<tr>
<td>Infant</td>
<td>14/17 (82)</td>
<td>12/17 (71)</td>
</tr>
<tr>
<td>P*</td>
<td>0.005</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Fisher’s Exact test

Only twenty percent infants developed otitis media before twelve months who breast fed compared to 53 percent who did not (p=0.04).
Conclusion

Significantly higher number of infants were colonized with 11A compared to their mothers. Vaccination of infants did not significantly decrease 11A colonization in mothers or infants. Incidence of otitis media was not affected by infant colonization, but was affected by breast feeding. Monitoring of CS within families may be useful to understand pneumococcal colonization and relationships between vaccine and NVST.

ISPPD-0026
THE INCIDENCE OF INVASIVE PNEUMOCOCCAL DISEASE IN IRELAND – CONCERNING INCREASE IN NON-VACCINE SEROTYPES FROM 2007-2017

1Irish Pneumococcal Reference Laboratory, Irish Meningitis & Sepsis Reference Laboratory, Dublin 1, Ireland
2Irish Pneumococcal Reference Laboratory, Temple Street Children’s University Hospital, Dublin, Ireland
3Health Protection Surveillance Centre, Health Service Executive, Dublin, Ireland
4Department of Clinical Microbiology- the Royal College of Surgeons in Ireland, Department of Microbiology- Beaumont Hospital- Dublin- Ireland, Dublin, Ireland

Background and Aims:

The pneumococcal conjugate vaccines (PCV7/13) provide protection against the predominant serotypes associated with invasive pneumococcal disease in children. The 23-valent polysaccharide vaccine (PPV23) is recommended for those ≥65 years old. We investigated the predominant serotypes circulating in the population to determine if the introduction of PCV13 may be of benefit to adults.

Methods:

Typing was performed using capsular co-agglutination and a multiplex-PCR. Susceptibility to antimicrobials was interpreted using EUCAST meningitis breakpoints. Incidence rate (IR) per epidemiological year and IR ratio (IRR) of typed cases was calculated using national census data.

Results:

The total number of IPD isolates typed from children <5 years old has fallen from 22.22/100,000 in 2007-08 to 7.03/100,000 in 2016-17, with the biggest decline in PCV7 (98%, IRR:0.02) and PCV13 serotypes (80%, IRR:0.17) serotypes. However, the total incidence of typed isolates in adults has remained high (28.66/100,000 to 30.38/100,000) during the ten years. This is due to any PCV herd-effect becoming masked by significant increases in PPV23-only serotypes included 8 (IRR:5.77), 22F (IRR:3.39), 33F (IRR:2.13), 9N (IRR:1.63) and non-vaccine types (NVTs) 15A (IRR:6.78) and 35B (IRR:1.51), which were also frequently associated with antimicrobial resistance.

Conclusion

PCVs reduced the circulation of particular serotypes previously associated with infection. However, this research highlights the importance of continued surveillance as the distribution of serotypes is evolving. Moreover, PPV23 only and NVTs are rapidly increasing, particularly in the older adult population and are also associated with antimicrobial resistance.
Surveillance data should be considered to inform future vaccine development initiatives and policies.

ISPPD-0027
SEROTYPE 19A - PERSISTENCE AND PENICILLIN RESISTANCE IN THE POST VACCINATION-ERA IN IRELAND, DATA FROM 2007-2017
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1Irish Pneumococcal Reference Laboratory, Irish Meningitis & Sepsis Reference Laboratory, Dublin 1, Ireland
2Irish Pneumococcal Reference Laboratory, Temple Street Children’s University Hospital, Dublin, Ireland
3Health Protection Surveillance Centre, Health Service Executive, Dublin, Ireland
4Department of Clinical Microbiology- the Royal College of Surgeons in Ireland, Department of Microbiology- Beaumont Hospital-, Dublin, Ireland

Background and Aims:

The pneumococcal conjugate vaccines provide protection against the predominant serotypes associated with invasive pneumococcal disease. Despite inclusion in the vaccine, the number of serotype 19A infections has remained high and this serotype is frequently associated with vaccine failures and antimicrobial resistance. The aim of this research was to investigate all serotype 19A isolates referred to the Irish Pneumococcal Reference Laboratory over the past ten years.

Methods:

Typing was performed using capsular co-agglutination and a multiplex-PCR. Susceptibility to antimicrobials was interpreted using EUCAST meningitis breakpoints. Multi Locus Sequence Typing was performed and assessed using pubMLST.

Results:

A total of 271 serotype 19A isolates from sterile sites were typed since 2007. Serotype 19A was responsible for 10 of 13 vaccine failures reported in fully vaccinated children. By the epidemiological year 2016-17, there was a decline in children <5 years of age (IR=0.28/100,000) in comparison to the pre-vaccine period 2009-10 (IR=1.19/100,000). However, the incidence in adults ≥65 years of age has increased from 0.69/100,000 in 2009-10 to 1.39/100,000 in 2016-17. Penicillin resistance has increased from 21% to 60% of 19A isolates and was mostly associated with ST230 and ST320, although a number of other STs have also recently emerged.

Conclusion

Serotype 19A continues to be associated with IPD cases in Ireland. The persistence of 19A highlights the need for continued surveillance work. Moreover, more in-depth analysis of strains may provide a better understanding of recombination events that may be responsible for the persistence of serotype 19A in the post- PCV13 era.

ISPPD-0693
MOLECULAR CHARACTERIZATION OF Streptococcus pneumoniae CAUSING OCULAR AND OTOLARYNGOLOGY INFECTIONS
Background and Aims:

The mucous membranes function as physical and immunological barriers to prevent pathogen invasion. To determine whether the pneumococcal population structure is shaped by defense mechanisms adapted to the distinct mucosas of the eye, ear and nose, we molecularly characterized isolates from ocular and otolaryngology infections.

Methods:

Isolates recovered from patients at Massachusetts Eye and Ear from January 2014 to January 2017 were included. Identification and antimicrobial susceptibility was performed using MicroScan. Whole genome sequencing was done using Illumina, followed by molecular serotyping and MLST.

Results:

Twenty-seven different serotypes were found, with serotypes 35B (13.3%), 3 (10.6%), 19A and 23A (6.2% each), 21 and 19F (5.3% each), 23B and 15B (4.4% each) being the most frequent. The distribution of serotypes was not random across different sites. Ear infections were predominantly caused by serotype 3/ST180 (29%), while sinusitis was frequently associated with serotype 35B (18.5%) particularly related to ST558. Eye infections were commonly caused by non-typeable isolates (28.6%), mainly from ST448. Overall, isolates were frequently resistant to erythromycin (37.8%), penicillin (21.6%) and less commonly resistant to amoxicillin/clavulanate (9%) and ceftriaxone (6.3%). Only 8.3% of serotype 3/ST180 isolates were resistant to erythromycin. Serotype 35B were commonly resistant to erythromycin and penicillin (73.3%). Non-typeable eye isolates were occasionally resistant to erythromycin (20%) and penicillin (10%).

Conclusion

A correlation between site of isolation and serotype/ST was found. Despite serotype 3 is included in PCV13, it is still circulating and causing otitis in our population. Surveillance studies are essential to detect vaccine effectiveness and establish the best antimicrobial therapy.

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**ISPPD-0299**

**EFFECTIVENESS OF PNEUMOCOCCAL CONJUGATE VACCINES (PCVS) TO PREVENT SEROTYPE 3 INVASIVE PNEUMOCOCCAL DISEASE (IPD) IN QUEBEC, CANADA**

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²Institut National de Santé Publique, Laboratoire de Santé Publique du Québec, Sainte-Anne-de-Bellevue, Canada
³Institut National de Santé Publique, Department of Occupational and Biological Risks, Québec- Qc, Canada
⁴Laval University, Department of Social and Preventive Medicine, Québec, Canada
Background and Aims:

In Quebec, a PCV program was implemented in December 2004 and the recommended schedule is 2+1 doses for low-risk infants. PCV-7 was first used, replaced by PCV-10 in June 2009, and by PCV-13 in January 2011. From the beginning, vaccine uptake has been high and stable: > 90% of children are receiving the recommended number of doses. The objective is to assess the effectiveness of PCV13 to prevent serotype (ST) 3 IPDs.

Methods:

IPD cases in children 2–59 months and reported during the years 2005–2016 were eligible and controls randomly identified in the provincial health insurance registry. Parents were interviewed by telephone and immunization records reviewed. Vaccine effectiveness (VE) was computed using unconditional logistic regression models, adjusting for underlying condition, year, season and age.

Results:

Out of 1090 IPD cases reported, full participation was obtained for 692 cases (63%), of these 36 were of serotype 3, and for 2,570 controls. VE are shown in the Table.

<table>
<thead>
<tr>
<th>Vaccine effectiveness of ≥ 1 dose of PCV13 against 3-serotype IPD</th>
<th>Vaccine effectiveness</th>
<th>95%IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any age</td>
<td>20%</td>
<td>[-265%;82%]</td>
</tr>
<tr>
<td>Age&lt; 24months</td>
<td>94%</td>
<td>[22%;99%]</td>
</tr>
<tr>
<td>Age≥24 months</td>
<td>-20%</td>
<td>[-1399%;90%]</td>
</tr>
<tr>
<td>In the first 365 days after the last dose</td>
<td>61%</td>
<td>[-164%-94%]</td>
</tr>
<tr>
<td>More than 365 days after the last dose</td>
<td>-58%</td>
<td>[-1010%;78%]</td>
</tr>
</tbody>
</table>

Conclusion

Although PCV13 VE estimates are statistically non-significant, results suggest some protection after immunisation which is waning rapidly.

ISPPD-0300
EFFECTIVENESS OF PNEUMOCOCCAL CONJUGATE VACCINES (PCVS) TO PREVENT SEROTYPE 19A INVASIVE PNEUMOCOCCAL DISEASE (IPD) IN QUEBEC, CANADA
G. Deceuninck1, B. Lefebvre2, G. De Serres1,3,4, P. De Wals1,3,4
1Quebec University Hospital Research Center, Unité de recherche en vaccination, Québec, Canada
2Institut National de Santé Publique du Québec, Laboratoire de Santé Publique du Québec, Sainte-Anne-De-Bellevue, Canada
Background and Aims:

In Quebec, a PCV program was implemented in December 2004 and the recommended schedule is 2+1 doses for low-risk infants. PCV-7 was first used, replaced by PCV-10 in June 2009, and by PCV-13 in January 2011. From the beginning, vaccine uptake has been high and stable: > 90% of children are receiving the recommended number of doses. The objective is to compare the effectiveness of PCVs to prevent serotype (ST) 19A IPD.

Methods:

IPD cases in children 2–59 months and reported during the years 2005–2016 were eligible and controls randomly identified in the provincial health insurance registry. Parents were interviewed by telephone and immunization records reviewed. Vaccine effectiveness (VE) was computed using unconditional logistic regression models, adjusting for underlying condition, year, season and age.

Results:

Out of 1090 IPD cases reported, full participation was obtained for 692 cases (63%), of these, 186 were serotype 19A, and for 2,570 controls. VE are shown in the Table.

<table>
<thead>
<tr>
<th>Number of PCV doses</th>
<th>Vaccine effectiveness against 19A-serotype IPD (n.d. = not determined)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCV10</td>
</tr>
<tr>
<td>≥ 1 dose</td>
<td>52%[21%;81%]</td>
</tr>
<tr>
<td>Age&lt; 24months, ≥ 1 dose</td>
<td>78%[28%;93%]</td>
</tr>
<tr>
<td>≥ 2 doses</td>
<td>42%[-74%;81%]</td>
</tr>
<tr>
<td>≥ 3 doses</td>
<td>60%[-36%;88%]</td>
</tr>
<tr>
<td>In the first 365 days after the 3rd dose</td>
<td>89%[37%;98%]</td>
</tr>
<tr>
<td>More than 365 days after the 3rd dose</td>
<td>-311%[-2445%;34%]</td>
</tr>
</tbody>
</table>

Conclusion

PCV10, PCV13 and PCV10+13 schedules are effective against ST 19A, but 3 doses seems needed to provide high level of protection which seems of rather short duration.

ISPPD-0624
SYSTEMATIC REVIEW COMPARING PCV PRODUCTS AND 3-DOSE SCHEDULES ON THE IMPACT ON VACCINE-TYPE NASOPHARYNGEAL CARRIAGE (NPC) AND INVASIVE PNEUMOCOCCAL DISEASE (IPD)
Background and Aims:

When deciding to introduce PCV as a 3-dose schedule into the national immunization program, countries choose between 2+1 and 3+0 schedules and between PCV10 and PCV13 products. Understanding how schedule and product choices could effect vaccine-type (VT) carriage and disease impact may inform this choice.

Methods:

The PCV Review of Impact Evidence (PRIME) project systematically reviewed clinical trials (RCT) or observational pre-post introduction studies evaluating impact of 3-dose schedules of PCV10 or PCV13 on VT (defined as serotypes within the product evaluated), NPC prevalence, and IPD incidence. Comparisons were descriptive due to heterogeneity in geography, income level, prior PCV7 use, serotype distribution, vaccine coverage, time since introduction, age, and presence of a catch-up program.

Results:

Only 2 trials directly compared products or schedules, so results primarily reflect between-study comparisons of observational, routine use studies. Impact increased with longer time since introduction.

Table. Range of percent reduction in VT-NPC or VT-IPD, by product and schedule

<table>
<thead>
<tr>
<th>Comparison</th>
<th>VT-NPC % Reduction</th>
<th>VT-IPD % Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCV13</td>
<td>PCV10</td>
</tr>
<tr>
<td>Product</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT: 22%</td>
<td>n=15</td>
<td>n=14</td>
</tr>
<tr>
<td>Pre/post: 28-96%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+0</td>
<td>n=15</td>
<td>n=12</td>
</tr>
<tr>
<td>RCTs: 8-35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre/post: 28-82%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*n= number of study arms (clinical trials, observational studies)

Conclusion

Both PCV products and both 3-dose schedules reduced VT-NPC and VT-IPD without evidence of differences in magnitude. A lack of head-to-head studies and substantial heterogeneity between study settings limit the ability to discern differences in effect magnitude if they exist.
ISPPD-0630
THE EFFECTIVENESS AND IMPACT OF 23-VALENT POLYSACCHARIDE PNEUMOCOCCAL VACCINE IN THE ELDERLY AND RISK GROUPS IN ENGLAND AND WALES
A. Djennad1, N. Andrews1, S. Collins2, R. Pebody3, N. Fry4, S. Ladhani5
3Public Health England, Respiratory Diseases, London, United Kingdom
4Public Health England, Respiratory and Vaccine Preventable Bacterial Reference Unit, London, United Kingdom

Background and Aims:

Prior to 2003 the PPV23 vaccine had been available for over 20 years in the UK. Since 2003 the PPV23 vaccine has been recommended for all those aged 65 administered by a single dose. The aims of the study is to measure the effectiveness and impact of PPV23 against IPD in the elderly ≥65 years eligible for vaccination in England and Wales.

Methods:

The methods include the indirect cohort method to measure the effectiveness of PPV23 vaccines and national IPD surveillance data to compare PPV23 IPD rates during the pre-PCV7 and PCV13 periods with the period post-PCV7 and PCV13 introduction.

Results:

The overall adjusted VE of PPV23 at any time of vaccination was 27%, 95% CI (17%, 35%) after adjusting for age, risk and year of infection. The effectiveness diminished by time since vaccination, from 40% (22, 54) for those vaccinated in less than two years, to 33% (15, 48) for those vaccinated within 2 to 4 years, to 24% (13, 33) for those vaccinated 5 years or more.

Conclusion

Overall the results show similar VE compared to the previous UK PPV23 study (VE=24%, 95% CI 10-36%). However this previous study was done when more vaccination had been recently given, so it might have been expected that the overall VE in the current study would be lower rather than higher as seen here (27%). This is because there is less clear evidence of waning in the current study, with the somewhat surprising finding that some VE remains beyond 5 and even 10 years.

ISPPD-0504
IMPACT OF PCV13 VACCINATION STATUS ON NASOPHARYNGEAL CARRIAGE RATES OF STREPTOCOCCUS PNEUMONIAE IN A RURAL COMMUNITY IN THE DOMINICAN REPUBLIC
1Children's Hospital of Philadelphia, Global Health Center, Philadelphia, USA
2Hospital Infantil Dr. Robert Reid Cabral, Department of Infectious Diseases, Santo Domingo, Dominican Republic

Results:

The overall adjusted VE of PCV13 at any time of vaccination was 27%, 95% CI (17%, 35%) after adjusting for age, risk and year of infection. The effectiveness diminished by time since vaccination, from 40% (22, 54) for those vaccinated in less than two years, to 33% (15, 48) for those vaccinated within 2 to 4 years, to 24% (13, 33) for those vaccinated 5 years or more.

Conclusion

Overall the results show similar VE compared to the previous UK PPV23 study (VE=24%, 95% CI 10-36%). However this previous study was done when more vaccination had been recently given, so it might have been expected that the overall VE in the current study would be lower rather than higher as seen here (27%). This is because there is less clear evidence of waning in the current study, with the somewhat surprising finding that some VE remains beyond 5 and even 10 years.
Background and Aims:

BACKGROUND

Infections caused by *Streptococcus pneumoniae* are an important cause of global childhood morbidity and mortality. Since the introduction of pneumococcal conjugate vaccines (PCVs), dramatic declines in disease have been noted, as well as shifts in serotype distribution and host colonization. The Dominican Republic (DR) introduced the 13-valent PCV (PCV13) in 2013, but limited post-vaccine epidemiologic data exists.

AIMS

To identify pneumococcal serotype distribution among nasopharyngeal carriers in a rural community and evaluate any association with vaccination status.

Methods:

We conducted a pilot prospective observational study of 125 pediatric subjects aged 2-35 months in Consuelo, DR from Nov 2016 – July 2017. For each subject, we collected a nasopharyngeal (NP) swab for isolation of *S. pneumoniae*, administered a health questionnaire, and abstracted vaccination data from the chart. All positive NP samples were serotyped using standard procedures.

Results:

Of 125 enrolled children (median age 17.5 months), 71 (56.8%) were up-to-date for age with PCV13 vaccine and 77 (61.6%) were colonized by *S. pneumoniae*. Most common vaccine-associated serotypes were 23F, 19F, 19A, 6A, and 6B. Up-to-date PCV13 vaccination status was associated with lower odds of colonization (OR 0.40, 95% CI 0.17-0.92, p=0.018). Use of antibiotics within the preceding 8 weeks was also associated with lower colonization rates (OR 0.24, 95% CI 0.09-0.59, p < 0.001).

Conclusion

Children up-to-date for age with PCV13, and children who had recently used antibiotics, were less likely to be colonized by *S. pneumoniae*. Our results support ongoing work to elucidate vaccine effectiveness in a community with high carriage rates.
Background and Aims:

Impact of pneumococcal conjugate vaccines (PCV) on antibiotic resistance patterns remains unclear in West Africa. PCV-7 was introduced in The Gambia in 2009 and PCV-13 in 2011. We determined antibiotic resistance patterns among pneumococci collected pre-and post-PCV introduction in The Gambia.

Methods:

Invasive pneumococcal isolates were obtained from surveillance studies and carriage isolates from healthy residents of The Gambia from 1995–2015. Pneumococcal serotypes and sequence types (ST) were determined by latex agglutination and MLST respectively. Antibiotic susceptibility testing (AST) was performed by Kirby-Bauer disk diffusion and Epsilometer (E-test) agar diffusion methods.

Results:

AST was performed on randomly selected 1,055 invasive and 2,884 carriage isolates. Resistance among invasive isolates was low for cefotaxime (0%), penicillin (0.2%), erythromycin (4.4%) and chloramphenicol (18.1%) but higher for tetracycline (59.2%) and co-trimoxazole (73.8%) with similar rates among carriage isolates. Resistance rates were the same in pre-and post PCV periods to all antibiotics tested except to co-trimoxazole (60.8% and 95.2% respectively; p<0.001). Resistance to chloramphenicol was higher among NVT (24.6%;63/256) mostly due to serotype 12F, compared to VT serotypes (16.0%;128/799) (p=0.002). Among serotype 1 genotypes, co-trimoxazole resistance was higher among newly emerging ST3081 (93.9%;77/82) than among previously existing ST618 (26.6%;25/94). Similarly, of serotype 14 genotypes, tetracycline resistance was higher among emerging ST2447 (100.0%;4/4) compared to previously existing ST3321 (0.0%;0/11).

Conclusion

The emergence of antibiotic resistant NVT and new variants of VT pneumococci could be important drivers of pneumococcal antibiotic resistance in post-PCV era in The Gambia. Continued monitoring of antibiotic resistance patterns would enable accurate assessment of vaccine impact.
**Background and Aims:**

An understanding of the population structure of *Streptococcus pneumoniae* is critical for guiding effective control. In The Gambia, PCV7 was introduced in 2009 and PCV13 in 2011. We determined the population structure of *S. pneumoniae* in The Gambia from 1995 - 2016.

**Methods:**

Data from invasive pneumococcal disease and nasopharyngeal carriage studies conducted in The Gambia between 1995 and 2016 were pooled together for this analysis. Invasive disease specimens were collected from sterile body fluids and nasopharyngeal swabs from healthy participants in the carriage studies. Pneumococcal isolates were serotyped by latex agglutination and genotyped by multi-locus sequence typing.

**Results:**

Of 1,355 invasive isolates collected pre-PCV13, serotypes 1 and 5 were the leading invasive serotypes (13.5% and 9.3% respectively) whilst of 847 invasive isolates collected post-PCV13 serotypes 1, 12F and 5 were predominant (7.4%, 7.3% and 5.5% respectively). Serotypes 1, 12F and 5 were rarely detected among 5,035 carriage isolates collected from 2003 - 2009 (0.9%, 0.7% and 0.6% respectively). PCV-7 serotypes decreased from 78.1% pre-PCV to 22.0% post PCV-7 (p<0.001). ST3081_serotype 1 emerged in 2007 as predominant serotype 1 ST, replacing previously dominant ST618. ST2447_serotype 14 and ST1526_serotype 23F emerged as dominant STs post-PCV-13 replacing ST63_serotype 14, ST3334_serotype 14 and ST802_serotype 23F which dominated pre-PCV-7. ST989_serotype 12F increased from 1.2% pre-PCV to 17.9% post PCV-13.

**Conclusion**

Emergence of the non-vaccine serotype 12F and new STs of PCV-13 serotypes following PCV introduction in The Gambia highlights the need for continuous surveillance of circulating pneumococcal serotypes and genotypes to inform effective strategies for control.

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**ISPPD-0434**

PRIVATE USE OF THE 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV13) HAS IMPACTED ON PNEUMOCOCCAL CARRIAGE AMONG PORTUGUESE CHILDREN

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**Background and Aims:**

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In Portugal, PCV7 became commercially available in 2001 and PCV13 in 2010. We evaluated the impact of PCV13 private use on serotypes carried by children attending day-care centers in an urban and a rural region.

Methods:

Three periods were studied: pre-PCV13 (2009-2010), early-PCV13 (2011-2012) and late-PCV13 (2015-2016). Pneumococci were isolated from nasopharyngeal samples of 4,232 children up to 6 years old. All isolates were serotyped.

Results:

Pneumococcal carriage remained stable in both regions (range: 59.5-62.8%). Vaccination with PCVs was high in both regions (range: 76.8-89.3%). Carriage of PCV13 serotypes decreased significantly from the pre- to late-PCV13 period (21.6% to 5.9% in the urban region; 15.9% to 6.8% in the rural region, p<0.001) mostly due to a decrease in the prevalence of serotype 19A (the most abundant in the pre-PCV13 period). Serotype 19F was the most prevalent PCV13-type in the late-PCV13 period in both regions albeit this reflected very different scenarios: it decreased in the urban region over time from 4.4% to 1.7% (p=0.009), while it increased in the rural region from 1.6% to 4.5% (p=0.017). The most prevalent non-PCV13-types in the late-PCV13 period were 15B/C (5.9%), 23B (5.7%) and 11D (5.6%) in the urban region, and 15A (6.4%), 23A (5.0%), and 35F (4.8%) in the rural region.

Conclusion

After 5-6 years of PCV13 use in the private market carriage of pneumococci remained stable among children attending day-care centers in Portugal and serotype replacement has occurred. As children are major reservoirs of pneumococci these results should trigger a herd effect in other age groups.

ISPPD-0527
IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) ON INVASIVE PNEUMOCOCCAL DISEASE AMONG CHILDREN IN MOZAMBIQUE, 2008-2016
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Background and Aims:

Mozambique introduced PCV10 in 2013 using a three-dose primary series schedule (2, 3 and 4 months). We evaluated PCV10 impact on invasive pneumococcal disease (IPD) and vaccine-type (VT) IPD.

Methods:
The incidence of IPD, VT-IPD and non-VT (NVT) IPD among children <5 years was calculated using surveillance data from Manhiça District Hospital and children-time denominator from Manhiça demographic surveillance. IPD was defined as pneumococcus detected by culture from blood or cerebral spinal fluid (CSF), or by polymerase chain reaction (PCR) on CSF. Serotyping of pneumococcus was done by Quellung (isolates) or PCR (lytA-positive specimens). We evaluated declines for each outcome from 2008–2016 using negative binomial regression models accounting for pre-PCV trends and excluding 2013 (PCV10 introduction year).

Results:

Incidence of overall IPD and VT-IPD per 1,000 children-year at risk was 2.35, 1.11 in 2008, and 0.41, 0.07 in 2016, respectively. IPD declined by 72.6% (95%CI: 38.6%–91.8%) and VT-IPD by 96.4% (95%CI: 79.1%-99.5%) post-PCV10 (Figure 1), while NVT-IPD incidence did not increase significantly (22.9% [95%CI: 0%-100%]). Prevalence of NVT among IPD in children <2 years (age-eligible for PCV10) increased from 40.7% (83/204) to 75.0% (30/40) (P<0.01), mainly driven by 19A (2.9% to 20.0%, P<.001).

Figure 1: Trend analysis for vaccine-type invasive pneumococcal disease among children <5 years in Mozambique, 2008-2016

Conclusion

Substantial declines in IPD and VT-IPD were observed in children <5 years after PCV10 introduction. Monitoring of serotype replacement, particularly serotype 19A, will be important.

ISPPD-0142
INVASIVE PNEUMOCOCCAL DISEASE (IPD) EMERGING SEROTYPES IN THE ERA OF GLOBAL PCV USE
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Background and Aims:

Despite widespread use of pneumococcal conjugate vaccines (PCV), substantial invasive pneumococcal disease (IPD) remains. The objective was to determine serotype distribution globally occurring between 2005-2015.

Methods:

Published data of IPD serotype distribution between 2005-2015; excluding non-sterile sites.

Results:

Data source: 24 publications; serotypes from 36,352 IPD cases; 18 countries.

PCV13 covered only 46%-51% (USA/EU/Japan), and 39.6% (Globally) of IPD serotypes; 10 of 13 PCV13 serotypes accounted for 8% of IPD (US/Canada); 19A, 3, and 7F accounted for 25.8%-37.5% (USA/EU/Japan) and 24.3% (Globally) of IPD. Serotype 1 associated with 3.3% (Globally) and 4.6% (EU) of IPD.


7 non-vaccine serotypes (NVT) accounted for 21% of IPD in the US (6C, 15A, 15C, 16F, 23A, 23B, 35B); 4 (13%) associated with antibiotic resistance (6C, 23A, 23B, and 35B). Regional variability in IPD serotypes occurred for 24F (Japan and EU) and 16F (US).

Conclusion

PCV13 IPD serotype coverage has declined worldwide to 39%, and 46%-57% in the US, EU, and Japan from the 2010 launch target of 85%-90%. Non-PCV13 and NVT serotypes now represent the majority of IPD serotypes globally. Emergence of NVT serotypes associated with antimicrobial resistance is of concern. The development of new PCV compositions need to address both the emergence of non-PCV13 serotypes as major contributors to IPD as well as emerging geographic differences in serotype distribution.
Background and Aims:

PCV10 was introduced in Nepal in 2015 and projects were in place to assess multiple aspects of vaccine impact. This study compared established in-country capacity for conventional serotyping with molecular serotyping by microarray to investigate potential benefits in carriage studies.

Methods:

In 2014-15 pre-vaccine era, nasopharyngeal swabs were collected from 1,904 community-dwelling children aged 6 months to <5 years. Swabs were transported in STGG to the laboratory for conventional serotyping in-country by Quellung(Q) and then frozen for shipment to the UK for molecular serotyping by microarray (M).

Results:

1,241 pneumococcal-positive swabs were analysed by Quellung and microarray. Overall concordance was 87% for detection of the same serotype (1,077/1,241). For the 13% samples with discordant results (164/1,241), 5% were non-typeable (NT) by Quellung but pneumococcal serotypes and/or related Streptococcal species by microarray; 8% were serotyped by Quellung and either partially/totally discrepant serotypes and/or related species by microarray.

Carriage of multiple pneumococcal serotypes was detected in 1% samples by Quellung (11/1,241) and 24% samples by microarray (296/1,241). Therefore, 32% more PCV10 VTs were detected by microarray than Quellung (Q:376, M:508), indicating VT carriage in 21% more children (Q:375, M:453).

Furthermore, microarray detected multiple carriage of pneumococcal serotypes, non-typeables and/or related species in 45% of samples (554/1,241) and antimicrobial resistance genes in 65% samples (810/1,241).

Conclusion

Concordance between serotyping methods was good, however, sensitive detection of multiple serotype carriage by microarray increases the power to assess vaccine impact upon circulating PCV10 VTs. This dataset presents a solid pre-vaccine baseline against which to compare post-vaccine results.
Background and Aims:

Finnish studies have shown a significant impact of ten-valent pneumococcal conjugate vaccine (PCV10) on non-notified clinically suspected invasive pneumococcal disease (‘suspected’ IPD). However, these studies have not been repeated elsewhere. We assessed PCV7 and PCV13 impact on suspected IPD, compared with notified (laboratory-confirmed) IPD, in New South Wales and Western Australian children.

Methods:

Children eligible for PCV7 (born 1/1/2008-31/12/2010) and PCV13 (born 1/5/2011-31/12/2012) were compared with season and age-matched pre-universal PCV cohorts (born in 2002-2004). Using linked notification and hospitalisation data, we calculated incidence rate ratios and absolute rate reductions (ARRs) for IPD notifications and suspected IPD (first hospitalisation coded with an International Classification of Diseases 10th Revision-Australian Modification primary or secondary diagnoses of: A40.3/A40.9/A41.9/A49.9/G00/I30.1/M00).

Results:

Compared to pre-universal cohorts, rates of suspected IPD reduced by 38% (95%CI: 32-42) in the PCV7-eligible cohort (ARR 122/100,000 person-years) and 63% (95%CI: 58-67) in the PCV13-eligible cohort (ARR 159/100,000 person-years). While relative rate reductions were higher for notified IPD in the PCV7 (64% [95%CI: 58-69]) and PCV13-eligible cohorts (86% [95%CI: 82-90]), ARRs were smaller (87/100,000 person-years for the PCV7-eligible cohort and 107/100,000 person-years for the PCV13-eligible cohort) than for suspected IPD.

Conclusion

This is the first study to examine the impact of PCV7 and PCV13 vaccination on non-notified clinically suspected IPD. Consistent with Finland’s experience, our results suggest that the absolute reductions in IPD (notified and suspected) due to universal childhood PCV vaccination are at least double those reported for IPD notifications alone. This additional benefit needs to be considered when evaluating PCV vaccination programs.

ISPPD-0394

VACCINE-INDUCED METABOLIC SHIFT (VIMS) IDENTIFIED IN PNEUMOCOCCAL CARRIAGE ISOLATES FOUR YEARS AFTER PROGRAMMATIC INTRODUCTION OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN MALAWI

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Background and Aims:

The concept of Vaccine-Induced Metabolic Shift (VIMS) has recently been described. Mathematical models suggest that under vaccine pressure and resource competition, pneumococcal vaccine serotypes (VT) with a favourable metabolic type (MT) are superseded.
by a non-vaccine serotypes (NVT) with the same MT. We have investigated the hypothesis that in high carriage, high multiple serotype carriage populations, VIMS has occurred soon after programmatic PCV13 introduction.

Methods:

870 Malawian pneumococcal carriage isolates from before (n=340) and after (n=530) vaccine introduction in 2011 underwent whole genome sequencing (WGS). The allelic profile of each strain for each of 800 pre-defined metabolic genes was used to calculate the pairwise distance between each isolate. Hierarchical clustering was used to define the discrete MT.

Results:

We identified up to 92 discrete MTs amongst these carriage isolates. Two different types of VIMS were detected: firstly, single serotypes exhibiting different MT before and after vaccine introduction (e.g. 23F, 35F, 38 and 23B); secondly, distinct MT after vaccine introduction associated with both VT and NVT.

Conclusion

We identified possible VIMS after vaccine introduction. NVT possessing MT previously associated with VT raises the possibility of less virulent serotypes with more invasive or transmissible phenotypes becoming more prominent under vaccine pressure, but proof of causality requires a longer period of observation. In the context of high rates of multiple serotype carriage, whether this VIMS is best explained by recent acquisition of invasive MT by NVT and other co-colonising Streptococci, or the ascendance of minor carriage NVT with invasive MT remains to be determined.

ISPPD-0772
POPULATION IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV) ON NASOPHARYNGEAL CARRIAGE OF STREPTOCOCCUS PNEUMONIAE IN KILIFI, KENYA

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Background and Aims:

PCV use in developed countries led to near-elimination of vaccine-type pneumococcal nasopharyngeal carriage, which contributed to indirect protection. Whether a similar pattern will be observed in developing countries that experience a higher force of infection and often use PCV without a booster is unknown.

Methods:
PCV10 was introduced into the infant vaccination program in Kenya in January 2011, accompanied by a catch-up campaign in Kilifi County for children <5yrs. We conducted annual nasopharyngeal carriage surveys among an age-stratified, random population sample for two years before (baseline) and seven years after PCV10 introduction (n=~500/year).

Results:

Throughout the PCV10 period, coverage with ≥1 PCV10 dose was documented in >2/3 of children <5. A reduction in PCV10-type pneumococcal carriage was observed in all age groups (<5yrs: 33.8%-->7.1%; 5-17yrs: 13.4%-->9.4%; ≥18yrs: 5.5%-->2.4%; baseline-->2017; p<0.001 for all; Figure). A significant increase in non-PCV10 type carriage was observed in children <18yrs but not adults (<5yrs: 40.6-->76.6%; 5-17yrs: 33.5%-->45.7%; ≥18yrs: 18.0%-->25.1%). Among children <5, serotype-specific carriage prevalence declined for 6B, 19F, and 23F, while 19A carriage increased (p<0.005 for all).

Conclusion

Vaccine-type carriage declined significantly in all ages after introduction of PCV10 but persists at unexpectedly high levels for a mature PCV program. This and the marked increase in carriage of non-vaccine serotypes necessitate continued surveillance. Further
reductions in vaccine-type carriage may require supplemental campaigns or incorporation of a booster dose.

**ISPPD-0579**

**PNEUMOCOCCAL VACCINATION IN ICELAND: THE EFFECT ON ANTIMICROBIAL SUSCEPTIBILITY AND SEROTYPE DISTRIBUTION**

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Background and Aims:

The proportion of penicillin non-susceptible pneumococci, PNSP, was increasing in the years before implementation of the 10-valent pneumococcal vaccine (PHiD-CV) into the childhood vaccination program in 2011, reaching 37.7% in 2010. The aim was to investigate antimicrobial susceptibility and serotype distribution in samples from patients in Iceland, 2011-2016.

Methods:

All pneumococcal isolates (except from nasopharynx and throat) from patients, identified in 2011-2016 were included (except repeat isolates within 30 days). Analyses were performed at the Department of Clinical Microbiology, Landspitali University Hospital, serving the greater capital area (about 2/3 of the Icelandic population) and as reference laboratory for the whole country. Susceptibility testing was performed using EUCAST methods and criteria. PNSP were serotyped using latex agglutination and/or PCR.

Results:

The number of pneumococcal isolates 2011-2016 was 1561 (2011;356, 2016;186). Total PNSPs were 473 (30.4%), (2011;147 (31.0%), 2016:59 (12.4%). In 2011 89% of PNSP had penicillin >0.5 mg/L but 40.7% in 2016, and respectively 92.3% and 67.8% were multi-resistant. In 2011, 84.4% of PNSP were of vaccine serotypes (VT) and 32.2% in 2016. The proportion of PNSPs from <2 years old children declined from 52.1% in 2011 to 4.7% in 2016 and the PNSP isolates of VTs from 92.0% to 12.5% (only one child).

Conclusion

The reduction of pneumococcal isolates, PNSPs, multi-resistant pneumococci and VTs was considerable following the vaccination. PNSP isolates of non-VTs have relatively low penicillin MICs. The proportion of PNSP remains high, both due to VTs found in the older population and overall non-VT replacement.

**ISPPD-0595**

**PNEUMOCOCCAL VACCINATION IN ICELAND: THE EFFECT ON PNEUMOCOCCI ISOLATED FROM THE MIDDLE EAR OF CHILDREN**


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Background and Aims:

The proportion of penicillin non-susceptible pneumococci, PNSP, was increasing in the years before implementation of the 10-valent pneumococcal vaccine (PHiD-CV) into the childhood vaccination program in 2011, reaching 37.7% in 2010. The aim was to investigate antimicrobial susceptibility and serotype distribution in samples from patients in Iceland, 2011-2016.

Methods:

All pneumococcal isolates (except from nasopharynx and throat) from patients, identified in 2011-2016 were included (except repeat isolates within 30 days). Analyses were performed at the Department of Clinical Microbiology, Landspitali University Hospital, serving the greater capital area (about 2/3 of the Icelandic population) and as reference laboratory for the whole country. Susceptibility testing was performed using EUCAST methods and criteria. PNSP were serotyped using latex agglutination and/or PCR.

Results:

The number of pneumococcal isolates 2011-2016 was 1561 (2011;356, 2016;186). Total PNSPs were 473 (30.4%), (2011;147 (31.0%), 2016:59 (12.4%). In 2011 89% of PNSP had penicillin >0.5 mg/L but 40.7% in 2016, and respectively 92.3% and 67.8% were multi-resistant. In 2011, 84.4% of PNSP were of vaccine serotypes (VT) and 32.2% in 2016. The proportion of PNSPs from <2 years old children declined from 52.1% in 2011 to 4.7% in 2016 and the PNSP isolates of VTs from 92.0% to 12.5% (only one child).

Conclusion

The reduction of pneumococcal isolates, PNSPs, multi-resistant pneumococci and VTs was considerable following the vaccination. PNSP isolates of non-VTs have relatively low penicillin MICs. The proportion of PNSP remains high, both due to VTs found in the older population and overall non-VT replacement.
Background and Aims:

The 10-valent pneumococcal vaccine (PHiD-CV) was introduced in Iceland in 2011. Our aim was to assess the impact of PHiD-CV on pneumococcal serotypes and genetic lineages isolated from middle ear (ME) specimens, by comparing data from three years before (2009-2011; PreVac), to six years after (2012-2017; PostVac) vaccine implementation.

Methods:

All pneumococci isolated from ME specimens of children <7 years old, submitted from health care facilities in the greater Reykjavik area (2/3 of Icelandic population), from 2009-2017 were included (n=976). Whole genome sequencing (WGS) was done on every other isolate from 2009-2014 (n=441). All isolates were serotyped using PCR and/or WGS, and multilocus sequence types (ST) were extracted from the WGS data. STs assigned to clonal complexes (CC) using Phyloviz.

Results:

The annual number of pneumococcal isolates decreased from 197 in 2009 to 23 in 2017. Serotypes included in PHiD-CV (VT) decreased from PreVac (n=399; 16.8/1000 children) to PostVac (n=102; 4.2/1000) while serotypes not included in PHiD-CV (NVT) increased from PreVac (n=144; 6.1/1000) to PostVac (n=331; 13.7/1000). The most prevalent NVTs PostVac were serotypes 15B/C, 6C, 6A, 23A and 19A. Isolates of serotypes 6C (n=1; 0.04/1000 PreVac and n=41; 1.7/1000 PostVac, mostly CC315/ST386) and 23A (n=2; 0.1/1000 PreVac and n=22; 0.9/1000 PostVac, mostly CC439/ST42) were double locus variants of VT lineages.

Conclusion

PHiD-CV vaccination has led to a reduction in ME specimens, pneumococci recovered from the ME and VTs. The increase of pneumococcal clones expressing NVTs, such as CC315/ST386, may indicate capsular switching events and requires additional monitoring in the future.
Background and Aims:

Since 2004 multiresistant isolates of serotype 19F, CC320, have been the most prominent penicillin non-susceptible pneumococci, (PNSP) in Iceland. In 2010, the last year prior to implementation of 10-valent vaccine (PHiD-CV) into childhood vaccination program, they represented almost a third of all pneumococcal isolates. The aim was to follow the epidemiology of pneumococci of serotype 19F, 2011-16.

Methods:

All PNSP isolates (except from nasopharynx and throat) from patients, identified in 2011-2016 were included (except repeat isolates within 30 days). Analyses were performed at the Department of Clinical Microbiology, Landspitali University Hospital, serving the greater capital area (about 2/3 of the Icelandic population) and as reference laboratory for the whole country. Serotyping was done using agglutination and/or PCR. Whole genome sequencing (WGS) was done on selected isolates from 2009-14.

Results:

There were 295 PNSP isolates of serotype 19F, or 62.4% of all PNSP (2011: 118 (80.3%), 2016: 13 (22.0%)). In 2011, 77.1% of the isolates were from children <7 year old but in 2016 7.7% (only one child), most from middle ear. In these years 22.9% and 92.3% were from adults, respectively, most from lower respiratory tract. Penicillin MICs ranged 0.094-8.0 mg/L, most commonly (27.5%) 2.0 mg/L, and were in concordance with the penicillin binding-proteins and ribosomal sequence-types. All multi-resistant isolates were of CC236/271/320 (single- or double-locus variants of Taiwan19F-14).

Conclusion

Vaccination has almost eliminated the multiresistant 19F clone in children. Reduction in their number is more than two fold in adults where it is still found, mostly in specimens from lower respiratory tract.

ISPPD-0616
PNEUMOCOCCAL VACCINATION IN ICELAND: THE EFFECT ON PNEUMOCOCCI ISOLATED FROM HEALTHY CHILDREN ATTENDING DAY CARE CENTRES
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Background and Aims:
The 10-valent pneumococcal vaccine (PHiD-CV) was introduced in Iceland in 2011. Our aim was to assess the effect of PHiD-CV on pneumococcal serotypes and genetic lineages carried by healthy children attending day care centres by comparing data from three years before (2009-2011; PreVac) to six years after (2012-2017; PostVac) vaccination.

Methods:

Nasopharyngeal swabs were collected annually (March, 2009-2017), from children 1-6 years old attending 15 DCCs in the greater Reykjavik area, for pneumococcal culture and serotyping. Whole genome sequencing (WGS) was done on every other isolate from 2009-2014 (n=987). All isolates were serotyped using latex agglutination and/or PCR and/or WGS. Multilocus sequence types (ST) were extracted from the WGS data and STs were assigned to clonal complexes (CC) using Phyloviz.

Results:

Overall, 4473 children were sampled, yielding 3020 pneumococcal isolates. Carriage rates ranged from 50-73%. Serotypes included in PHiD-CV (VT) decreased from PreVac (n=446; 323.2/1000 samples) to PostVac (n=304; 98.4/1000) while serotypes not included in PHiD-CV (NVT) increased from PreVac (n=545; 394.9/1000) to PostVac (n=1725; 558.1/1000). The most prevalent NVTs PostVac were serotypes 23B, 6A, 15B/C, 19A and 6C. Isolates of serotypes 23B (n=1; 0.7 PreVac and n=152; 49.2/1000 PostVac, mainly CC439/ST439) and 6C (n=9; 6.6/1000 PreVac and n=138; 44.6/1000 PostVac, CC315/ST386) belonged to lineages related to VTs.

Conclusion

Considerably fewer children carried pneumococci of VTs following PHiD-CV implementation; however, due to serotype replacement of NVTs the overall carriage rate remained unchanged. VT lineages expressing NVTs, such as the multidrug resistant CC315/ST3866C, which may represent a capsular switching event, will require further monitoring.

Background and Aims:

The 10-valent pneumococcal vaccine (PHiD-CV), which uses Protein-D (PD) from H. influenzae as a conjugate, was introduced to the childhood vaccination schedule in Iceland in 2011. The hpd gene, coding for PD, is well preserved, but cannot be found in all strains. The aim was to evaluate the impact of vaccination on H. influenzae colonizing healthy children attending day care centers (DCC), and in middle ear (ME).
Approximately 500 nasopharyngeal swabs were collected annually (March, 2009, and 2012-2017), from healthy children attending 15 DCC in the greater Reykjavik area. In addition, all samples from ME (from 2012-2016) sent to the Department of Clinical Microbiology, Landspitali University Hospital, serving the greater Reykjavik area, were used. *H. influenzae* was cultured using standard methods, and the *hpd* gene detected with PCR.

**Results:**

A total of 3,603 DCC samples yielded 2,574 *H. influenzae* isolates. The carriage rate was 86.9% in 2009 and 61.5%, 73.5%, 65.2%, 77.9%, 75.2%, and 58.9% in 2012-2017, respectively. A total of 6,230 ME samples yielded 1,541 *H. influenzae* isolates. The annual number of ME samples was 966, 926, 951, 849, 894, 687, 452, and 505 in 2009-2016, respectively. However, there were no changes in the proportion of *H. influenzae* positive samples. There was no change in the proportion of *hpd* negative isolates, between children born after the initiation of the vaccine and those older, in neither sample groups.

**Conclusion**

The PHid-CV reduced the number of samples received from ME, but did not increase the proportion of *hpd* negative isolates.

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**ISPPD-0568**

**ESTIMATED DISEASE PREVENTED AND LIVES SAVED: A DECADE OF PNEUMOCOCCAL CONJUGATE VACCINATION IN DENMARK**


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**Background and Aims:**

The 7-valent Pneumococcal Conjugate Vaccine (PCV7) was introduced in Denmark in 2007 and was replaced by PCV13 in 2010. We estimated the number of cases and deaths due to invasive pneumococcal diseases (IPD) prevented after the introduction of PCVs.

**Methods:**

We analyzed trends in confirmed IPD cases reported to the National Laboratory Surveillance from 1994 to 2016. Deaths were attributed to IPD if they occurred within 30 days of the diagnosis. Controlling for harmonic variations unrelated to the vaccine, we estimated vaccine-associated declines in cases and deaths using a hierarchical Bayesian regression approach. The overall and serotype-specific number of cases and deaths prevented by PCV7/13 were estimated from the model in each year and stratum.

**Results:**

Approximately 1000 cases and 150 deaths due to IPD were seen annually in the pre-PCV years, as compared to 750 cases and 110 deaths annually in the post-vaccine period. In 2016 we estimated that PCV13 prevented approximately 400 cases of IPD, which resulted
from a reduction of 600 cases caused by PCV13 serotypes and an increase of >150 cases caused by non-PCV serotypes. Overall, between 30-70 deaths annually are prevented by the introduction of PCV13.

**Conclusion**

PCVs have had a major impact on the observed morbidity and mortality related to IPD due to vaccine serotypes ten years after the introduction of the first PCV in Denmark.

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**ISPPD-0476**

**GLOBAL LANDSCAPE OF PNEUMOCOCCAL CONJUGATE VACCINE (PCV) IMPACT STUDIES: EVIDENCE AVAILABILITY AND POLICY IMPLICATIONS**

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**Background and Aims:**

Current national immunization programs use different PCV products (PCV10/PCV13) in a variety of schedules (3+1/3+0/2+1). Evaluation of factors affecting PCV impact may guide future policies but there may be gaps in key impact data availability.

**Methods:**

We characterized published and ongoing PCV10/13 impact studies globally through June 2017, by study location, health (invasive pneumococcal disease (IPD), pneumonia, carriage, mortality, herd effects) and economic outcomes assessed, and vaccine product and schedule. Data were obtained from VIEW-hub, a free online database that systematically tracks these data.

**Results:**

Of 141 countries using PCV10/13, 77 (55%) assessed impact on a health outcome: SEAR=3/4 (75%), AMR=16/25 (64%), EUR=26/42 (62%), AFR=18/38 (47%), WPR=9/17 (53%) and EMR=5/15 (33%). Of 58 Gavi-eligible countries using PCV, 26 (45%) evaluated health impact. Of 63 middle-income countries, 32 (51%) introduced PCV of which 17 (53%) evaluated health impact. Pneumonia (n=52 countries) and IPD (n=54 countries) were the most frequently assessed; 43 countries examined herd effects. Among countries measuring health impact, 55 (71%) use PCV13, 18 (23%) use PCV10, and 4 (5%) both; 65 (84%) use a 3-dose schedule (n=40 [52%] 2+1, n=25 [32%] 3+0). Of 63 countries that evaluated economic impact, 48 (76%) assessed cost-effectiveness or cost-utility, 15 (24%) were Gavi-eligible, 17 (27%) were middle-income, and only 2 (3%) were lower-middle-income.

**Conclusion**

PCV impact studies are accruing globally; quality was not assessed. Few economic impact evaluations were found for Gavi and lower-middle-income countries which may inform decisions around sustainability of self-financed PCV programs for Gavi-transiting countries and introduction.

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**ISPPD-0541**
Background and Aims:

WHO recommends including PCV in routine immunization programmes, using either a 2+1 or 3+0 regimen. Currently, PCV10 or PCV13 are used in 151 countries. We sought to evaluate if evidence supports a particular product or schedule choice.

Methods:

The PCV Review of Impact Evidence (PRIME) systematically reviewed studies evaluating PCV10 and PCV13 impact on vaccine-type (VT) carriage prevalence, VT invasive disease incidence, pneumonia incidence, acute otitis media (AOM), mortality and immunogenicity in published literature from 01/01/1994-12/31/2016 plus ad-hoc and unpublished reports through 10/01/2017.

We abstracted serotype-specific responses, product, dosing schedule, previous PCV7 use, ages assessed, geographic location, pre-introduction prevalence/incidence, years since introduction, catch-up program, and statistical power, among others. Results from clinical trials, pre/post-introduction observational studies and case-control studies were included. We required 3+ years of PCV10/13 use for studies of indirect effects. We excluded studies in immunocompromised and special populations.

Results:

Of 12,715 articles screened, 192 met inclusion criteria, some having data for multiple product or dosing arms: immunogenicity n=119 study arms, carriage n=29, IPD n=39, pneumonia n=35, mortality n=18, AOM n=20. Study setting often correlated with product or schedule (e.g., 3+0 schedule primarily studied in Africa); data were sparse for some settings. Immunogenicity data for most serotypes were sufficient for meta-analyses to compare schedules and products. For the other outcomes, evidence was limited, from heterogeneous settings, and generated using dissimilar methods, requiring descriptive analyses.

Conclusion

Despite widespread use of PCVs and a growing evidence base of benefits, appropriately-designed studies to inform product and schedule choice remain sparse, especially for disease outcomes.
Background and Aims:

Understanding nasopharyngeal Streptococcal co-colonization dynamics is critical to understanding pneumococcal conjugate vaccine (PCV) impact.

Methods:

Nasopharyngeal samples were collected monthly from 892 Peruvian children age <3 years enrolled in a prospective cohort from 2009-2011. PCV7 was introduced in late 2009; vaccination dates were recorded for cohort members. A pilot study included 96 pneumococcal positive samples (culture and/or PCR) from both vaccinated and unvaccinated children to define patterns of colonization with pneumococcus and/or other Streptococcal species using molecular serotyping by microarray.

Results:

We detected pneumococcus and/or other Streptococcal species in 88/96 (92%) samples; 83/96 (86%) samples contained at least one pneumococcal serotype. Co-colonization with >1 Streptococcal strain occurred in 30/96 (31%) samples; co-colonization with >1 pneumococcal serotype occurred in 13/96 (14%) samples. PCV7 vaccine types (VT) were present in 22/96 (23%) samples, including 18/68 (26%) samples from unvaccinated children and 4/28 (14%) samples from children vaccinated with ≥1 dose (p=0.286). When present, PCV7-VT were the sole or dominant (>70% total abundance) species in 20/22 samples. Non-vaccine serotypes, non-typeable strains, and other Streptococcal species were detected in 46/96 (48%), 23/96 (24%), and 20/96 (21%) samples, respectively. 35/96 (36%) samples contained a resistance marker associated with a mobile genetic element. 24/25 individuals with multiple longitudinal samples demonstrated changes in carriage and co-colonization over time, indicating a dynamic nature of colonization.

Conclusion

Co-colonization with pneumococcus and other Streptococcal species was common in this initial study. We will apply this approach to study co-colonization dynamics and the impact of PCV7 in the entire cohort.
Background and Aims:

Pneumococcal upper respiratory infections (URI) have declined due to vaccine related serotypes (ST) post introduction of the 13-valent pneumococcal conjugate vaccine (PCV13). This pediatric pneumococcal multicenter study analyzed otitis media, sinusitis and mastoiditis pneumococcal infections from 2014-2016.

Methods:

Patients were identified from a prospective surveillance study database containing pneumococcal infections data from 8 United States children’s hospitals since 1993. STs were assigned using Quellung reaction. Fisher’s exact was used for analysis; P<0.05 was considered significant.

Results:

362 patients were identified (Table). PCV13 STs caused 19% of the otitis media and sinusitis infections vs 71% of the mastoiditis cases (p<0.0001). Among 329 patients with known vaccine status, 63% with a PCV13 isolate vs. 83% with a non-PCV13 ST isolate had received >2 doses of the PCV13 vaccine (p=0.001).

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Otitis Media n=316</th>
<th>Sinusitis n=22</th>
<th>Mastoiditis n=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (median, range)</td>
<td>1.7, 0-25.4</td>
<td>4.4 (0.9-16.5)</td>
<td>1.9, 0.1-12.3</td>
</tr>
<tr>
<td>PCV13 ST</td>
<td>58 (18%)</td>
<td>5 (23%)</td>
<td>17 (71%)</td>
</tr>
<tr>
<td>Top PCV13 ST</td>
<td>3 (7%), 19A (6%)</td>
<td>19F (14%), 19A (9%)</td>
<td>3 (29%), 19F (29%), 19A (13%)</td>
</tr>
<tr>
<td>Top non-PCV13 ST</td>
<td>35B (17%), 15B (9%), 23B (9%)</td>
<td>35B (27%), 23A (9%)</td>
<td>35B (13%)</td>
</tr>
<tr>
<td>&gt; 2 PCV13 doses</td>
<td>82%</td>
<td>57%</td>
<td>63%</td>
</tr>
<tr>
<td>Penicillin MIC ≤ 2</td>
<td>92%</td>
<td>69%</td>
<td>86%</td>
</tr>
<tr>
<td>Ceftriaxone MIC ≤ 1</td>
<td>98%</td>
<td>92%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Conclusion

ST35B has emerged an important serotype associated with pneumococcal URIs. STs 3 and 19A/F predominated as causes of mastoiditis, while otitis media and sinusitis mainly were caused by non-PCV13 serotypes suggesting STs 3 and 19A/F remain more likely to cause mastoiditis in an era when non-PCV13 serotypes predominate as a cause of otitis media and sinusitis.
Background and Aims:

The heptavalent pneumococcal conjugate vaccine (PCV7) was introduced in Japan in 2010 and switched to 13-valent vaccine (PCV13) in 2013. The incidence of invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP) in children declined after the introduction of PCV7. The aim of this study was to clarify the epidemiological changes of IPD and PP after the introduction of PCV13 in Japan.

Methods:

To determine the precise incidence of IPD in Chiba prefecture, we have conducted a surveillance system since 2007. We also implemented the survey of community-acquired pneumonia (CAP) in children in Chiba-city. Serotype of pneumococcal strains isolated from blood samples of IPD patients and sputum samples of PP patients were analyzed.

Results:

The highest annual incidence rate of IPD among children <5 years of age during the study period was 26.1 (in 2009) per 100,000; the corresponding lowest annual incidence rate was 6.7 (in 2014). PCV13 coverage among S. pneumoniae strains isolated from IPD and PP in 2012 was 43.8% and 37.5%, respectively. On the other hand, PCV13 coverage among S. pneumoniae strains isolated from IPD and PP in 2016 was 15.0% and 15.4%, respectively. Most prevalent serotype of IPD and PP in 2016 was 12F (ST4846) and 15A (ST63), respectively.

Conclusion

There were great reductions in IPD and PP following the introduction of pediatric vaccination program. The serotype distribution changed in IPD and PP from vaccine types to non-vaccine types. Continuous surveillance is necessary to follow this observed trend.
Methods:
We searched PubMed for citations reporting bacterial meningitis incidence/cases before and after the implementation of PCV7, PCV13 or PHiD-CV in NIPs in children <2 and <5 years old published between 01/01/2000 and 01/09/2017. The current abstract focuses on citations reporting PM incidence.

Results:
Of 111 publications selected for full text screening, 21 were included in the analysis. Impact of PCVs on overall PM incidence was most pronounced in children <2; the decrease ranged from 48% to 66% for PCV7, from 40% to 60% for PHiD-CV and from 43% to 44% for PCV13 compared to the pre-PCV era. In children <5 the impact was lower and varied across studies. An increase of PM cases caused by non-vaccine serotypes was observed in all age groups.

Figure. Flowchart of the literature search

Conclusion
PCV implementation in pediatric NIPs had a significant impact on PM, which was less pronounced than that on non-meningitis or overall IPD reported previously. Non-vaccine serotypes represent a major concern.

Funding: GlaxoSmithKline Biologicals SA

ISPPD-0293
RISK FACTORS FOR INVASIVE PNEUMOCOCCAL DISEASE (IPD) IN CHILDREN - A POPULATION BASED DATA LINKAGE STUDY
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Background and Aims:

Children with certain underlying medical conditions associated with increased risk of IPD have an additional dose of pneumococcal conjugate vaccine (PCV) recommended. We assessed prevalence and contribution to IPD burden of risk factors (RF) and impact of vaccination program strategy changes in at-risk children.

Methods:

We used a retrospective cohort of all live births between 2002 and 2012 in New South Wales, Australia, linked to IPD notifications, hospitalisations and deaths to compare incidence of IPD among children identified as being at-risk, from perinatal (birth) and hospital records, with others. Cox models were used to estimate hazard ratios (HR) for IPD for each risk factor category allowing calculation of population-attributable fractions. IPD incidence rates pre (2002-4) and post (2005-12) universal PCV were compared.

Results:

Among 1,109,216 children in the cohort, 75,069 (6.8%) had at least one of specified RF. Chronic respiratory (4%) and cardiac (1.2%) diseases were most common. IPD incidence rates were highest for asplenia, conditions causing immunosuppression, CSF leak and chronic liver disease (all >400 per 100,000 person-years) compared with no RFs (14 per 100,000 person-years). Overall ~20% of IPD in the population was attributable to RFs. Pre to post universal vaccination IPD incidence increased in children at highest risk (i.e. with HR: 11-40) compared to a 62% (95% CI: 55.4 to 67.8%) decline in those with no RFs.

Conclusion

Pneumococcal vaccine impact is substantially lower in those at highest IPD risk. Measures to increase compliance with additional vaccine recommendations in place for children with RFs would help narrow disparity.
Background and Aims:

In the US the 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in 2010. We compared the clinical characteristics of children, especially with respect to underlying conditions (UC), with IPD due to PCV13 v non PCV13 ST isolates from 2014 to 2016.

Methods:

Children with IPD were prospectively identified at 8 US children’s hospitals from 2014-2016. Data were collected on case report forms and isolates sent to a central laboratory for serotyping. Chi-square was used to compare proportions.

Results:

Over the 3 years, 24% (86/360) isolates were PCV13 ST. The main sites of infection differed between the PCV13 vs non PCV13 isolates (bacteremia-15% vs 47%, pneumonia-40% vs 18%, meningitis-10% vs 16%, musculoskeletal-1% vs 6%). (p<0.001) An UC was significantly (p<0.0001) more common among patients with IPD due to non PCV13 ST (147/274, 54%) compared with those with PCV13 ST IPD (16/86, 19%). The most common UCs among patients with non PCV13 ST IPD were leukemia (n=34), genetic (n=19), other malignancies (n=14), cardiac (n=13), hemoglobinopathy (n=11) and central nervous system or renal (n=10 each). The most common non PCV13 ST isolates (n,% of children with UCs) were: 35B (36,35%), 23B (29, 66%), 33F (23, 39%) and 22F (20, 35%). Patients with ST3 IPD were less likely to have any UC (1/33) than those with ST19A (9/24) or 19F (5/20). (p< 0.001)

Conclusion

IPD caused by non PCV13 ST isolates were more likely associated with an UC than IPD due to a PCV13 ST isolate adding to the challenge of further preventing IPD by vaccines.
Nasopharyngeal swabs were collected from 52 HIV-infected children before and after vaccination (6 months) with 7-valent pneumococcal conjugated vaccine (PCV7) in 2013. The specimens were cultured on Blood Agar media for isolating \textit{S. pneumoniae}. Serotyping was performed by sequential multiplex PCR. Meanwhile, disk diffusion was conducted to measure antibiotic susceptibility of isolates.

Results:

Prevalence of \textit{S. pneumoniae} carriage before vaccination was 50\% while prevalence after vaccination was 42\%. Before vaccination, serotype 34 was most common serotype (6\%) followed by 6A, 6C and 16F (4\% each). Most isolates were susceptible to Penicillin (96\%) followed by erythromycin, clindamycin, and chloramphenicol (93\% each). Sulphamethoxazole/trimethoprim was less susceptible among tested antibiotics (79\%). To date, serotyping and antibiotic susceptibility confirmation for post vaccination are ongoing.

Conclusion

Non vaccine serotypes were most common serotype colonizing nasopharynx in HIV-infected children. Among all antibiotics, Sulphamethoxazole/trimethoprim was less susceptible to \textit{S. pneumoniae} carried by HIV-infected children.

ISPPD-0393
PNEUMOCOCCAL SEROTYPES PRE AND POST PCV10 VACCINE INTRODUCTION INTO ROUTINE IMMUNIZATION PROGRAM IN UGANDA, 2011 - 2016
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\textsuperscript{2}Mulago National Referral Hospital, Paediatrics, Kampala, Uganda
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\textsuperscript{4}Uganda National Expanded Programme on Immunization, Immunization, Kampala, Uganda

Background and Aims:

Disease surveillance systems are important to inform decision-making and document impact of new vaccines for sustainability purposes. Uganda introduced pneumococcal conjugate vaccine (PCV10) into its routine immunization program in April 2013 with national roll out in January 2014. We aim to show the impact three years since introduction.

Methods:

A cross sectional study using Pediatric Bacterial Meningitis (PBM) sentinel surveillance system. A child < 5 years admitted with suspected PBM between 1\textsuperscript{st} January 2013 and 31\textsuperscript{st} December 2016 was enrolled. A Cerebral spinal fluid was collected, culture and sensitivity done and positive isolates sent to NICD, South Africa for serotyping. An analysis of serotypes detected pre (2011-2013) and post (2014 – 2016) PCV10 introduction was conducted.

Results:

4,799 cases were enrolled of which 2,797 (58\%) and 2,002 (42\%) occurred pre and post PCV10 vaccine introduction respectively. The under one year old were commonly affected for both periods. Serotype 1 was a predominate vaccine serotype pre vaccine period while 19F was on the increase post vaccine period, figure 1. A 70\% (77 serotypes vs 23) reduction in the total number of vaccine PCV10 serotypes three years post introduction is observed.
Conclusion

A reduction in PCV10 vaccine serotypes is observed within three years of vaccine introduction into routine immunization program contributing to a reduction in PBM in Uganda a positive trend towards its impact. However a significant proportion of PBM is caused by non- vaccine serotypes an indication of ongoing replacement of serotypes.
medical conditions (aOR=0.5, p<0.001). HIV status did not differ significantly between patients with PM and nmIPD.

Conclusion

Patients with PM tended to be younger, infected with a non-PCV serotype, had a longer duration of hospitalisation, and were more likely to die, than nmIPD patients. An elevated CFR was observed among patients with PM as well as patients with nmIPD, and further improvements in prevention and clinical management should be explored.

ISPPD-0254
COMPARING USE OF SURVEILLANCE DATA FOR PNEUMOCOCCAL MENINGITIS AND TOTAL INVASIVE PNEUMOCOCCAL DISEASE FOR ESTIMATION OF IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINE, SOUTH AFRICA, 2005-2016

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2University of Pretoria, School of Health Systems and Public Health - Faculty of Health Sciences, Pretoria, South Africa
3National Institute for Communicable Diseases, South African Field Epidemiology Training Programme, Johannesburg, South Africa
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5U.S. Centers for Disease Control and Prevention, Influenza Division, Atlanta, USA
6U.S. Centers for Disease Control and Prevention - South Africa, Influenza Program, Pretoria, South Africa
7National Institute for Communicable Diseases, Division of Public Health Surveillance and Response, Johannesburg, South Africa
8University of the Witwatersrand, School of Pathology - Faculty of Health Sciences, Johannesburg, South Africa

Background and Aims:

South Africa (SA) introduced seven-valent pneumococcal conjugate vaccine (PCV7) in 2009 and PCV13 in 2011. We aimed to determine whether the estimated impact of PCV was similar for pneumococcal meningitis (PM) and total invasive pneumococcal disease IPD (tIPD) in SA.

Methods:

We conducted national, laboratory-based surveillance for tIPD during 2005-2016. We estimated and compared rates (cases per mid-year population) of PCV13 and non-PCV13 serotype disease among tIPD and PM in individuals aged <5 and ≥5 years, and compared these rates between the 2005-2008 pre-PCV introduction period and 2016 as percentage differences.

Results:

During 2005-2016 we enrolled 45,853 tIPD cases; 17,251 (38%) were PM. Among children aged <5 years, no significant difference (p=0.2) was observed between the percentage reduction (2005-2008 vs 2016) of PCV13 serotype tIPD rates (-95%; 95%CI -96% to -93%) and that of PM (-96%; 95%CI -97% to -94%). Among individuals aged ≥5 years, this
percentage reduction was significantly different by syndrome (p=0.03) (tIPD: -75%; 95%CI: -77% to -73% vs PM: -79%; 95%CI: -82 to -76%). No significant difference (p=0.3) in the percentage increase of non-PCV serotype disease (p=0.3) between the two periods was observed by syndrome for all ages combined (tIPD: 27%; 95%CI 20-34% vs PM: 20%; 95%CI 10-31%).

Conclusion

Seven years post-PCV introduction, PM surveillance can be used to show similar reductions to tIPD in vaccine serotype disease in those <5 years, and increases in non-vaccine serotype disease in all ages. PM may slightly overestimate the impact of PCV on PCV13 serotype disease in individuals aged ≥5 years.

ISPPD-0197
THE IMPACT OF VACCINATION ON THE SITUATION OF IPD, CZECH REPUBLIC
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Background and Aims:

First conjugate pneumococcal vaccine registered in the Czech Republic was PCV7 in 2005. In following years PCV10 and PCV13 were registered and infants with underlying diseases were vaccinated. The conjugate pneumococcal vaccine was introduced into the National immunisation programme (NIP) for infants in 2010 in the scheme 3+1. Both vaccines are available for the NIP, but only PCV10 is fully covered by insurance system. In case of PCV13 there is co-payment paid by parents.

The surveillance database is bringing together the data from the National Reference Laboratory (NRL) for Streptococcal Infections and EPIDAT data.

Methods:

The surveillance of IPD started in the Czech Republic since 2008 and the EU case definition of IPD was adopted. The typing of S. pneumoniae was performed in the NRL by the classical Quellung reaction and from 2013 by the PCR method.

Results:

Seventeen cases were reported in vaccinated patients, with an increase in vaccinated adults, and the age distribution was as follows: five cases in 1-4-year-olds, three cases in 5-9-year-old children, three cases in adults aged 40-64 years, and six cases in the age group 65 years and over. Three cases were reported in vaccinated children under five years of age and were caused by a serotype included in the vaccine.

Acknowledgements

Supported by Ministry of Health of the Czech Republic, grant nr.17-29256A. All rights reserved.

ISPPD-0340
SEROTYPE DISTRIBUTION OF INVASIVE STREPTOCOCCUS PNEUMONIAE STRAINS IN ≥5 YEARS OLD IN QUEBEC, 2010-2016
B. Lefebvre1, P. De Wals2, G. Deceuninck3, I. Martin4, W. Demczuk4, F. Markowski5,
Background and Aims:

The Quebec provincial invasive pneumococcal disease (IPD) surveillance program was based on a sentinel network consisting of 21 hospitals in addition to strains from every children <5 years old. In 2014, the program was converted to a universal program in order to increase accuracy.

Methods:

All invasive Streptococcus pneumoniae strains isolated from patients ≥5 years old through a sentinel network (2010 to 2016) and from all hospitals (2014 to 2016) were analyzed and compared. Serotypes were determined by Quellung reaction.

Results:

By 2016, the 5 most frequent serotypes were 22F (13%), 3 (11%), 19A (9%), 9N (6%) and 15A (6%) in ≥5 years old from all hospitals. Proportion of PCV-13, additional PPV-23 serotypes and NVT (non-vaccine serotype) was 26%, 36%, 38%, respectively in the ≥65 age group.

In 2014-2016, the proportion of NVT was higher in sentinel than in non-sentinel sites for the 5-19 years old group (44 vs 28%) whereas it was respectively 32% and 36% in the ≥65 age group.

A decrease in PCV-13 serotypes was observed between 2010 and 2016 while NVT and additional PPV-23 serotypes increased, especially among patients from 5-19 years old from sentinel sites.

Conclusion

The overrepresentation of pediatric patients with immunodeficiency in the sentinel system may be responsible of higher proportion of NVT observed in this age group in the sentinel sites. Due to approval of PCV-13 vaccine in adults and changing serotype distribution, extended surveillance of circulating serotypes in this population is important to maintain.

Acknowledgements

This work was partially supported by Pfizer.
Background and Aims:

Senegal introduced 13-valent pneumococcal conjugate vaccine (PCV13) in October 2013, at 6, 10, and 14 weeks of age. We utilized hospital administrative data to understand the burden of pneumonia before and after PCV introduction.

Methods:

From October 2010–October 2016, hospitalization data for clinical pneumonia in children aged <5 years was abstracted from admission logbooks at Albert Royer Children’s Hospital, a large tertiary pediatric hospital in Dakar. We used a set of predetermined keywords to define included cases. We assessed PCV13 impact through an interrupted time series analysis, comparing cases before and after PCV introduction, accounting for seasonality; the initial PCV uptake period (October 2013–September 2014) was excluded.

Results:

From October 2010–October 2016, 1,836 hospitalized pneumonia cases occurred in children <5 years. Before PCV introduction, an average of 104 pneumonia cases in children <11 months and 228 cases among children 12–59 months occurred annually. Post-PCV introduction, an average of 93 pneumonia cases among children <11 months and 175 cases among children 12–59 months occurred annually. In children <11 months, a small, significant reduction was observed post-PCV13 (-3.8%, p < 0.05). In children 12–59 months, a small, significant decline occurred prior to PCV introduction; post-PCV introduction cases continued to decline, but not significantly.

Conclusion

We were able to use data from one hospital to detect a small, but significant reduction in pneumonia hospitalizations two years post-PCV introduction in infants; the same trend was not measurable in children 12–59 months.

ISPPD-0564

CONTINUED SURVEILLANCE OF INVASIVE PNEUMOCOCCAL DISEASE IN AFRICAN COUNTRIES IS NEEDED TO GUIDE OPTIMAL VACCINE DESIGN

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²National Institute for Communicable Diseases,
Background and Aims:

Despite the success of PCVs, invasive pneumococcal disease (IPD) remains an important health priority with an increasing proportion of IPD caused by non-vaccine serotypes (NVTs). We investigated the changes in prevalent serotypes causing IPD and identified underlying lineages among children ≤2yr surrounding PCV introductions in South Africa, Malawi and The Gambia, drawing comparisons with the USA.

Methods:
Randomly selected invasive isolates (Table 1) were whole-genome sequenced. Serotype and lineages were assigned using SeroBA and kmer-based genome-wide similarity, respectively.

Results:
VT disease decreased after PCV13 in each country, and NVTs became the major cause of IPD in children within 2-5 years (Table 1). In the collection of isolates collected 2-5 years after PCV13 introduction, the top-five serotypes varied between countries, with only serotypes 12F and 15B/15C common to South Africa (2013-2014), The Gambia (2013-2014), and the USA (2012). The lineages associated with the top-five serotypes also differed between the USA and African countries, except lineage GPSC8, which accounted for 96% (54/56) of the serotype 8 pneumococci in South Africa and 100% (34/34) of serotype 33F in the USA. Following PCV7/PCV13 introduction, serotype diversity in South Africa, Malawi and The Gambia showed an increasing trend over the collection period.

Conclusion

We show differences in serotypes and lineages between countries. Compared to the pre-PCV period when only a few VTs were predominant, increasing serotype diversity suggests a larger number of serotypes circulating with the same relative distribution post-PCV. Continued surveillance is needed to help guide future vaccine formulation.
Table 1. The prevalent serotypes causing invasive pneumococcal disease in children ≤ 2-year-old from the USA, South Africa, Malawi, and The Gambia.

<table>
<thead>
<tr>
<th>Country</th>
<th>USA</th>
<th>South Africa</th>
<th>Malawi</th>
<th>The Gambia</th>
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<td>n</td>
<td>674</td>
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</table>

**Source**

<table>
<thead>
<tr>
<th>Source</th>
<th>Blood</th>
<th>CSF</th>
<th>Other sites</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>626</td>
<td>31</td>
<td>17</td>
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<tr>
<td></td>
<td>916</td>
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<td>108</td>
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<td></td>
<td>117</td>
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<td>28</td>
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</table>

**Vaccine period**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV7</td>
<td>2001-2009</td>
<td>2010-2011</td>
<td>-</td>
<td>2010-2011</td>
</tr>
</tbody>
</table>

**Five most prevalent serotype**

<table>
<thead>
<tr>
<th>Pre-PCV</th>
<th>14, 18C, 19F-4 6A/6B/9V</th>
<th>14, 23F, 6B, 19F</th>
<th>5′ 23F, 6B′ 6A, 1</th>
<th>1, 5, 14′ 23F, 6B</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV7</td>
<td>19A, 7F, 22F, 33F, 15B/C</td>
<td>19A, 6A, 14, 19F, 23F</td>
<td>-</td>
<td>1, 5, 12F, 6B</td>
</tr>
</tbody>
</table>

**Serotype diversity (95% confidence interval)**

<table>
<thead>
<tr>
<th>Last year of pre-PCV (baseline)</th>
<th>0.87 (0.83 to 0.91)</th>
<th>0.91 (0.89 to 0.92)</th>
<th>0.84 (0.73 to 0.94)</th>
<th>0.80 (0.64 to 0.96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last year of PCV7</td>
<td>0.79* (0.74 to 0.84)</td>
<td>0.93* (0.91 to 0.95)</td>
<td>-</td>
<td>0.92* (0.87 to 0.98)</td>
</tr>
<tr>
<td>Last year of post-PCV13</td>
<td>0.94* (0.93 to 0.96)</td>
<td>0.95* (0.94 to 0.96)</td>
<td>0.95* (0.85 to 1)</td>
<td>0.93* (0.89 to 0.97)</td>
</tr>
</tbody>
</table>

*The non-vaccine serotypes were written in red. Serotypes < 2 isolates were not listed.

Serotype diversity was measured by Simpson’s index of diversity. The index ranged between 0 and 1. The greater the value, the greater the sample diversity. To test whether estimates of D were significantly different between post-PCV7/PCV13 era and pre-PCV7 period, p values were calculated by two tailed Welch’s tests. P < 0.05 is statistically significant and asterisked on the table.

ISPPD-0440
IMPACT OF UNIVERSAL VACCINATION WITH PNEUMOCOCCAL CONJUGATE VACCINE 13-VALENT (PCV13v) ON HOSPITALIZATIONS FOR INVASIVE PNEUMOCOCCAL DISEASE (IPD) IN CHILDREN FROM ROSARIO CITY, ARGENTINA

S. Lopez Papucci1, A. Badano2, M. Galicchio3, A. Chiossone1, G. Ensink1, A. Aletti1, P. Lopez Papucci1, A. Ernst2, S. Larini2, R. Sempio2, F. Pigozzi4, P. Cottet4, M. Regueira5, C. Sorhouet6

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2Hospital de Niños Victor J. Vilela, Laboratory, Rosario, Argentina

587
Background and Aims:

In January 2012 PCV13v was introduced in Argentina using 2+1 schedule and catch-up program until 2 yo. Vaccination coverage for 1st and 3rd doses were 96.6% and 85.3% in 2013, 87.6% and 82.3% in 2016 respectively. We used our pneumococcal surveillance program to analyze the effects of PCV13v on hospitalizations for IPD in Rosario Children Hospital, Argentina.

Methods:

We compared pre-vaccination (preVp) 2008-2011 and post-vaccination (postVp) 2013-2016 periods, including epidemiological, clinical, immunological and vaccination status data from those children admitted with IPD, also serotypes and antimicrobial susceptibilities of the strains isolated in both periods.

Results:

From preVp to postVp, hospitalizations rate/10^4 outcomes due to IPD decreased by 52% (95%CI: 10.3;74.3), 79.3% (40.3;92.8), 69.9% (37.4;85.5) and 51.3% (5.9;74.7) in children <1 yo, 1 yo, 2 to 4 yo and 5 to 12 yo, respectively. Hospitalization rates for pneumococcal uncomplicated pneumonia and empyema declined significantly 73.06% and 85.12%, 67.13% and 86.6% respectively in children <2 yo, 2 to 4 yo and 5 to 12 yo respectively. Hospitalization rate for meningitis decreased by 33.4%

PCV13v serotypes decreased from 91.04% in preVp to 46.15% in postVp (p<0.001).

IPD was detected in two immunocompetent and four hipogammaglobulinemic fully immunized children. Only one isolate (ST 19A) in meningitis was cefotaxime non-susceptible. Erythromycin resistance in pneumonia decreased from 29.4% in preVp to 16% in postVp.

Conclusion

From preVp to postVp, hospitalization rates due to IPD declined markedly in all pediatric ages. The largest reduction was observed in empyemas. PCV13v serotypes decreased significantly in postVp. Vaccine failure surveillance is mandatory.

ISPPD-0577
10 YEARS OF POPULATION-BASED SURVEILLANCE MEASURING THE IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINE ON INVASIVE PNEUMOCOCCAL DISEASE IN THE GAMBIA: EXTENDED FOLLOW-UP INCLUDING 2016
G. Mackenzie¹, P. Hill², D. Jeffries³, M. Ndiaye¹, I. Hossain¹, B. Adeshola¹, G. Lobga¹, Y. Olatunji¹, A. Odutola¹, R. Salaudeen¹, H. Badji¹, N. Ikumapayi¹, L. Ceesay⁴, D. Sowe⁵, K. Mulholland⁶, M. Knoll⁷, O. Levine⁸, S. Howie⁹, B. Greenwood¹⁰, T. Corrah¹¹
¹Medical Research Council Unit- The Gambia, Disease Control and Elimination, Basse, The Gambia
²University of Otago, Centre for International Health, Dunedin, New Zealand
³Medical Research Council Unit- The Gambia, Statistics, Fajara, The Gambia
Background and Aims:

We measured the impact of Gambia’s PCV programme which introduced PCV7 in Aug 2009 and PCV13 in May 2011.

Methods:

We used standardised clinical and laboratory criteria to conduct population-based surveillance for IPD among those aged 2 months and greater in the Basse demographic surveillance area. We have published results to the end of 2014 (Lancet ID 2016) and here we update our analysis with an additional 2 years of surveillance, including 2016.

Results:

We investigated 24,189 patients, identifying 350 cases of IPD. Counts of vaccine-type IPD in children have fallen steeply, including serotype 1 (Fig 1) while non-vaccine type IPD has increased slightly (Fig 2). The number of NVTs causing IPD has expanded. In those aged 5 years and greater vaccine-type IPD has fallen (Fig 3). Comparing incidence pre- and post-PCV, VT IPD in young children has fallen 93% with non-significant changes in NVT IPD and an overall reduction in IPD of 76%.
Conclusion

The impact of PCV on IPD in The Gambia is substantial. Indications of herd protection in older children and adults are limited by small numbers of events and will be strengthened with additional observation in 2017.

ISPPD-0323

PNEUMOCOCCAL AND OTHER BACTERIAL MENINGITIS IN CHILDREN IN URBAN NEPAL 2005-2016

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³Patan Academy of Health Sciences, Microbiology Laboratory, Lalitpur, Nepal
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⁵NIHR Oxford Biomedical Research Centre, NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom
⁶University of Otago, Department of Pathology, Christchurch, New Zealand

Background and Aims:

Streptococcus pneumoniae (pneumococcus), Haemophilus influenzae type b (Hib), Neisseria meningitidis (Nm) are major causes of childhood meningitis. Nepal introduced Hib vaccine in 2009 and pneumococcal conjugate vaccine (PCV10) in 2015. We examined meningitis pathogens in children admitted to Patan Hospital in Kathmandu, Nepal.

Methods:

From 2005-2006 and 2010-2016, data were collected from all admitted children <14 years with suspected invasive bacterial disease. From 2007-2009, only those with any positive culture or >5 white blood cells in cerebrospinal fluid (CSF) were recorded. CSF was evaluated for pneumococcus, Hib, and Nm by culture/PCR; for Hib (latex) and pneumococcus (BinaxNOW) by antigen testing; and by Quellung for pneumococcal serotype.

Results:

30% (4150/13,756) of hospitalized children had CSF sampled. Of these, 15% (600/4150) met WHO “probable bacterial meningitis” criteria. Of hospitalized children, 8% (1130/13,756) had meningitis discharge diagnoses based on clinical/CSF parameters. Pneumococcus, the
commonest CSF pathogen, was found in 5% (52/1130) of meningitis cases; only 36% (19/52) were detected by CSF culture. Of 28 pneumococci isolated in CSF/blood from meningitis cases, 39% (11/28) were PCV10 serotypes.

In the 16 months since PCV10 use, 7 CSF were Binax-positive, all from PCV-unvaccinated children, while 0 were culture-positive, compared to 45 pneumococcal CSF-positive cases in the 124 months prior. Hib was identified in 1% (13/1130) of meningitis-diagnosed children; no cases were identified following Hib vaccine introduction. Nm was identified by culture/PCR in 7 children.

Conclusion

Early results show a decline in pneumococcal isolates from CSF. Ongoing monitoring of PCV10 impact on vaccine-type bacterial meningitis and residual serotype disease is important.

ISPPD-0156
TRENDS IN INVASIVE PNEUMOCOCCAL DISEASE IN MANITOBA, CANADA IN THE VACCINE ERA
R. Gieni1, S. Mahmud1
1University of Manitoba, Vaccine and Drug Evaluation Centre- Community Health Sciences, Winnipeg, Canada

Background and Aims:

We examined long-term serotype-specific trends in mortality and incidence of invasive pneumococcal disease (IPD) in Manitoba from 2001-2014, including a 2-year period during which the capital city of Winnipeg witnessed the largest ever-reported outbreak of IPD due to serotype 12F. We characterized the outbreak clone and determined its relationship to previously isolated 12F clones.

Methods:

IPD patients were identified using provincial reportable diseases data. Molecular typing and whole-genome sequencing techniques were used to characterize outbreak isolates and to compare them to isolates from outbreak and non-outbreak 12F cases.

Results:

In Manitoba, overall IPD rates have not decreased from 2001 to 2014 despite the implementation of 3 vaccination programs during this period. Pediatric vaccination utilizing protein conjugate vaccines (PCV) dramatically reduced vaccine type IPD, but this was offset by increases in IPD caused by non-vaccine serotypes and by serotypes found only in the adult-targeted 23-valent polysaccharide vaccine (PPV23). A high burden of disease impacts inner-city neighborhoods and northern rural regions of Manitoba. The Winnipeg outbreak 12F clone incorporated a newly identified gene cassette conferring macrolide resistance and further evolution during the course of the outbreak introduced additional quinolone resistance.

Conclusion

Increases in IPD caused by non-vaccine and PPV23-only serotypes is a serious concern. The dramatic drop in rates of IPD due to PCV-vaccine types suggests a limited utility of
targeting adults with PCV. The Winnipeg outbreak 12F clone has now spread to other jurisdictions replacing antibiotic sensitive 12F clones, and alarmingly some isolates have become multidrug resistant.

ISPPD-0704
USE OF STANDARDIZED INTERPRETATION OF CHEST RADIOGRAPHS TO IDENTIFY CHILDREN AND ADULTS WITH BACTERIAL PNEUMONIA—GUATEMALA, 2016–2017
H.G. Maldonado1, I.L. Contreras1, M.M. Vidal2, N.M. Pinillos3, C. Ruiz4, N. Sandoval5, M.A. Melgar6
1Universidad del Valle de Guatemala, Centro de Estudios en Salud, Guatemala, Guatemala
2Hospital Roosevelt, Pediatrics, Guatemala, Guatemala
3Hospital San Juan de Dios, Pediatrics, Guatemala, Guatemala
4Hospital San Juan de Dios, Internal Medicine, Guatemala, Guatemala
5Hospital Roosevelt, Internal Medicine, Guatemala, Guatemala

Background and Aims:

Bacterial pneumonia is an important cause of morbidity and mortality worldwide. Streptococcus pneumoniae (SN) conjugated vaccines led to a decrease in pneumonia and invasive pneumococcal disease (IPD) among children and unvaccinated adults in developed countries. It is not known whether protection will be observed in low-and middle-income countries. We aimed to use of the World Health Organization standardized interpretation of chest radiographs (CXRs) to identify subjects with bacterial pneumonia.

Methods:

From March 2016 to September 2017, we conducted surveillance of pneumonia and IPD in two hospitals in Guatemala. CXRs images were sent to three standardized readers through email link, interpretation included ‘endpoint consolidation’, ‘other infiltrate’, or ‘normal’ findings. We enrolled cases after obtained written consent. If pleural fluid were available we performed RT-PCR for SN, Antigen urinary detection for SN was performed in > 15 years old.

Results:

Overall, 2196 screenings were performed, among 242 (11%) were suspected IPD and 1954 (89%) were pneumonia; 609 (31%) met criteria for radiological pneumonia, and 487 (25%) were enrolled. 75 (15%) had pleural effusion, among 25 were tested by RT-PCR and 13 (64%) were born after the date of implementation of the conjugate vaccine in Guatemala, among 158 (50%) have received at least one dose. 121 (24.8%) patients were older than 15 years, and 6/60 (10%) had positive antigen detection for SN.

Conclusion

Standardized evaluation of CXRs is useful to identify bacterial pneumonia in both children and adults. SN is a frequent cause of pneumonia in admitted patients.

ISPPD-0015
IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINES ON SELECTED HEAD AND NECK INFECTIONS IN HOSPITALIZED ISRAELI CHILDREN
T. Marom1, S. Ovnat Tamir2
Background and Aims:

*Streptococcus pneumoniae* is a major pathogen of pediatric head and neck infections (HNIs), e.g. acute otitis media (AOM), acute mastoiditis (AM), acute bacterial sinusitis (ABS) and meningitis. The aim of the study was to characterize the epidemiology of pneumococcal HNIs (pHNIs) before, during, and after the introduction of pneumococcal conjugate vaccines (PCVs).

Methods:

Children 0-16 years of age who were hospitalized with HNIs in the Pediatrics Department in a general hospital between 1/1/2007-12/31/2014 were retrospectively identified. Study years were categorized according to the PCV introduction timeline: 2007-2008, ‘pre-PCV years’, 2009-2011, ‘transition years’, and 2012-2014, ‘post-PCV years’. pHNIs episodes were defined if pneumococcal culture or urine antigen was positive. Children who received ≥2 doses of PCV7/PCV13 were considered as "immunized". All other children were considered as "unimmunized".

Results:

HNIs accounted for 2.5-4.7% of the total admissions; 3-17% of them were pHNIs. 87 pHNI episodes were identified: AOM (n=42), AM (n=28) and meningitis (n=17). There was a downward trend in the overall incidence of HNIs, and particularly of pHNIs, in the post-PCV years. The average age and hospitalization duration of children with HNIs/pHNIs remained stable during the study years. In 2009-2010, pHNIs incidence sharply decreased, from 7 to 1.74/1,000 hospitalized children/year, due to ~55% reduction of pneumococcal AOM episodes. An additional decrease was observed in the post-PCV years (1.62/1,000 hospitalized children/year). Immunized children were less likely to present with pHNIs (p=0.001), but were more likely to undergo surgery (p=0.042).

Conclusion

We observed a reduction in pHNIs incidence after PCV program implementation.
We studied the incidence and susceptibility patterns of Spn in cultures from children with OM during the PCV era. Charts of children <8 years who presented with OM and had positive pneumococcal cultures during 1/1/2007-12/31/2014 were reviewed. Data recorded included demographics, pre-admission antibiotics, culture source, and antibiotic susceptibility tests. We compared the pre-PCV years (2007-8) with the transition years (2009-11) and the post-PCV13 years (2012-4).

Results:

We identified 134 children (76 boys, 57%) who contributed 162 pneumococcal cultures. There was a downward trend in the annual incidence rate of Spn cultures between the pre-PCV years, transition years, and post-PCV13 years: 11.12, 8.48 and 4.11/1000 hospitalized children/year, respectively (p=0.08, p=0.04). Had there been no interventions, and based on the 2007-2009 average, the observed over the expected Spn cultures ratio rates for 2010-4 were 0.59, 0.45, 0.40, 0.40 and 0.25, respectively. In parallel, the susceptibility of Spn strains to 4 commonly tested antibiotics significantly increased from the pre-PCV years to the transition years and the post-PCV13 years. In each period, Spn strains were penicillin sensitive in 37%, 51% and 100%; for erythromycin, 46%, 71% and 82%; for trimethoprim/sulfamethoxazole, 32%, 71% and 97%; and for ceftriaxone, 95%, 96% and 100%, respectively.

Conclusion

The introduction of PCVs significantly decreased the incidence rate of pneumococcal OM, and increased Spn susceptibility to common antibiotics.

Background and Aims:

*Streptococcus pneumoniae* is a leading cause of severe bacterial infections globally. WHO-AFRO coordinates and supports member states to implement, strengthen and expand invasive pneumococcal disease surveillance. Harare Central hospital is a sentinel site for paediatric bacterial meningitis (PBM) surveillance. In Zimbabwe, the pneumococcal conjugate vaccine (PCV 13) was introduced in July 2012.

**Aim:** To assess the trend in bacterial meningitis in children under 5 at Harare Children’s hospital over 6 years, 2011-2016

**Methods:**

PBM surveillance recruits children aged 0-59 months who meet the case definition. Data was extracted from the surveillance database from 2011 to 2016. Hospitalisation trend due to meningitis over same period was determined.

**Results:**
3725 cases were entered into the PBM database between 2011 and 2016. There were 143 culture-confirmed cases meningitis. *S.pneumoniae* was the commonest single organism isolated (63/143) followed by *H.influenza* (9/143). The commonest pneumococcal serotype isolated was 14 followed by serotype 6A/B. Non-PCV 13 strains were 18%.

The odds of getting pneumococcal meningitis post PCV introduction was 0.425 (95%CI 0.216-0.787) p- value = 0.0039

Conclusion

There is a significant reduction in the cases of pneumococcal meningitis seen at Harare Children’s hospital post PCV 13 introduction.

Acknowledgements: WHO, NICD South Africa, MOHCC
Background and Aims:

The 13-valent Pneumococcal Conjugate Vaccine (PCV13) was introduced into the universal childhood immunization schedule in Peru in 2015. The aim of this study was to determine the change in serotypes and antibiotic resistance of pneumococcal strains isolated from invasive pneumococcal disease (IPD) in children from Lima before and after introduction of PCV13.

Methods:

Multicenter, passive surveillance study from Nov-2016 to Oct-2017, in 6 hospitals and 5 private laboratories in Lima, in children less than 18 years with IPD. We compared the data with two previous similar surveillance studies conducted in 2006-2008 and 2009-2011 in the same setting. Antibiotic susceptibility was performed by E-test. Strains were serotyped by PCR.

Results:

204 S. pneumoniae isolates were recovered: 101 from 2006-2008, 58 from 2009-2011 and 37 from 2016-2017. The most prevalent diagnosis were pneumonia [48%(48/101), 52%(58/58) and 65%(37/57)] and meningoencephalitis [39%(39/101), 22%(13/58) and 14%(5/37)] in each period, respectively. After PCV13 introduction, 57% of all IPD cases were caused by vaccine-preventable serotypes. We observed an increase of serotypes 19A [4%(4/101), 9%(5/58) and 27%(10/37)] and 24F [0%(0/101), 3%(2/58) and 27%(10/37)] and a significant decrease of serotypes 14 and 6B (p<0.01). Resistance to macrolides (25%, 38% and 81%, p<0.001) and clindamycin (14%, 16% and 78%, p<0.001) increased over time. There was a trend to higher penicillin resistance rates in meningitis cases (46%, 50% and 60%).

Conclusion

The frequency of serotype 19A and 24F as well as the resistance to macrolides and clindamycin increased after PCV13 introduction. Additional follow up studies are necessary.
Background and Aims:
Invasive pneumococcal disease (IPD) is an important cause of infant morbidity and mortality. In Colombia, PCV10 has been administered since 2012. An increase in the prevalence of serotype 3 has been documented after the introduction of conjugate vaccines. Our objective is to describe the clinical, microbiological and epidemiological characteristics of serotype 3 in Bogotá Colombia.

Methods:
Ambispective case series study (2008 - 2017) among pediatric patients admitted to 10 hospitals in Bogotá with IPD. Patients with an isolation of S. pneumoniae serotype 3 were described.

Results:
There were 444 cases of IPD. The serotype was obtained in 302 (68%). The prevalence of IPD by S. pneumoniae serotype 3 is 10.5%(32 cases), the fourth in frequency after serotypes 14, 19 A and 1. 90.6%(29) of cases were in children under 5 years. 9.3% (3) were classified as meningitis, 12.5%(4) bacteremia and 78%(25) pneumonia, 6 had pleural effusion, There is an increase from 3.4%(4/116) in 2008-2011 to 11.8%(11/93) in 2012-2014 and 18.2%(17/93) in 2015-2017. An antibiogram was obtained in 27 non-meningeal isolates, of which 26 (96.2%) were susceptible to penicillin. The average hospital stay was 16.7 days (2 - 74), 46.8% (15) entered the ICU, with an average stay of 9.6 days (1 - 30). The mortality rate was 12.5%(4). All had pneumonia, while 3 of these were complicated.

Conclusion
The epidemiological characterization of IPD caused by S. pneumoniae serotype 3 shows a tendency to increase over time, with prolonged hospital stays and admission to the ICU.

ISPPD-0410
IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) ON
Background and Aims:

Pneumococcus is a leading cause of pneumonia. Zambia introduced PCV10 in July 2013 using a schedule of three doses at 6, 10, and 14 weeks of age. We evaluated the impact of PCV10 on pneumonia hospitalizations.

Methods:

We used discharge data from the largest pediatric teaching hospital in Lusaka to identify children aged <5 years hospitalized with pneumonia from January 2010-December 2016. ICD-10 codes were used to capture hospitalizations related to pneumonia, bronchiolitis (due to potential misclassification of pneumonia hospitalizations into this category) and injury (control condition). We used segmented Poisson regression analyses to measure the effect of PCV10 on monthly case counts for each outcome and age group, accounting for seasonality. We defined pre- and post-PCV10 periods as January 2010-December 2012 and from January 2014-December 2016, respectively.

Results:

Of 38,767 and 34,298 hospitalizations in children<5 years pre- and post-PCV10, pneumonia accounted for 6,373 (16.4%) and 3,870 (11.3%), respectively. Pneumonia hospitalizations declined 22% (95%CI: 18%–25%) annually for children <1 year and 31% (95%CI: 27%–35%) for children 1-4 years. No changes in bronchiolitis hospitalizations were observed after PCV10 introduction, while hospitalizations related to injuries declined by 30% (95%CI: 23%–36%) in children <1 year and increased 30% (95%CI: 23%–38%) for those 1-4 years. Post-PCV10, in-hospital mortality with a discharge code of pneumonia declined by 39% (95%CI: 28%–49%) for children 1-4 years.

Conclusion

PCV10 introduction had an impact on Pneumonia hospitalizations and pneumonia-associated deaths declined in Zambia, especially in children 1-4 years old.

Impact of 10-Valent Pneumococcal Conjugate Vaccine on Radiologically Confirmed Pneumonia Among Children in Mozambique

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2Centro de Investigação em Saúde de Manhiça, Mozambique
Background and Aims:

Mozambique introduced 10-valent pneumococcal conjugate vaccine (PCV10) in 2013 using a three-dose primary series at 2, 3 and 4 months of age without a catch-up. We evaluated PCV10 impact on radiologically confirmed pneumonia among children <2 years of age in Mozambique.

Methods:

We conducted longitudinal population-based surveillance for radiologically-confirmed pneumonia (using World Health Organization standardized definitions) among children hospitalized at Manhiça District Hospital. Incidence of radiologically-confirmed pneumonia was calculated using child-month at risk (CMAR) from Manhiça demographic surveillance system. Negative binomial regression model was used to measure the effect of PCV10 on radiologically confirmed pneumonia monthly incidence accounting for seasonality and pre-PCV10 trends. We defined pre-PCV period from 2010-2012 and post-PCV from 2014-2016; 2013 was excluded from the analysis to allow for vaccine uptake.

Results:

The incidence of radiologically-confirmed pneumonia per 1,000 children at risk went from 7.66 in 2010 to 0.95 in 2016. A reduction of 64.4% (95% CI: 32.9%-87.0%) in radiologically-confirmed pneumonia were observed in children <2 years of age after PCV10 introduction (Figure).

Conclusion

PCV10 introduction into the routine immunization program in Mozambique had a dramatic impact on pneumonia hospitalization among children.
both since 2008.

Results:

Of 803 identified publications, 46 reported VT-IPD after PHiD-CV/PCV13 vaccination. For the primary analysis, we identified 6 case-control or cohort studies with a robust description of cases. Only these 6 are included in this analysis, with 314 VT-IPD cases documented (Figure 2).

Conclusion

For several serotypes a trend towards more VT-IPD cases after only 1 dose, compared to 2 or 3 doses, was observed. This suggests that only 1 priming dose provides less protection
against VT-IPD than 2 or more doses. For serotype 19A, a reduction in case numbers was only seen after 3 doses of PCV, indicating 3 priming doses may be required for robust protection.

**Funding:** GlaxoSmithKline Biologicals SA

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**ISPPD-0186**

**PROPORTION OF REMAINING DISEASE FOLLOWING PNEUMOCOCCAL CONJUGATE VACCINE INTRODUCTIONS**

B. Mungall\(^1\), J. Nieto Guevara\(^2\), B. Hoet\(^3\)

\(^1\)GSK, Vaccines, Singapore, Singapore

\(^2\)GSK, Vaccines, Panama City, Panama

\(^3\)GSK, Vaccines, Wavre, Belgium

**Background and Aims:**

Pneumococcal conjugate vaccine (PCV) introduction has resulted in substantial reductions in vaccine type invasive disease (IPD). However, considerable variability in pneumococcal epidemiology and PCV programs worldwide remains, limiting comparisons between individual countries. We evaluated the trends in the proportion of disease due to non-vaccine types (NVT) and serotype 19A in developed countries.

**Methods:**

IPD data sets for children <5 and adults ≥65 years were identified by literature search/from publicly available surveillance reports until December 2016 as previously described.\(^1\)

**Results:**

Trends are graphically illustrated in Figures 1-2.

**Figure 1. Changes in NVT and serotype 19A in children <5 years in developed countries**

![Figure 1](image-url)
Figure 2. Changes in NVT and serotype 19A in adults ≥65 years in developed countries

* No prior PCV7 (licensed 7-valent vaccine) use
** Quebec data for ≥65 years

PHID-CV: 10-valent pneumococcal non-typeable Haemophilus influenzae (NTHi) protein D conjugate vaccine; PCV13: Licensed 13-valent vaccine.
Conclusion

In developed countries, NVT IPD has steadily increased in all countries in subjects <5 and ≥65 years old, except for Finland, where the increase has been slower. Serotype 19A continues to circulate in children, returning to levels before PCV7 introduction in some countries. In Finland, an increasing trend for serotype 19A in subjects <5 years has recently reversed. The proportion of 19A in older adults has remained low since PHiD-CV/PCV13 introduction, however, further surveillance is warranted to evaluate trends over the coming years.

Reference:

Funding: GlaxoSmithKline Biologicals SA

ISPPD-0269
COMPARISON OF PNEUMOCOCCAL CONJUGATE VACCINE (PCV) IMPACT ON INVASIVE PNEUMOCOCCAL DISEASE IN HIGH AND LOW INCIDENCE COUNTRIES
K.B. Oh1, B. Mungall2, B. Hoet3
1GSK, Vaccines, Bangkok, Thailand
2GSK, Vaccines, Singapore, Singapore
3GSK, Vaccines, Wavre, Belgium

Background and Aims:

To determine if PCVs provide similar disease reductions under different circumstances, we assessed the changes in the incidence of invasive pneumococcal disease (IPD) in <5-year-olds in countries stratified by the pre-PCV burden of IPD.

Methods:

IPD data sets for children <5 years, ≥2 years before any PCV and ≥3 years after PHiD-CV/PCV13 were identified by literature search and from publicly available surveillance reports until December 2016 as previously described. Latin American country data was derived from SIREVA II reports.2

Results:
Results are graphically illustrated in Figures 1-3.

Conclusion

The baseline incidence of total IPD appears to mildly influence the observed impact of PCVs in high income countries, but less so in Latin America. The impact of PCVs on serotype 19A was not related to the incidence of 19A IPD. Observed PHiD-CV/PCV13 impact is more likely to have been influenced by previous PCV7 use, surveillance systems, vaccination schedules and coverage thus making it difficult to predict vaccine impact for some serotypes such as 19A.
Figure 1. Total IPD (high income countries) post-PCV7 (A) and post-PHiD-CV/PCV13 (B)

Incidence rate ratios (IRR) were calculated and countries were stratified as low or high disease burden based on the median IRR for all countries. PCV7, PCV13: 7-12-valent pneumococcal conjugate vaccines; PHiD-CV: pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine.

Figure 2. Total IPD (Latin American countries) post-PHiD-CV/PCV13

Correlation coefficients calculated as \( \frac{\sum (x - \bar{x})(y - \bar{y})}{\sqrt{\sum (x - \bar{x})^2 \sum (y - \bar{y})^2}} \)
References:

Funding: GlaxoSmithKline Biologicals SA

ISPPD-0347
VIEW-HUB AT YOUR FINGERTIPS: REAL-TIME MONITORING AND EVALUATION OF PCV10/13 USE, COVERAGE, AND IMPACT
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¹Johns Hopkins Bloomberg School of Public Health, International Vaccine Access Center, Baltimore, USA

Background and Aims:
PCV10/13 has been widely introduced, using various products and schedules, in a diverse range of epidemiological settings. Its impact is being monitored in numerous studies. These data are essential to address policy-relevant questions on product choice and dosing.
schedule. We sought to collate this information, package it into presentation-ready visuals and facilitate its use to support and enhance PCV10/13 programs worldwide.

Methods:

We evaluated the number of countries using PCV10/13 and the number of health impact publications using the VIEW-hub website, a free, publicly-accessible interactive platform with real-time information on PCV10/13 use, product, coverage, and PCV10/13 economic and health impact studies. The VIEW-hub database includes PCV10/13 health impact studies identified from literature searches and ISPPD abstracts (or communication with investigators/sponsors for ongoing and unpublished studies), with details on study characteristics and outcomes evaluated.

Results:

The Table describes study characteristics of 491 studies evaluating PCV10/13 health impact in routine use settings included in VIEW-Hub.

Table: Number and Distribution of PCV10/13 impact studies

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>NUMBER OF STUDIES (% of studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gavi Status</strong></td>
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<tr>
<td>Gavi</td>
<td>94 (19%)</td>
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<tr>
<td>Non-Gavi</td>
<td>397 (81%)</td>
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<td><strong>Product</strong></td>
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<tr>
<td>PCV10</td>
<td>168 (34%)</td>
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<tr>
<td>PCV13</td>
<td>368 (75%)</td>
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<td><strong>Dosing Schedule</strong></td>
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<tr>
<td>2+1</td>
<td>298 (61%)</td>
</tr>
<tr>
<td>3+0</td>
<td>102 (21%)</td>
</tr>
<tr>
<td>3+1</td>
<td>84 (17%)</td>
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<tr>
<td><strong>Outcome</strong></td>
<td></td>
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<tr>
<td>IPD</td>
<td>220 (45%)</td>
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<tr>
<td>Pneumonia</td>
<td>159 (32%)</td>
</tr>
<tr>
<td>NP Carriage</td>
<td>129 (26%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>54 (11%)</td>
</tr>
<tr>
<td>Herd Effects</td>
<td>149 (30%)</td>
</tr>
</tbody>
</table>

Conclusion

There is substantial PCV10/13 health impact data on a range of syndromes. These data are available for use by decision makers and others to address PCV10/13 policy and use issues.

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ISPPD-0633
PNEUMOCOCCAL CARRIAGE AND SEROTYPES DISTRIBUTION PRE- AND POST-PCV10 VACCINATION CAMPAIGN IN ADJUMANI REFUGEE CAMPS, UGANDA


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Background and Aims:

Acute respiratory infections account for high morbidity and mortality in emergency settings. In 2014, MSF conducted a mass vaccination campaign (MVC) with PCV10 among children 6 weeks to 23 months in refugee settlements in Adjumani, Uganda. This presentation describes the impact of the MVC on the all-age pneumococcal carriage and serotype distribution.

Methods:

Three age-stratified, cross-sectional, community-based surveys were conducted in 3 refugee settlements in Adjumani, Uganda prior to and 9 months post-MVC; pneumococcal strains from nasopharyngeal (NP) samples were isolated and serotyped by the Quellung method at Epicentre laboratory, Uganda.

Results:

Among eligible children, 96% (95%CI: 94-98) received at least 1 dose, while 51% of children 0-11 months and 78% of those 12-23 months were considered fully vaccinated. At 9 months post-MVC, overall pneumococcal carriage had increased from 58% (95%CI: 56-61) to 67% (95%CI: 64-69); among children <24 months, carriage increased from 86% (95%CI: 83-90) to 92% (95%CI: 90-94). Total carriage of vaccine-targeted serotypes decreased from 37% (95%CI: 34-40) to 15% (95%CI: 14-18) and from 49% (95%CI: 44-54) to 17% (95%CI: 14-21) among children <24months.

Conclusion

This is the first study reporting pneumococcal carriage estimates pre-and post-vaccination in Uganda. Overall NP pneumococcal carriage increased, with significant and rapid replacement of vaccines serotypes by non-vaccines serotypes in all age-groups. Though difficult to implement in these settings, high-quality surveillance of invasive pneumococcal disease is necessary to evaluate the impact of PCV immunization.
Methods:

Spn isolates from sterile fluids (150 hospitals/24 provinces) were received at NRL between Jan-2010 and Dec-2016 and serotyped by Quellung. MIC was performed by agar dilution (CLSI). Three periods were defined and compared: pre-PCV13 (2010-11), transitional (2012) and post-PCV13 (2013-2016).

Results:

From 1821 Spn isolated in children <5y.o, 1029 (56.5%) were <2y.o. Diagnosis: pneumonia (42%), meningitis (28%), sepsis (16%), other (16%). The number of IPD cases received at NRL decreased 55.3%, from 235 in pre-PCV13 to 105 (annual average <2y.o.) in post-PCV13.

PCV13-serotypes decreased from 86.3% (prePCV13) to 22.0% (postPCV13) related to serotypes 14, 6A, 6B, 19A. In the last period we have not received any serotype 5. Non-PCV13-serotypes increased 64%, mainly due to 24F/A/B (16.8%), 12F (12%) and 23B (4.2%).

Comparing pre-PCV13/post-PCV13 periods we observed: Penicillin No-susceptibility (PEN-NS) 38.2% (31.4%) MIC = 0.12-1mg/L, 6.6% MIC = 2mg/L, 0.2% MIC = 4mg/L, 37.9% (33.7%) MIC = 0.12-1mg/L, 3.8% MIC = 2mg/L, 0.5% MIC = 4mg/L, cefotaxime (meningitis) 5.7%/3.3%, (non-meningitis) 0.6%/0.2%; amoxicillin 0.2%/0%; meropenem 7.6%/3.8%; erythromycin 32.3%/26%; tetracycline 20.8%/31.3%; trimethoprim-sulfamethoxazole (SXT) 38.9%/43.7%. No resistance to chloramphenicol, levofloxacin, rifampicin, ceftaroline or vancomycin was detected. We observed a significant (p<0.05) increase in tetracycline and SXT resistance, and a decrease in erythromycin. Main serotypes associated with PEN-NS were (pre-PCV13/post-PCV13): 14 (43%/9.5%), 24 (3.9%/39.2%), 19A (12.8%/9.5%), 6A (13.4%/2.5%), 6B (11.2%/3.8%).

Conclusion

The PCV13-serotypes show a constant decrease since the introduction of the vaccine in the NVP. The non-PCV13-serotypes remain rising. The increase in penicillin, erythromycin and tetracycline was mainly associated with the increase in serotype 24 isolates in post-PCV13.

ISPPD-0137

STREPTOCOCCUS PNEUMONIAE (SPN) NASOPHARYNGEAL CARRIAGE (NPC) IN CHILDREN UNDER 3 YEARS OLD, ATTENDING DAY CARE CENTERS IN ARGENTINA.

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Background and Aims:

In 2012 the 13-valent conjugated pneumococcal vaccine (PCV13) was introduced in the National Immunization Program. In a pre-vaccinal carriage study performed in 2007-08 a 51.5% carriage rate was found mainly associated with PCV13-serotypes (56.3%). Aims: 1) to assess the rate of Spn NPC in healthy <3 y.o., attending public and private day care centers from 5 cities of Argentina, between June-September 2015, 2) to determine serotype distribution and antimicrobial susceptibility.

Methods:

Nasopharyngeal samples were analyzed at references hospitals of each city and isolates were submitted to the National Reference Laboratory. Serotyping by Quellung and antimicrobial susceptibility by agar dilution method (CLSI) were performed.

Results:

The carriage rate was 61.6% (221/359). The non-PCV13 serotype represent 90.9% of the total. The most frequent serotypes were 15B, 23B and 11A (29.9%). Antimicrobial non-susceptibility according meningitis breakpoint was (MIC mg/L): 39.2% penicillin ≥0.12 (36.9% 0.12-1; 2.3% ≥2); 2.8% cefotaxime MIC≥1 (2.3% 1, 0.5%≥2), 2.3% meropenem, and nonmeningitis breakpoint: penicillin 1.4%, amoxicillin 0% and cefotaxime 0.5%. Non-susceptibility was: erythromycin 17.1% (phenotypes M/MLSb: 54%/46%), tetracycline and doxycycline 13.8%, trimethoprim-sulfamethoxazole 76.5% and 0% for rifampicin, chloramphenicol, levofloxacin and vancomycin. Main serotypes associated with penicillin non-susceptibility were non-PCV13: 23B (25%), 16F (13.6%), 15B (10.2%), 35B (4.5%) and 11A, 15C, 19A and 24F, 3.4% each one.

Conclusion

NPC was higher than the previous study (p<0.05). Most of the serotypes were non-PCV13 (90%). Almost 40% of Spn were penicillin non-susceptibility, mostly associated to non-PCV13 serotypes (>60%). The new serotypes distribution in NPC and its associated antibiotic resistance pattern highlights the importance of this study.
Structured CRF forms were used to collect paediatric patient metadata of enrolled patients for the surveillance. All data collected are sent to the WHO/IST to update single database; CSF/isolates samples are sent to the WHO collaborating centre at MRC Gambia for further sensitive testing and analyses.

Results:

The main challenges in data collection were the receipt of biological samples that could not be linked to any patient information and missing data for variables in-patient CRF forms. Between 2010 and 2016 percentage data linkage rose from 37% to 91% (p-value: 0.001). This improvement was due to the introduction of data managers in 2014 at the CC, linking patient metadata to samples collected by the sentinel sites. Across all sites, vaccine history was only available for 2937 patients (8%) and clinical patient diagnosis were available for 34122 (92%). Among 36901 patients, at least one laboratory test result was recorded in 27885 (76%) patients from the sentinel sites.

Conclusion

Incomplete or missing data hampered our ability to infer causality of paediatric meningitis and identify risk factors. Improving our data quality and integrity has enhanced our ability to measure vaccine impact on paediatric bacterial meningitis.

![Percent Linkage Graph](chart.png)

ISPPD-0780
SURVEILLANCE OF IMPACT OF PCV-10 VACCINE ON PNEUMOCOCCAL MENINGITIS IN MOZAMBIQUE, 2013 – 2015
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4Universidade Feevale, Rio Grande de Sul, Brazil
5Universidade Federal de Ciências de Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil
6Instituto Nacional de Saúde, Ministério da Saúde, Maputo, Mozambique

Background

Vaccination using the 10-valent conjugate vaccine (PCV-10) was introduced into the
Extended Program on Immunization in Mozambique in March 2013, however its impact on pediatric pneumococcal meningitis is unknown. In this study, we assessed for the first time the impact of PCV10 on the burden of pneumococcal meningitis in children less than 5 years of age at the three largest hospitals in Mozambique.

**Methods**

Between March 2013 and December 2015, a total of 744 cerebrospinal fluid (CSF) samples were collected from eligible children in three PBM surveillance sentinel sites which are regional hospitals, namely, Maputo Central Hospital (HCM), Beira Central Hospital (HCB) and Nampula Central Hospital (HCN), situated in the southern, central, and northern regions of the country, respectively. Of which 160 (21.5%) were positive for S. pneumoniae. Of these, only 86 samples met the criteria for serotyping and were subsequently serotyped using sequential multiplex PCR (SM-PCR), but 17 samples were non-typable.

**Results**

The proportion of cases of pneumococcal meningitis decreased from 33.6% (124 of 369) in 2013 to 1.9% (3 of 160) in 2015 (p < 0.001). The relative frequency of PCV10 serotype cases also decreased from 84.2% (48 of 57) in 2013 to 0% (0 of 3) in 2015 (p = 0.006). Between 2013 and 2015, serotype coverage of PCV-10 and PCV13 vaccine formulations was 66.7% and 81.2%, respectively.

**Conclusion**

Our study provides preliminary evidence on the impact of pneumococcal vaccination on pneumococcal meningitis in Mozambique, showing a rapid and consistent decline in the frequency of pneumococcal meningitis, accompanied by more discrete change in the serotype distribution and serotype coverage over the first three years post introduction of PCV10 formulation into the EPI in Mozambique.

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**ISPPD-0431**

**INTERCHANGEABILITY BETWEEN PNEUMOCOCCAL CONJUGATE VACCINES (PCVS): A LITERATURE REVIEW**

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²Imperial College, Public Health, London, United Kingdom
³GSK, Wavre, Belgium

**Background and Aims:**

Three pneumococcal conjugate vaccines (PCVs) have been licensed and implemented in national immunization programs (NIPs), sometimes sequentially. Recent analyses have shown a similar impact of the pneumococcal non-typeable Haemophilus influenzae protein D-conjugate vaccine (PHiD-CV) and the 13-valent PCV (PCV13) on pneumococcal disease. There is limited but growing evidence on the use of mixed PHiD-CV/PCV13 schedules in individuals and NIPs. We performed a literature search to review the available evidence for interchangeability between these higher-valent PCVs.

**Methods:**

An integrated literature search was conducted until January 2018 in PubMed/Scopus databases, evaluating programmatic approaches, immunogenicity, safety and effectiveness/impact of mixed/cold-switching higher-valent PCV schedules. Primary research and reviews were included without geographic or temporal limitations. Studies evaluating disease burden and cost-effectiveness were excluded. Retrieved articles were screened and reviewed following set criteria. A descriptive analysis was performed following the quality assessment, integration and extraction of the reviewed data.
Results: 1268 articles were identified of which 7 were included in our review (Figure). Eligible studies reported programmatic, immunogenicity, safety and effectiveness/impact outcomes on mixed/switched PHI-D-CV/PCV13 schedules in different regions. An adequate immunogenicity and safety profile was observed in the studies reporting these outcomes.

Conclusion: The currently available evidence on programmatic approaches, immunogenicity and safety does not raise major concerns about switching between PCVs or using mixed PCV schedules. More data are needed to further assess interchangeability between PCVs.

ISPPD-0565
PREVALENCE OF PNEUMOCOCCAL NASOPHARYNGEAL CARRIAGE AND SEROTYPE DISTRIBUTION IN CHILDREN IN CAMEROON AFTER 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV13) INTRODUCTION
1National Institute for Health and Welfare, Vaccine Impact Assessment, Tampere, Finland
2University of Tampere, Epidemiology, Tampere, Finland
3Expanded Programme on Immunization, Planning- Monitoring and Evaluation, Yaounde, Cameroon
4Institute of Biomedicine- Research Center for Cancer- Infections and Immunity-
Background and Aims:

Streptococcus pneumoniae (pneumococcus) remains a major contributor to childhood infections and deaths globally. To monitor the effects of the PCV13 introduced in July 2011 in Cameroon, with a 3-dose schedule vaccination at the age of 6, 10 and 14 weeks; we assessed pneumococcal nasopharyngeal carriage and serotype distribution of pneumococci isolated from children.

Methods:

Two rounds of cross-sectional studies to collect nasopharyngeal swabs (NPS) in children aged 24 to 36 months were conducted between March and July in 2013 (PCV13-unvaccinated, n=198) and 2015 (PCV13-vaccinated, n=689), respectively in Yaoundé, Cameroon. NPS samples were collected and processed following WHO recommendations. Bacterial cultures for pneumococcal identification were performed using standard microbiological techniques and serotyping of isolates was achieved using sequential multiplex PCR method supplemented with Quellung reaction, when needed.

Results:

Pneumococcal carriage prevalence was 57.6% (114/198) and 62.0% (426/689) for the unvaccinated and vaccinated cohorts, respectively. In the unvaccinated 2013 cohort, 36.8% (42/114) of the isolates were vaccine-serotypes, 6.1% (7/114) vaccine-related and 57.0% (65/114) non-vaccine-serotypes. Among the vaccinated children in 2015, 29.1% (123/422, 4 serotype results pending) of the isolated pneumococci were vaccine-serotypes; 8.8% (37/422) vaccine-related-serotypes; 62.1% (262/422) were non-vaccine-serotypes. The most frequent serotypes in 2013 were 19F (12.3%, 14/114), 23F (8.8%, 10/114) and 15C (8.8%, 10/114); compared to serotypes 19F 7.3% (31/422), 15C 6.2% (26/422) in 2015.

Conclusion

PCV13 infant vaccination reduced vaccine-serotype carriage. However, replacement by non-PCV13 serotypes was observed resulting in similar overall carriage prevalence.

ISPPD-0060
DEVELOPMENT OF A SEROTYPE-SPECIFIC URINE ANTIGEN DETECTION ASSAY (SSUAD) TO DETECT POLYSACCHARIDES FOR SEROTYPES 1/3/4/5/6A/6B/7F/9V/14/18C/19A/19F/22F/23F/33F IN CLINICAL URINE SAMPLES
K. Nolan1, R. Klein1, R. Panemangalore1, L. Ciminera1, H. Pham1, H. Tang1, T. Steinmetz2,
Background and Aims:

Pneumococcal disease remains a significant cause of morbidity and mortality in adults globally. The majority of pneumococcal pneumonia cases (~75%) are non-invasive, yet there is limited information on incidence and serotype distribution in non-bacteremic pneumococcal pneumonia (NBPP). While a Pfizer-proprietary SSUAD has been used to determine serotype distribution in adult NBPP cases following the introduction of PCV programs in infants and in a clinical efficacy trial in adults, the assay only tests for the PCV13 types. A broader SSUAD would allow us to better understand the disease burden and serotype distribution of NBPP in adults, particularly the contribution of 22F and 33F.

Methods:

A multiplexed immunoassay using Luminex® beads was developed to detect serotype-specific *S. pneumoniae* polysaccharides for the serotypes in an investigational 15-valent Pneumococcal Conjugate Vaccine (V114). Assay development focused on the selection of monoclonal antibody pairs to balance specificity with sensitivity. Single-plex and multiplex Design of Experiments (DoE) were implemented to further optimize assay parameters.

Results:

Monoclonal antibody pairs with optimal specificity and binding affinity for each of the fifteen serotypes were identified. The assay conditions determined from the DoE will be verified in a comprehensive qualification study to define assay performance characteristics for precision, ruggedness, dilutability, relative accuracy, sensitivity (serotype specific cut-off), and specificity.

Conclusion

The assay will support studies to demonstrate the burden of NBPP in adults, particularly for serotypes 22F and 33F, and the impact of NBPP on health-related quality of life and costs in order to inform vaccine policy and programs.
pneumococcal disease (IPD) incidence in adults after 6 years of infant PCV10 vaccination by using two analytic methods.

**Methods:**

IPD cases in persons >18 years (n=5564) were identified through national, population-based laboratory surveillance; data were linked with population registry to conduct nationwide observational follow-up and quasi-experimental studies. We compared serotype-specific incidence rates in 2011-2016 (PCV10-period) with those in 2004-2010 (pre-PCV10 baseline) by using Poisson regression (before-after) and interrupted time-series (ITSA) models.

**Results:**

During the pre-PCV10 period, overall IPD incidence in adults >18 years increased yearly by 2.4%. Table shows the Incidence Rate Ratios (IRRs) for comparing overall, PCV10 serotype and non-PCV10 serotype IPD rates at the end of PCV10-period (2015-2016) with the pre-PCV10 baseline period (before-after), and the expected and estimated IPD rates (ITSA).

**Conclusion**

Both methods demonstrated significant herd protection for PCV10 serotype IPD and increases in non-PCV10 serotype IPD; estimates for overall absolute IPD incidence after PCV10 introduction were similar. In the ITSA model, however, point estimates were larger for relative reduction in overall IPD and smaller for non-PCV10 serotype increase. In the presence of increasing pre-vaccine trend, before-after analysis may have underestimated the overall herd effects, but overestimated replacement. The time-series method, however, may have overestimated herd effects and underestimated replacement disease.

**ISPPD-0513**

HIGH RATES OF IPD CAUSED BY SEROTYPE 3 IN CHILDREN LESS THAN 5 YEARS OLD AGE IN AUSTRALIA, DESPITE HIGH VACCINE UPTAKE

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3NSW Health, Communicable Diseases Branch, Sydney, Australia
The University of Sydney, Marie Bashir Institute for Infectious Diseases and Biosecurity, Sydney, Australia

Background and Aims:

In Australia, the PCV7 was introduced to the routine vaccination schedule, in 2005, for children (at 2, 4 and 6 months) and was replaced with PCV13 in 2011. Although the numbers of most vaccine serotypes have dramatically decreased among IPD isolates, vaccine failure cases have been noted and are predominately due to serotype 3 and 19A.

Methods:

In this study serotype 3 IPD cases in young Australian children was investigated using IPD surveillance data.

Results:

Prior to the introduction of PCV13, serotype 3 caused 3% (24/812) of IPD cases in Australian children less than 5 year old. In 2012-2015 the proportion of serotype 3 isolates has increased to 9% (58/653) and, to date, in 2017, it has been responsible for 14% (18/132) of IPD cases and now is the most prevalent IPD-causing serotype. More concerning is that almost half (48%, 37/76) of the serotype 3 IPD cases are from fully vaccinated children.

Conclusion

The low immunogenicity of serotype 3 antigen in PCV13 might explain to some extent the increasing incidence of serotype 3 IPD in Australia and elsewhere. However, our preliminary data highlight the role of diversity in the polysaccharide capsule antigen of Streptococcus pneumoniae, as the main surface antigen and the target of the currently used pneumococcal vaccines, in limiting vaccine efficacy. Our limited understanding of this diversity creates a major obstacle in eliminating pneumococcal disease. Further research is warranted to monitor diversity and evolution of the serotype 3 capsular genes and antigens in order to improve and maintain vaccine efficacy.

ISPPD-0717
VACCINATION AGAINST INVASIVE PNEUMOCOCCAL DISEASE AND MOLECULAR MONITORING OF VACCINE FAILURE IN THE CZECH REPUBLIC
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Background and Aims:

In the CR, two conjugate vaccines against invasive disease caused by Streptococcus pneumoniae covering different serotypes have been currently registered, PCV13 and PCV10. It is crucial to differentiate between vaccine failure and infection by a non-vaccine serotype. We retrospectively analysed vaccine failure in children under 5 years of age since 2012.

Methods:
The identification of *S. pneumoniae* was based on optochin test, bile solubility test, real-time PCR. Typing was done by a combination of the Quellung reaction and multiplex PCR. Sequence characterization was performed by MLST.

**Results:**

Retrospective analysis of strains from 2012-2014 identified eight strains of *S. pneumoniae* possibly linked to vaccine failure in the age group under 5 years of age. These strains were further analysed by molecular methods. They were assigned to serotypes 1 (n=4), 14 (n=2), and 3 (n=2). In serotype 1, a single sequence type, ST 306, typical for serotype 1, was identified. Similarly, in serotype 14, a single sequence type, ST 124, was identified, which is typically linked to serotype 14 in the Czech Republic while in other geographical areas, other STs are also common. Serotype 3 is highly heterogeneous as is also reflected by a variety of STs reported. Clonal complexes ST 505 and ST 124 were identified. ST 124 was discovered in *S. pneumoniae* of serotype 3 for the first time in the world.

**Acknowledgements**

Supported by grant no.17-29256A from the Ministry of Health of the Czech Republic. All rights reserved.

**ISPPD-0590**

**RESIDUAL NASOPHARYNGEAL CARRIAGE OF VACCINE TYPE PNEUMOCOCCI IN A MATURE PCV10 IMMUNISATION PROGRAMME IN KENYA**

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**Background and Aims:**

We conducted a multi-site carriage survey in three locations in Kenya to determine residual vaccine-type (VT) pneumococcal carriage 6 years post-PCV10 introduction ahead of plans to simplify the PCV schedule.

**Methods:**

Cross-sectional pneumococcal carriage surveys were conducted in June-October 2017 among randomly selected (age-stratified) samples of 514, 496 and 431 children and adults in Nairobi, Siaya and Kilifi, respectively. We cultured nasopharyngeal swabs to identify pneumococci and collected data on demographic characteristics. We calculated crude and age-standardised carriage prevalence (against the INDEPTH 2013 network’s standard population).

**Results:**
<table>
<thead>
<tr>
<th>Site</th>
<th>Nairobi (urban)</th>
<th>Siaya (rural-Western)</th>
<th>Kilifi (rural-Coast)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Crude prevalence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>255 50</td>
<td>245 49</td>
<td>222 52</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>128 79</td>
<td>117 79</td>
<td>115 82</td>
</tr>
<tr>
<td>≥5 years</td>
<td>127 36</td>
<td>128 37</td>
<td>107 37</td>
</tr>
<tr>
<td>PCV10 Serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>14 3</td>
<td>32 6</td>
<td>21 5</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>7 4</td>
<td>16 11</td>
<td>9 6</td>
</tr>
<tr>
<td>≥5 years</td>
<td>7 2</td>
<td>16 5</td>
<td>12 4</td>
</tr>
<tr>
<td>Age-standardized prevalence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All serotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>255 43</td>
<td>245 49</td>
<td>222 47</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>128 79</td>
<td>117 80</td>
<td>115 79</td>
</tr>
<tr>
<td>≥5 years</td>
<td>127 37</td>
<td>128 43</td>
<td>107 41</td>
</tr>
</tbody>
</table>

The top 3 serotypes by site were 3, 35B and 6A; 3, 35B and 19A and 35B, 19A and 23B respectively. In Siaya and Kilifi, the commonest circulating VT was 19F and 14, respectively.

**Conclusion**

There is significant residual VT-pneumococcal carriage across Kenya 6 years post-PCV10 introduction. Interventions to eliminate VT carriage are necessary before vaccine dose simplification in this high burden setting.

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**ISPPD-0083**

**INDIRECT IMPACT OF TEN-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) AGAINST CLINICALLY SUSPECTED INVASIVE PNEUMOCOCCAL DISEASE (IPD) IN UNVACCINATED POPULATIONS IN FINLAND**

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**Background and Aims:**

PCV10 was introduced into National Vaccination Programme (NVP) for children born after May 2010 using 2+1 schedule without catch-up. We assessed changes in rates of clinically suspected IPD in unvaccinated children (age groups of older siblings) and working-age adults (age groups of parents) after NVP-introduction to estimate herd effects.

**Methods:**
We followed unvaccinated children aged 7-14 years who were not eligible for NVP (born before 06/2010) and adults aged 18-49 years during 2012-2016 (target cohorts) and compared those with age- and season-matched reference cohorts during 2006-2010. In/outpatient hospital discharge reports with ICD-10 diagnoses compatible with IPD (ICD-10 A40.3/B95.3/G00.1/M00.1) and unspecified sepsis (A40.9/A41.9/A49.9/G00/G00.9/I30.1/M00/M00.9/B95.5) were collected from national hospital discharge register. Cases of IPD detected by culture or nucleic acid detection were excluded.

Results:

Table shows the observed rates of suspected and laboratory-confirmed IPD by cohort and the estimated rate reductions in 2012-2016 compared with season and age-matched cohorts before NVP. Because of increasing pre-vaccine trend, interrupted time-series analysis was also conducted for non-laboratory-confirmed IPD/unspecified sepsis. Relative rate reductions of 39% (95%CI 12 to 56) in children and 10% (95%CI -1 to 20) in adults by 2015-16 were seen with considerable absolute reductions compared to the expected rates without NVP.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Outcome</th>
<th>Unvaccinated reference cohort</th>
<th>Unvaccinated target cohort</th>
<th>Relative Rate Reduction</th>
<th>Absolute Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Incidence rate /100 000</td>
<td>% (95%CI)</td>
<td>Incidence rate /100 000</td>
<td></td>
</tr>
<tr>
<td>Children 7 to 14 years of age</td>
<td>Non-laboratory-confirmed IPD or unspecified sepsis</td>
<td>32.5</td>
<td>32.8</td>
<td>-1 (-11, 8)</td>
<td>-0.4</td>
</tr>
<tr>
<td></td>
<td>Non-laboratory-confirmed IPD</td>
<td>2.7</td>
<td>1.3</td>
<td>53 (30, 69)</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Culture-confirmed IPD</td>
<td>1.7</td>
<td>1.3</td>
<td>24 (-17, 52)</td>
<td>0.4</td>
</tr>
<tr>
<td>Adults 18 to 49 years of age</td>
<td>Non-laboratory-confirmed IPD or unspecified sepsis</td>
<td>75.8</td>
<td>111.3</td>
<td>-47 (-51, -43)</td>
<td>-35</td>
</tr>
<tr>
<td></td>
<td>Non-laboratory-confirmed IPD</td>
<td>2.8</td>
<td>1.1</td>
<td>61 (52, 69)</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Culture-confirmed IPD</td>
<td>8.6</td>
<td>6.7</td>
<td>22 (14, 28)</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Conclusion

Non-laboratory-confirmed IPD decreased in unvaccinated children and adults compatible with herd effects and added substantially to the public health benefits already seen for culture-confirmed IPD in these age groups.

ISPPD-0147
THE EFFECTS OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) AMONG PRETERM AND LOW-BIRTH WEIGHT (LBW) INFANTS AGAINST INVASIVE PNEUMOCOCCAL DISEASE (IPD) AND PNEUMONIA IN FINLAND
H. Nieminen¹, H. Rinta-Kokko², M. Toropainen³, J.P. Nuorti³, H. Nohynek³, J. Jokinen²,
Background and Aims:

PCV10 was introduced into National Vaccination Programme (NVP) in 9/2010 using a 2+1 schedule. We evaluated impact of PCV10 on IPD and pneumonia among preterm and LBW infants up to 6 years post-introduction using before-after design.

Methods:

The target cohort eligible for NVP (children born 06/2010-09/2016) was compared with a calendar-time and age-matched pre-introduction reference cohort. In 2014 vaccination coverage was 94%. Preterm (gestational age <37 weeks, ~5% of total) and LBW (<2500g, ~4% of total) children were identified from birth register. Data on culture-confirmed IPD and pneumonia were obtained from national registers. Hospital-diagnosed pneumonia (HDP) was defined as any ICD10-code compatible with pneumonia in any hospital out/inpatient visit/admission. Hospital-treated primary pneumonia (HTPP) was any HDP with primary pneumonia diagnosis at hospitalization discharge.

Results:

IPD and pneumonia incidences were higher in preterm and LBW children (table). While relative rate reductions (RRR) for vaccine-type IPD were high in preterm and LBW children, the corresponding estimates for all IPD were lower than in all children. For pneumonia, the RRR were similar for all groups for HTPP, but no reduction was observed in the incidence of HDP among preterm and LBW children.

Table. Number (N), incidence rate and relative rate reduction (RRR) of invasive pneumococcal disease (IPD) and hospital-treated primary pneumonia (HTPP) and hospital-diagnosed pneumonia (HDP) among preterm, LBW and all children.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Preterm</th>
<th>Low birth-weight</th>
<th>All children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence /100000 py*</td>
<td>RRR, % (95%CI)</td>
<td>Incidence /100000 py</td>
<td>RRR, % (95%CI)</td>
</tr>
<tr>
<td>All IPD</td>
<td>Reference</td>
<td>50</td>
<td>48 (8 to 72)</td>
</tr>
<tr>
<td></td>
<td>Target</td>
<td>26</td>
<td>6 (59 to 95)</td>
</tr>
<tr>
<td>Vaccine-type IPD</td>
<td>Reference</td>
<td>39</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>Target</td>
<td>6</td>
<td>6 (10 to 30)</td>
</tr>
<tr>
<td>HTPP</td>
<td>Reference</td>
<td>910</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Target</td>
<td>724</td>
<td>10 (10 to 30)</td>
</tr>
<tr>
<td>HDP</td>
<td>Reference</td>
<td>1544</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Target</td>
<td>1537</td>
<td>(-9 to 9)</td>
</tr>
</tbody>
</table>

*pY, person-years, RRR, relative rate reduction

Conclusion
Reductions in IPD and pneumonia were seen in preterm and LBW children, but reductions were lower than in all children for the more sensitive case definitions. This may be related to higher degree of replacement in high-risk children.

ISPPD-0149
INDIRECT IMPACT OF TEN-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) AGAINST OUTPATIENT ANTIMICROBIAL PRESCRIPTIONS DURING THE FINNISH NATIONAL VACCINATION PROGRAMME (NVP)
A.A. Palmu¹, H. Rinta-Kokko², H. Nohynek³, J.P. Nuorti⁴, J. Jokinen²
¹National Institute for Health and Welfare, Department of Public Health Solutions, Tampere, Finland
²National Institute for Health and Welfare, Department of Public Health Solutions, Helsinki, Finland
³National Institute for Health and Welfare, Department of Health Security, Helsinki, Finland
⁴National Institute for Health and Welfare, Department of Health Security, Tampere, Finland

Background and Aims:
Respiratory infections are the most common reasons for antimicrobial use in children. Infant PCV10 NVP began in Sep-2010 (2+1 schedule without catch-up). We evaluated changes in antimicrobial purchases in unvaccinated children after NVP-introduction to estimate indirect impact.

Methods:
Using before-after design, unvaccinated children not eligible for NVP (born 01/2006-05/2010) were followed-up during 2012-2016 (target cohort, age 1.5-7 years). Children who received PCV10 in FinIP trial during 2009-2010 (N=30,972) were excluded. The target cohort was compared with an age- and season-matched reference cohort (born 01/2000-05/2004) during 2006-2010 (Figure). Antimicrobial purchase data were obtained from the Social Insurance Institution of Finland benefits register. Follow-up before 2006 (2010-11 in the target cohort) was excluded due to absence of full data on antimicrobial purchases. We assessed the relative reduction in outpatient purchases of antibiotics recommended for treatment of acute otitis media (AOM) in the Finnish guidelines (amoxicillin with/without enzyme inhibitor, cefuroxime, cefaclor, clarithromycin, azithromycin); full data on penicillin, and sulfadiazine/trimethoprim were not available.

Figure. Target and reference cohorts for comparing indirect impact of PCV10.
Results:

The rate of outpatient purchases of antimicrobials recommended for AOM was 0.40 in the unvaccinated reference cohort and 0.33 per person-year in the target cohort; Relative rate reduction, 16.6% (95%CI 16.2-16.9) and absolute rate reduction, 0.07 per person-year.

Conclusion

PCV10 can substantially reduce antimicrobial use, including unvaccinated children through herd effects. These results suggest that PCVs are excellent tools in combating antimicrobial resistance.

ISPPD-0732
REANALYSING ABC SURVEILLANCE DATA: DIFFERENTIAL DECLINE IN HOSPITAL-ADMITTED AND OUTPATIENT IPD SUGGESTS MASKING OF REPLACEMENT AND OVERESTIMATION OF THE CONJUGATE VACCINATION PROGRAM EFFECT
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²Université Laval, Département de médecine sociale et préventive, Quebec City, Canada
³National Institute for Public Health and the Environment RIVM, Center of Infectious Disease Prevention, Bilthoven, The Netherlands
⁴University Medical Center Utrecht, Department of Pediatric Immunology and Infectious Diseases, Utrecht, The Netherlands
⁵Public Health England, Immunisation Hepatitis and Blood Safety Department, London, United Kingdom

Background and Aims:

USA introduced PCV7 in 2000, replaced by PCV13 in 2010 (3+1 schedule). The high invasive pneumococcal disease (IPD) incidence before the introduction declined remarkably in vaccinated and non-vaccinated populations outweighing reductions seen elsewhere. We reanalyzed the published data to explore the PCV impact on hospitalized and outpatient IPD separately, as outpatient blood cultures was a probable reason for the high incidence in the ABC surveillance.

Methods:

We extracted the proportions of hospitalized and outpatient IPD cases from the published literature. We divided the reported (https://www.cdc.gov/abcs/reports-findings/survreports/spneu-types.html) incidences into hospitalized and outpatient categories for which we assumed similar serotype-group distributions.

Results:

The reported proportions of hospitalized IPD increased by calendar-time in children, but not in adults (Figure 1). In children, the relative rate reduction in hospitalized IPD was lower (79% in 2015 versus 1998-99) compared to the outpatient IPD (97%). The results diverged especially for the replacement; while 2-fold increase in the adjusted non-PCV13 serotypes was observed for hospitalized IPD, there was a 60% reduction in outpatient non-PCV13 IPD. In the elderly, reported lack of replacement in outpatient IPD and bacteremia suggests similar bias with a minor impact.
Conclusion

These observations would be explained by changes in blood culture practices. Accurate estimation of serotype-specific results requires analysis of the original data. PCV impact on hospitalized IPD remains excellent in children and is concordant with other countries’ results.

ISPPD-0515
LUNG ULTRASOUND FEATURES OF PNEUMONIA IN CHILDREN AS PART OF A PNEUMOCOCCAL CONJUGATE VACCINE EFFECTIVENESS STUDY IN SYLHET, BANGLADESH
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Background and Aims:

Current guidelines for the diagnosis of pediatric pneumonia focus on clinical signs and symptoms, with chest X-ray (CXR) reserved for ambiguous or severe cases. Lung ultrasound (LUS) is an emerging tool for the point-of-care diagnosis of pediatric pneumonia. We sought to evaluate the features used to diagnose pneumonia with LUS in a resource-poor setting in Bangladesh.

Methods:

Children aged 3-35 months enrolled in the PCV-10 impact evaluation underwent LUS after clinical diagnosis of pneumonia. We defined pneumonia on LUS as; consolidation ≥ 1 cm, and/or pleural effusion with any of the following, consolidation < 1cm, ≥ 3 B-lines, air bronchograms. Our definition is broken down into alternative definitions; consolidations ≥ 1 cm, consolidation <1cm with a pleural effusion, ≥ 3 B-lines with a pleural effusion, and air bronchograms with a pleural effusion.
Results:

We analyzed LUS data from 8,308 children enrolled into the PCV-10 study with clinical pneumonia. LUS was positive for pneumonia in 27% of these children using our definition. Consolidation ≥ 1 cm was present in 23.5% of children. Consolidation <1 cm with a pleural effusion was present in 0.2% of children. 1.6% of children had ≥ 3 B-lines with a pleural effusion. As well, 1.7% of children had air bronchograms with a pleural effusion.

Conclusion

LUS is a promising tool with the potential to improve diagnostic capabilities, however, diagnostic validity of the LUS definition of pneumonia needs to be assessed. Further analysis of the data obtained through the PCV-10 study may be used to improve our LUS definition.

Background and Aims:

Recent evidence suggests that clinically suspected invasive pneumococcal disease (CSIPD) described by hospitalisation discharge codes and excluding laboratory confirmed disease, captures a larger proportion of clinically significant invasive pneumococcal disease (IPD) than laboratory confirmed sterile site positive cultures alone. The aim of this study was to examine pneumococcal conjugate vaccines (PCV) vaccine effectiveness (VE) against CSIPD in NZ children

Methods:

We did a retrospective cohort study using linked NZ national administrative data from 2008-2015. All children under 6 years of age eligible to receive the NZ infant schedule (3+1) were included. We defined CSIPD based on ICD-10 codes compatible with IPD (ICD-10 A40.3/B95.3/G00.1/M00.1) and unspecified sepsis and/or infection (A40.9/A41.9/A49.9/G00/G00.9/I30.1/M00/M00.9/B95.5). Vaccinated was defined as 14 days after receiving 2 doses at least 3 weeks apart, after 38 days of age. Laboratory confirmed cases were excluded. VE was estimated using 1-Odds Ratios (OR).

Results:

The study cohort included 556,435 children, with an estimated vaccine coverage of 83.8%. There were 258 cases of IPD, compared to 1417 cases of CSIPD. Using a risk ratio, vaccinated participants had 0.41 times the risk of a CSIPD event as unvaccinated. After adjustment for sex, NZ deprivation index 2013 quintiles, prioritised ethnicity, district health board, and year of birth, the PCV vaccines had an overall VE against CSIPD of 64% (95% CI; 60, 68).

Conclusion

We observed more CSIPD then IPD, and a high VE against CSIPD in NZ.
SYSTEMATIC REVIEW OF PNEUMOCOCCAL CONJUGATE VACCINE (PCV) IMPACT WHEN ADMINISTERED IN 2+1 VERSUS 3+0 SCHEDULES ON SEROTYPES (ST) 1, 6A, 6B, 19A, 19F, AND 23F

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Background and Aims:

WHO recommends countries include PCV in routine programmes using either 2+1 or 3+0 regimen. We examined data from a large systematic review to determine if schedule affected PCV performance for 6 key serotypes.

Methods:

We systematically reviewed studies of PCV10 or PCV13 (PCV7-only excluded). Analyses were stratified by outcome, serotype, product, and prior PCV7 use; results focused on serotypes causing outbreaks, breakthrough cases and those with differential immunogenicity by schedule.

Results:

Table 1. Summary of findings comparing schedules for selected serotypes

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Immunogenicity (each n=31)</th>
<th>Nasopharyngeal carriage (NPC)</th>
<th>Invasive pneumococcal disease (IPD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV13 (non-PCV10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6A</td>
<td>Favors 3+0</td>
<td>GMC favors 2+1; similar %responders</td>
<td>(NPC n=20; IPD n=11) Unable to assess due to previous PCV7 use</td>
</tr>
<tr>
<td>19A</td>
<td>GMC favors 3+0; similar %responders</td>
<td>3+0 and 2+1 similar</td>
<td>(NPC n=23; IPD n=21) No evidence of schedule difference after accounting for product</td>
</tr>
<tr>
<td>Both products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19F</td>
<td>3+0 and 2+1 similar</td>
<td>GMC favors 2+1; similar %responders</td>
<td>(n=13) Both demonstrated impact</td>
</tr>
<tr>
<td>1</td>
<td>GMC favors 3+0; similar %responders</td>
<td>GMC favors 2+1; similar %responders</td>
<td>Not assessed</td>
</tr>
<tr>
<td>6B</td>
<td>Favors 3+0</td>
<td>(n=13) Reductions with both; 2+1 had little residual carriage due to previous PCV7 use</td>
<td></td>
</tr>
<tr>
<td>23F</td>
<td>Favors 3+0</td>
<td>GMC favors 2+1; similar %responders</td>
<td>Not assessed</td>
</tr>
</tbody>
</table>

*n=total number of analytic data points
GMC=geometric mean concentration

Conclusion
No consistent differences were observed between schedules for assessed serotypes after stratifying by product. Data paucity, particularly for 3+0, limited ability for full comparisons.

**ISPPD-0659**

**SYSTEMATIC REVIEW OF THE IMPACT OF 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINES (PCV10 AND PCV13) ON SEROTYPES 3, 6A, 6C, 19A AND 19F**

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⁴Agence de Médecine Préventive, Meningitis and Pneumonia, Paris, France
⁵University College London, ICH Infect- Imm- Infla. & Physio Med, London, United Kingdom

**Background and Aims:**

WHO recommends countries include PCV10 or PCV13 in routine immunization programmes using either a 2+1 or 3+0 regimen. We evaluated serotype-specific differences in PCV performance by product.

**Methods:**

We conducted a systematic review of PCV10 and PCV13 studies. Analyses were stratified by outcome, schedule, and prior PCV7 use. We focused on PCV13-non10 serotypes 3, 6A, 19A and serotypes 6C (potentially cross-reactive) and 19F (breakthrough cases).

**Results:**

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Immunogenicity (each n≥30)</th>
<th>Nasopharyngeal carriage (NPC)</th>
<th>Invasive pneumococcal disease (IPD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV13 (non-PCV10)</td>
<td>3 PCV13 immunogenic; limited PCV10 data</td>
<td>(NPC n=16; IPD n=11)</td>
<td>No consistent impact from either product</td>
</tr>
<tr>
<td>6A</td>
<td>PCV13 immunogenic; PCV10 immunogenic only with 2+1 regimen</td>
<td>(n=20) Impact with both products; faster declines with PCV13</td>
<td>(n=11) Impact with both products; data limited for PCV13 due to prior PCV7 use</td>
</tr>
<tr>
<td>19A</td>
<td>Not evaluated</td>
<td>(n=23) Impact with PCV13 but not PCV10</td>
<td>(n=21) Impact with PCV13; PCV10 limited data, mixed findings</td>
</tr>
<tr>
<td>Vaccine-related</td>
<td>6C</td>
<td>Not evaluated</td>
<td>(n=6) Limited data for both products but favors PCV13</td>
</tr>
<tr>
<td>Both products</td>
<td>19F Similar percent responders, but PCV10 had higher GMC than PCV13 for 3+0 regimen</td>
<td>(n=13) Impact from both products</td>
<td>(n=5) Data limited for PCV13 due to prior PCV7 use; PCV10 data limited</td>
</tr>
</tbody>
</table>

n=number of analytic data points
GMC=geometric mean concentration

**Conclusion**
Data for these select serotypes were limited but suggest greater impact with PCV13 than PCV10 for ST19A and perhaps ST6C; neither product consistently impacted ST3 carriage or IPD. More data are needed to evaluate product impact on ST6C and ST19F IPD.

ISPPD-0696
IMPACT OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV13) USE ON INVASIVE PNEUMOCOCCAL DISEASE (IPD) AMONG ADULTS IN THE UNITED STATES

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5Oregon Public Health Division, Emerging Infections Program, Portland, USA
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7Johns Hopkins Bloomberg School of Public Health, Department of International Health, Baltimore, USA
8Minnesota Department of Health, Emerging Infections Unit, St. Paul, USA
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11Colorado Department of Public Health and Environment, Communicable Disease Branch, Denver, USA
12New Mexico Department of Health, New Mexico Emerging Infections Program, Santa Fe, USA

Background and Aims:

PCV13 was introduced for U.S. children in 2010 and for adults >65 years in late 2014. We evaluated PCV13 impact on adult invasive pneumococcal disease (IPD) burden.

Methods:

IPD cases (pneumococcus isolated from sterile sites) were identified through Active Bacterial Core surveillance (ABCs) during 2007–2016. Isolates were serotyped and classified as PCV13 (plus 6C), PPSV23-unique, and non-vaccine. We estimated percent changes in incidence comparing post-PCV13 (2016) to pre-PCV13 (2007-2008) period. We evaluated PCV13 direct and indirect effects among adults by comparing trends in monthly PCV13-type IPD rates among adults 50-64 years to adults >65 years.

Results:

ABCs identified 30,604 IPD cases among adults >19 years. Overall and PCV13-type rates declined significantly (Table), with reductions driven by serotypes 19A, 7F, and 6C. No changes in serotype 3, PPSV23-unique, or non-vaccine-types were observed. The most common serotypes in 2016 were 3(13%), 22F(11%), 15A/B/C(7%). During 2014-2016, rates among adults 50-64 years declined by 0.29% per month (indirect effects), while those among adults >65 years dropped by 0.73% per month (direct+indirect effects) (Figure).
Conclusion

PCV13 use reduced IPD incidence among adults of all age groups. While reductions were slightly more pronounced among adults >65 years vs. 50-64 years during 2014-2016, whether this difference can be attributed to PCV13 direct effects is unclear.

Table. IPD rates (cases per 100,000) before and after PCV13 introduction among adults aged 19-64 and >65 years old by serotype group, United States

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Overall</td>
<td>19-64</td>
<td>12.2</td>
<td>8.4</td>
<td>31 (27, 36)</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>40.0</td>
<td>24.2</td>
<td>40 (35, 44)</td>
</tr>
<tr>
<td>PCV13-type+6C</td>
<td>19-64</td>
<td>6.5</td>
<td>2.3</td>
<td>64 (60, 68)</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>20.1</td>
<td>6.5</td>
<td>68 (63, 72)</td>
</tr>
<tr>
<td>Unique PPSV23-type</td>
<td>19-64</td>
<td>3.4</td>
<td>3.7</td>
<td>-11 (-23, 0.8)</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>9.9</td>
<td>9.1</td>
<td>8 (-6, 20)</td>
</tr>
<tr>
<td>Non-vaccine-type</td>
<td>19-64</td>
<td>2.4</td>
<td>2.4</td>
<td>-2 (-16, 11)</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>10.1</td>
<td>8.6</td>
<td>15 (1, 26)</td>
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Figure. Monthly PCV13-type IPD incidence trends among adults 50-64 years vs adults >65 years, pre- vs post- PCV13 introduction for adults >65 years old

ISPPD-0462
HOSPITAL BASED SURVEILLANCE FOR PAEDIATRIC BACTERIAL MENINGITIS IN GHANA; 2010-2016
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3Medical Research Council Unit, WHO Collaborating Centre for New Vaccines Surveillance, Banjul, The Gambia
4London School of Hygiene and Tropical Medicine, Faculty of Infectious and Tropical Diseases, London, United Kingdom
**Background and Aims:**

Global surveillance for vaccine preventable invasive bacterial diseases has been set up by WHO. Ghana has two sentinel sites that form part of the West Africa network. We present here data collected from 2010 to 2016.

**Methods:**

Data were collected for children under 5 years of age presenting at the two major teaching hospitals in Ghana. Cerebrospinal fluid specimens were collected and processed first at sentinel site laboratory with conventional microbiology methods and subsequently with molecular analysis at WHO regional reference laboratory at the MRC Unit The Gambia for identification of *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis*, the three most common bacteria causing meningitis.

**Results:**

There were 4008 suspected cases of meningitis during the surveillance period. Suspected meningitis cases decreased from 923 in 2010 to 219 in 2016. Out of 3817 patients with outcome data, 226 (5.9%) died. *S. pneumoniae* was the most common bacterial pathogen 68.5% (50/73) of confirmed cases. *H. influenzae* and *N. meningitidis* 6.8% (5/73) and 21.9% (16/73) respectively. Following pneumococcal conjugate vaccine (PCV) introduction, PCV13 vaccine serotypes decreased from 81.3% (13/16) to 40.0% (8/20) with an increase in non-vaccine serotypes from 18.7% (3/16) to 60.0% (12/20) comparing pre (2010-2012) and post (2013-2016) vaccine periods. Among five isolates of *H. influenzae*, one was type b and one non-typeable strain. Among eight isolates of *N. meningitidis* serotyped, four were serogroup B and one was serogroup W.

**Conclusion**

Suspected meningitis decreased among children under 5 years between 2010 and 2016, with changes in distribution of bacterial serotypes which warrants continuous surveillance.
Background and Aims:

PCV10 was introduced into Finnish National Vaccination Programme (NVP) in September 2010 with 2+1 schedule without catch-up. We evaluated the impact of PCV10 on IPD among vaccine-eligible children up to six years post-introduction.

Methods:

Children eligible for NVP (born 06/2010-09/2016) were compared with a calendar-time and age-matched pre-introduction reference cohort. Vaccination uptake of at least one dose was estimated at 94% in the birth cohort of 2014. National surveillance data were used for calculating culture-confirmed serotype-specific IPD-rates in the study cohorts.

Results:

Table shows IPD rates by cohort, and the absolute and relative rate changes in the target cohort compared with the reference cohort. The incidence of 6A IPD decreased significantly. The incidence of 19A was low shortly after PCV10 introduction, but afterwards increased by time and age compared to the reference cohort (Figure).

Conclusion

PCV10 impact on overall IPD in vaccine-eligible children has remained considerable. There was direct cross-protection against 6A IPD but no net reduction was observed for 19A. Replacement due to other serotypes was non-significant.
ISPPD-0013  
DECLINE IN CHILD HOSPITALIZATION AND MORTALITY AFTER THE INTRODUCTION OF THE 7-VALENT PNEUMOCOCCAL CONJUGATIVE VACCINE (PCV-7) IN RWANDA  
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2University Of Rwanda, Department of Biomedical laboratory Sciences, kigali, Rwanda  

Background and Aims:  
Pneumonia is a public health problem in many developing countries where it takes many lives of children before the age of 5 years. The 7-valent pneumococcal vaccine (PCV-7) has been introduced in an effort to prevent the disease and therefore reduce the rate of childhood mortality and morbidity. In Rwanda, the vaccine was introduced in April 2009, and is now part of routine childhood vaccination. The aim of this study was to determine the impact of this effort on the rate of child hospitalization/mortality due to pneumonia in Huye District, Rwanda.  

Methods:  
A retrospective and comparative study was conducted on data recorded from archives of Kabutare District hospital located in Huye District in Rwanda. Hospitalization rates as well as death cases were compared between two periods i.e. before the introduction of PCV-7 (2007-2009) and after the introduction of PCV-7 (2010-2013).  

Results:  
Statistical analysis showed a reduction in hospitalization of 53% (t=2.258; p=0.037) and a significant decline in death cases (t=3.002; p=0.015) following the introduction of the PCV-7 vaccine in Kabutare District Hospital. Interestingly, 30% of pneumonia positive children after the introduction of PCV-7 had also malaria, 11% had bronchiolitis, 7.4% harbored intestinal parasites, 2% were HIV positive and 6.7% presented signs of malnutrition.  

Conclusion  
The PCV-7 vaccine has significantly reduced the rate of child hospitalization and mortality in Rwanda but co-infections and malnutrition may be additional risk factors for pneumonia that need to be tackled.  

ISPPD-0441  
CLONAL CHANGES IN PNEUMOCOCCAL POPULATION FOLLOWING PRIVATE USE OF PCV13 IN PORTUGAL  
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4Faculdade de Ciências da Universidade de Lisboa, Departamento de Biologia Vegetal, Lisboa, Portugal
**Background and Aims:**

In Portugal, the seven-valent pneumococcal conjugate vaccine (PCV7) became commercially available in 2001. In January 2010, PCV7 was replaced by PCV13. Although not included in the national immunization plan until July 2015, use of PCVs through the private market was significant (76.8-89.3% in our studies). We evaluated the impact of PCV13 use on clonal distribution of pneumococci carried by children attending day-care centers, in an urban and a rural region of Portugal.

**Methods:**

We selected 657 isolates from three periods - pre-PCV13 (2009-2010), early-PCV13 (2011-2012) and late-PCV13 (2015-2016) - to be typed by multilocus sequence typing (MLST).

**Results:**

We identified 171 sequence types (STs), of which 39 were new. For most serotypes covered by the vaccine, antibiotic resistant clones were selected overtime. Serotype 19A was the most diverse serotype in the pre-PCV13 period being associated with 13 STs; however, in the late-PCV13 period 19A was associated with only three STs (ST193, ST276, ST809), all of which were multiresistant. Serotype 19F was associated with the multiresistant ST179 in all periods. Among non-vaccine types, in the late-PCV13 period, antibiotic-susceptible previously undetected clones were identified among serotypes 15A (ST5139, ST473), 16F (ST9976), 22F (ST445), 24 (ST162), 34 (ST4083) and NT (ST393).

**Conclusion**

Use of PCV13 has led to significant changes in the pneumococcal population. Several novel clones associated with non-vaccine types are now in circulation. The few vaccine-type clones that are maintained in the population are frequently antibiotic-resistant suggesting that antibiotic pressure remains a key determinant for their maintenance in the population.

**ISPPD-0574**

**IMPACT OF VACCINATION ON NASOPHARYNGEAL PNEUMOCOCCAL CARRIAGE GENOTYPIC DIVERSITY AMONG CHILDREN IN THE GAMBIA: A LONGITUDINAL STUDY**

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²The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, United Kingdom
³Global Health Institute, Emory University, Atlanta, USA
⁴GSK, Vaccines, wavre, Belgium

**Background and Aims:**

Pneumococcal Conjugate Vaccines (PCV) contribute to changes in pneumococcal serotype populations in the nasopharynx. We investigated the effect of PCV7 on the genotypic diversity of pneumococcal carriage among children in The Gambia.

**Methods:**
Nasopharyngeal Swabs (NPS) were collected at bi-weekly intervals during the first 6 months of life and 1 monthly intervals for the subsequent 6 months in 3 groups of children. Group 1 (n=33) came from unvaccinated communities and only received PCV7 after 6 months. Group 2 (n=30) and Group 3 (n=39) received 3 doses of PCV7 at 2, 3 and 4 months and came from unvaccinated and vaccinated communities respectively. Sequence Type (ST) of each isolate was determined and genotypic diversity was studied based on whole genome phylogeny.

Results:

A total of 373, 323 and 445 isolates were sequenced from groups 1, 2 and 3 respectively. ST847 entirely associated with serotype 19A was the most common ST in groups 1&2 (n=10 & n=7). ST913 represented entirely by serotype 6A was the most common ST in group 3 (n=10). 85% (11/13) of STs among Vaccine Types (VT) isolates from group 1 identified post vaccination were represented pre-vaccination. Isolates from consecutive sampling points that differed in serotype also differed in genotype except in 3 cases (15C→17F: ST910, 9L→19A: ST1735 and 15B→15C: ST4033). Some non-vaccine serotypes like serotype 19A and 35B formed multiple phylogenetic lineages that were widespread across different villages. serotype 13 formed phylogenetically diverse clades that were all localised to vaccinated communities in group 3.

Conclusion

Our data shows a strong association between Serotype and ST. Furthermore, vaccination does not significantly alter the diversity of STs of VT isolates.
RAxML. Recombination analysis and pan genome analysis were performed using Gubbins and Roary, respectively.

Results:

Phylogenetic analysis clustered isolates belonging to the three main circulating STs; ST289 (40/112), ST 3339 (17/112) and ST 3404 (51/112) and by year of collection. ST3404 clustered into 2 subclades, that were dominated by strains isolated pre and post PCV7 introduction respectively. Pan genome and recombination analysis revealed differences between the subclades. ST289 was dominant in the post PCV13 era (32, 60.4%). Most of the ST289 isolates (36, 90%) formed a monophyletic clade that was predominantly isolated in the post-PCV13 era. This ST289 clade evolved through large-scale recombination and possessed a unique accessory genome that encompassed unique variants genes that encode bacteriocin proteins.

Conclusion

The high prevalence of serotype 5 ST289 post PCV13 among children under five in West Africa is an important finding and warrants further investigation.

ISPPD-0085
DISCOVERY AND STRUCTURAL ANALYSIS OF A NEW SEROGROUP 7 STREPTOCOCCUS PNEUMONIAE SEROTYPE, 7D
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²SSI Diagnostica, Pneumococcus laboratory, Hilleroed, Denmark
³Technical University of Denmark, Department of Chemistry, Kgs. Lyngby, Denmark

Background and Aims:

Streptococcus pneumoniae is characterised into 92 serotypes based on antigenic reactions of commercial rabbit sera (SSI Diagnostica A/S, Denmark). During development of the PneumoCaT automated pipeline at Public Health England for serotype assignment from whole genome sequence (WGS) data, a putative novel serotype within serogroup 7 was discovered. We aimed to fully characterise this new serotype.

Methods:

The pneumococcal isolate with the putative new serotype was analysed by WGS, slide agglutination and Quellung and nuclear magnetic resonance spectroscopy (NMR).

Results:

WGS analysis revealed a novel codon at residue 385 of the glycosyltransferase gene, \textit{wcwK}, encoding a distinct amino acid (CTT (Leu), compared to ACT (Thr) serotype 40, TTT (Phe) 7B and TGT (Cys) 7C). The rest of the variant profile used for differentiation of genogroup 7 isolates matched serotype 7B. Further investigation by serotyping at PHE and Quellung at SSI revealed a novel pattern of factor sera reactions giving reactions with both 7e and 7f sera. The isolate reacted very strongly with factor 7f, but also showed agglutination with factor 7e. The capsular polysaccharide structure was determined by high field NMR to be ca.
5:1 mixture between structures of serotype 7C and 7B, but the precise arrangement and composition of the two repeating units could not be determined.

**Conclusion**

All data from WGS, NMR of capsular polysaccharide, production of antisera and serotyping of the novel 7 strain clearly supported the description of a new serotype, which will be named in the Danish nomenclature as serotype 7D.

**ISPPD-0569**

**CLINICAL CHARACTERISTICS, ANTIMICROBIAL SUSCEPTIBILITY AND SEROTYPE DISTRIBUTION OF INVASIVE PNEUMOCOCCAL DISEASES AMONG ADULTS IN JAPAN: A NATIONWIDE SURVEILLANCE**


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⁸Kurume University School of Medicine, Department of Infection Control and Prevention, Kurume, Japan
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¹³University of the Ryukyus, Department of Infectious Diseases-Respiratory and Digestive Medicine-Faculty of Medicine, Nishihara, Japan
¹⁴Kochi Medical School-Kochi University, Department of Hematology and Respiratory Medicine, Nangoku, Japan

**Background and Aims:**

In Japan, PCV7 was subsidized by the government for infants since November 2010, and PCV13 was included in the routine schedule in November 2013. PPSV23 was included in routine immunization for the adults older than 65 years since November 2014. Invasive pneumococcal disease (IPD) was included in the notifiable diseases since April 2013.

**Methods:**
Between April 2013 and March 2017, an enhanced surveillance of IPD surveillance was conducted among adults older than 15 years in 10 prefectures of Japan. The reported IPD case was registered and the clinical information was collected. The serotype distribution of the pneumococcal isolates from normally sterile sites of IPD cases was analyzed.

Results:

The analysis included 893 patients: 61% were male and the median age was 70 years. While 15% were meningitis cases, non-meningitis cases were 85%; majority were bacteremic pneumonia cases (60%). The case fatality proportion for meningitis case (9%) was lower than that for non-meningitis case (20%). The proportions of non-susceptible strains against cefotaxime and meropenem were both 7.1% among isolates from 146 meningitis case. In the fiscal year 2016, the proportion of PCV13-type IPD declined (from 43% in the fiscal year 2013) to 31%, but the proportion of PPSV23-type IPD was unchanged since the fiscal year 2013 (68%) because of a rapid increase of 12F serotype-IPD cases during the last 2 years.

Conclusion

A lower proportion of PCV13-type IPD suggests an indirect effect by infant immunization. Antimicrobial susceptibility and serotype distribution of isolates from adult IPD cases should be carefully monitored.

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**ISPPD-0134**

**THE COST OF HOSPITAL CARE FOR PNEUMOCOCCAL MENINGITIS AND SEPTICAEMIA INFECTIONS IN ENGLAND**

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3Public Health England, Birmingham Public Health Laboratory, Birmingham, United Kingdom
4University of Warwick, Population Evidence and Technologies, Coventry, United Kingdom
5University of Warwick, Warwick Clinical Trials Unit, Coventry, United Kingdom

Background and Aims:

Pneumococcal meningitis and septicaemia are major causes of serious illness and death. We estimate the direct costs of hospital care and length of stay (LoS) using hospital records for cases of meningitis and septicaemia admitted in England between 2003 and 2016.

Methods:

Patient-level hospitalisation admissions for pneumococcal meningitis and septicaemia were identified from hospital episode statistics. Healthcare resource group (HRG) codes associated with diagnoses and treatment procedures for each finished consultant episode (FCE) were derived using the NHS Local Payment Grouper software. These codes were then mapped to reimbursement costs by referring to the 2015/2016 NHS national tariff.

Results:

Our sample included 16 643 and 48 670 FCEs for meningitis and septicaemia, respectively. The average cost for meningitis care ranged from £3643 (range £3142 - £4211) in children <2 years to £8714 (£5476 - £8330) in adults 45-64 years, and the cost for septicaemia care ranged from £2463 (£2048 - £2851) in children 2-4 years to £4685 (£3465-£6533) in adults.
≥85 years old. The average LoS for meningitis admissions ranged from 7 (range 6 – 8) days in children <2 years to 19 (15 – 25) days in adults 45-64 years old, and that of septicaemia ranged from 2 (1 – 4) days in children 2-4 years to 13 (8 – 19) days in adults ≥85 years.

Conclusion

Hospital care costs and LoS are significantly higher in adults than in children. Because HRG-coded procedures dominate costs, identification of the correct inclusion/exclusion criteria is essential for accurate costing.

ISPPD-0285
THE IMPACT OF PNEUMOCOCCAL VACCINATION ON THE BURDEN OF HOSPITALISATION FOR PNEUMOCOCCAL DISEASE IN CHILDREN IN ENGLAND
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Background and Aims:
Pneumococcal infections are major cause of morbidity and mortality worldwide. We evaluated the impact of pneumococcal vaccination on the incidence of hospitalisations for pneumococcal disease.

Methods:
Inpatient admissions for pneumococcal meningitis (ICD-10 code G001), septicaemia (A403), pneumonia (J13) and acute otitis media (H67), were identified from national Hospital Episode Statistics covering England. Trends in incidence of hospitalisation between 2003 and 2015 in children <5 years of age were analysed by comparing crude incidence rates of hospital episodes and regression analysis. Case fatality rates were also calculated.

Results:
The annual incidence (per 100 000 population) of hospital admissions for meningitis, septicaemia, pneumonia and otitis media declined from 19.1 to 6.4 (incidence rate ratio IRR 0.33 (95% confidence interval CI 0.26, 0.43)), 11.5 to 6.0 (IRR 0.52 (95% CI 0.39, 0.69)), 13.2 to 3.2 (IRR 0.24 (95% CI 0.17, 0.34)) and 2.1 to 0.8 (IRR 0.37 (95% CI 0.17, 0.78)) between the pre-PCV era and 2015 among children <2 years old, respectively. In children 2-4 years of age, the annual incidence of meningitis declined from 1.4 to 0.7 (IRR 0.49 (95% CI 0.24, 0.99)) and that of pneumonia declined from 4.5 to 1.7 (IRR 0.37 (95% CI 0.25, 0.56)). The month-by-month rate of decline for meningitis, septicaemia, and pneumonia hospitalisations was 1.0% over the study period. The case fatality rates for children hospitalised for meningitis, septicaemia and pneumonia disease were 3.6%, 2.1% and 0.4%, respectively.

Conclusion

Pneumococcal vaccination was associated with significant reduction in the incidence of hospitalisations for pneumococcal infections in children in England.
ISPPD-0329
IMPACT OF PCV10 VACCINATION ON NASOPHARYNGEAL CARRIAGE OF STREPTOCOCCUS PNEUMONIAE IN RURAL AND URBAN COMMUNITIES IN NEPAL
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Background and Aims:
Nepal introduced PCV10 in 2015; the vaccine reached urban Kathmandu in August 2015 and rural Okhaldhunga in October 2015. We measured the impact of PCV10 on nasopharyngeal (NP) carriage of pneumococcal vaccine serotypes (VTs) in community-based children in both settings.

Methods:
Nasopharyngeal swabs were taken from children aged 6-23 months. In Kathmandu, NP swabs were collected from children who presented to Patan Hospital for vaccination, routine checkups, or minor injuries from April 2014 to June 2017. In Okhaldhunga, NP swabs were collected from community-based children in February 2015 and in February 2017. Swabs were transported in STGG and serotyped at Patan Hospital.

Results:
In Kathmandu, all-serotype pneumococcal carriage prevalence was 65% (1143/1749) in 2014/2015 and 63% (954/1505) in 2016/2017 (p=0.243). VT carriage was 19% (334/1749) in 2014/2015, 12% (134/1152) in 2016, and 9% (31/353) in 2017 (p<0.001). Of those in 2017 who received 3 doses of PCV10, VT carriage prevalence was 6% (19/330)—a 70% decrease from pre-vaccine prevalence (p<0.001).

In Okhaldhunga, all-serotype pneumococcal carriage prevalence was 83% (495/600) in 2015 and 84% (769/914) in 2017 (p=0.402). VT carriage prevalence was 28% (166/600) in 2015 and 10% (95/914) in 2017 (p<0.001). VT carriage prevalence in children with 3 doses of PCV10 was 9% (55/585)—a 66% reduction from 2015 (p<0.001).

Conclusion
The nasopharyngeal carriage of PCV10 serotypes of S.pneumoniae declined after vaccine introduction in both urban and rural communities of Nepal. Preliminary vaccine-type NP carriage impact data suggest PCV10 will likely have an important impact on the health of Nepali children.

ISPPD-0570
EFFECTIVENESS OF PCV-10 AGAINST INVASIVE PNEUMOCOCCAL DISEASE AND RADIOLOGICALLY CONFIRMED PNEUMONIA IN SOUTHERN MOZAMBIQUE
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638
Background and Aims:

*Streptococcus pneumoniae* is an important cause of morbidity and mortality among children worldwide. A highly effective pneumococcal conjugate vaccine (PCV) is widely used in developed countries, where it has resulted in dramatic declines in invasive pneumococcal disease (IPD) among vaccinated children. Mozambique introduced the PCV10 in the national expanded program on immunization on April 2013, using a 3+0 infant schedule. We aims to estimate PCV10 effectiveness against IPD and X-ray confirmed pneumonia (XRCP) in Mozambique.

Methods:

During April 2013 – March 2016, we used a matched case-control study design to evaluate PCV10 effectiveness against IPD and XRCP. IPD and XRCP cases among children age-eligible to receive PCV10 were identified prospectively through on-going surveillance. Nasopharyngeal swabs samples was collected from XRCP cases. Neighbourhood controls matched by date of birth and date of enrolment to each case were enrolled at community. PCV effectiveness was calculated using unconditional logistic regression models adjusting for potential confounders.

Results:

24 IPD cases and 91 controls were included, only 26 pairs in vaccination status were discordant. The VE model did not converge for all IPD and vaccine-types IPD due to high vaccination coverage and limited number of vaccine-type IPD cases. For XRCP, 794 cases and 2,479 controls were included in analysis. Overall PCV protection against XRCP was 48% (95% CI:23-65%), and not significant against XRCP colonized by vaccine or related serotypes; 47% (95%CI -4-73%).

Conclusion

These result confirm the effectiveness of PCV10 for XRCP following its introduction. VE model for IDP did not converge.

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**ISPPD-0077**

PNEUMOCOCCAL CARRIAGE AMONG CHILDREN UNDER FIVE IN ACCRA, GHANA, FIVE YEARS AFTER INTRODUCTION OF PNEUMOCOCCAL CONJUGATE VACCINE

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Background and Aims:
The objective of the study was to determine the carriage and serotype distribution of *Streptococcus pneumoniae* among children in Accra, Ghana, five years after the introduction of the pneumococcal conjugate vaccine (PCV-13) in 2012.

**Methods:**

In the autumn of 2016, nasopharyngeal swab samples were collected from 410 children below 5 years of age in kindergartens and nursery schools in Accra, Ghana. The swab specimens were stored in STGG medium. *S. pneumoniae* were identified based on optochin sensitivity, bile solubility, α-hemolysis and/or capsular reaction. Serotyping was performed with the Pneumotest latex agglutination kit and the Quellung reaction using serotype specific antisera.

**Results:**

The carriage prevalence was found to be approximately 54 %, and 19 % of the samples contained serotypes covered by the PCV-13, while 38 % of the samples (including NT isolates) were found to contain non-PCV-13 serotypes. Based on the serotype distribution, 33 % of all observed serotypes were included in PCV-13 while 66 % were non-PCV-13 serotypes. The dominating non-PCV-13 serotypes were 23B, 16F, and 11A followed by PCV-13 serotypes 23F and 19F.

**Conclusion**

The data indicate that the serotypes included in the PCV-13 still appear on a large scale in children five years after the PCV-13 introduction in Accra, Ghana. However, a reduction in the observed number of PCV-13 serotypes from 49 % in 2012 to 33 % in 2016 and an increase in the non-PCV serotypes has been observed. Particularly, serotypes 23B and 16F have increased dramatically since the PCV-13 introduction.

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**ISPPD-0079**

**DANISH CHILDREN SEEM NOT TO BE MAIN CARRIERS OF PNEUMOCOCCAL SEROTYPES CAUSING INVASIVE PNEUMOCOCCAL DISEASE IN THE ELDERLY**

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**Background and Aims:**

The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in the Danish childhood immunization program in 2007 and replaced by PCV13 in 2010. Serotypes 8, 7F, 3, 1 and 22F were causing the majority of invasive pneumococcal diseases (IPDs) in elderly in Denmark in 2014 and 2015. In this study, we aimed to evaluate whether children aged 8-19 months were carrying these serotypes during this period.

**Methods:**

Nasal swabs were cultured from 141 children aged 8-13 months just before starting daycare, and again after having been in daycare for 6 months. *Streptococcus pneumoniae* were identified based on optochin sensitivity, bile solubility, α-hemolysis and/or capsular reaction.
Serotyping was performed by Pneumotest latex agglutination kit and the Quellung reaction using serotype specific antisera.

Results:

The carriage rate of *S. pneumoniae* in 8-13 months old children before attending daycare was 27.7 %, and increased to 68.5 % when the same children had attended daycare for 6 months. Serotype 8 was carried by one child aged 10 months, but was not found in any of the children from daycare. Serotype 22F was found in one child aged 9 months and 4 daycare children. Serotype 7F, 3 and 1 were not observed.

Conclusion

This study shows that children aged 8-19 months are carriers of pneumococcal serotypes causing IPD in children. However, the children seem not to be carriers of the serotypes causing IPD in the elderly. Therefore, carriage studies for all age groups are needed to find the serotypes causing IPD in elderly.

ISPPD-0148

TEN YEARS OF PNEUMOCOCCAL CONJUGATED VACCINE IN DENMARK HAS NOT REMOVED IPD CAUSED BY VACCINE SEROTYPES

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Background and Aims:

The seven-valent pneumococcal conjugate vaccine PCV-7 was included in the Danish childhood immunization program in 2007 and replaced by PCV13 in 2010. This study provides a status on invasive pneumococcal disease (IPD) cases in Denmark.

Methods:

The study included all Danish IPD-13 (PCV13 serotypes) cases from 2000 to 2016 submitted to the national reference laboratory as part of the mandatory surveillance.

Results:

The incidence of IPD-7 cases varied from 6.29 to 8.73 per 100,000 in the period 2000 – 2007 and from 5.42 in 2008 to 0.42 in 2016. The incidence for IPD-13add (additional six PCV-13 serotypes not included in PCV-7) varied from 4.30 to 8.60 in the period from 2000 – 2010, and from 7.35 in 2011 to 1.75 in 2016. IPD cases were observed for all PCV-7 serotypes and PCV-13 serotypes 1, 3, 7F and 19A in 2015 and 2016. IPD cases in 2016 for different age groups was highest in age group 64+ showing an incidence of 1.40 (IPD-7) and 6.14 (IPD-13add). Aside from serotype 3 being the second highest cause of IPD in Denmark in 2016, does a low number of IPD-13 cases continue to appear, except in vaccinated children as only seven PCV failures were registered (2007-2016).

Conclusion
Although a significant reduction in incidence is observed since the introduction of PCV-7/PCV-13 in Denmark, PCV serotypes have not disappeared in IPD. Thus, continuation of PCV vaccination of the children is important in order to reduce the risk of reappearance of IPD cases due to the circulating PCV serotypes.

Background and Aims:

We evaluated 13-valent pneumococcal conjugate vaccine (PCV13) impact on pneumococcal meningitis in Burkina Faso. PCV13 was introduced in October 2013.

Methods:

Burkina Faso has conducted nationwide case-based meningitis surveillance since 2011. Pneumococcal cases are confirmed by culture, polymerase chain reaction (PCR), or latex agglutination; strains are serotyped using PCR. We compared incidence (cases per 100,000) three years following PCV13 introduction (2016) to average pre-PCV13 incidence (2011–2013). We adjusted incidence for age and proportion of cases with CSF tested at national laboratories.

Results:

In 2016, age-specific pneumococcal meningitis incidences were 9.0 (<1 year), 2.4 (1–4 years), 4.6 (5–14 years), and 1.7 (≥15 years). Compared to 2011–2013, PCV13-serotype incidence among all age groups decreased significantly, with greatest declines among children aged <1 year (-91%; 95%CI: -95%–-83%) and 1–4 years (-73%, 95%CI: -81%–-56%) (See Figure). Herd effects among persons aged ≥15 years were more pronounced for PCV13 serotypes excluding serotype 1 (-72%; 95%CI: -86%–-46%) than for serotype 1 (-41%; 95%CI: -54%–-24%). Among all ages, incidence of non-PCV13 serotypes also decreased (-38%; 95%CI: -53%–-18%). In 2016, 52% of serotyped cases among all ages were serotype 1 and 9% were PCV13 serotypes excluding serotype 1.
Conclusion

Following PCV13 introduction, PCV13-serotype meningitis incidence in young children significantly decreased. PCV13 impact on serotype 1 and disease in older children and adults requires continued monitoring.

Background and Aims:

The 13-valent pneumococcal conjugate vaccine (PCV13) was introduced into the Australian national immunisation program in July 2011, for all children under 2 years of age, replacing PCV7 and included all PCV7 serotypes in addition to 1, 3, 5, 6A, 7F, and 19A. The aims of this study were to compare isolate numbers, serotypes and geographic distribution of IPD isolates from patients aged <5 years, 5-64 years and >=65 years before (2006-2011) and after (2012-2017*) the introduction of PCV13.

*Data current to October 2017

Methods:

In Queensland, IPD isolates are referred by hospitals and private pathology laboratories to the Queensland Pneumococcal Reference Laboratory within Public Health Microbiology, Queensland Department of Health for serotyping. All isolates were serotyped by Quellung reaction using antisera supplied by Statens Serum Institut (Copenhagen, Denmark). Isolates were assigned to one of three Queensland regions by postcode.

Results:
A total of 3110 IPD isolates were received by the reference laboratory (excluding duplicates). Reductions in IPD due to most PCV13 serotypes were observed in all age groups, with the exceptions of 3, 7F and 19F. A number of non-PCV13 serotypes increased in number across all age groups post vaccine, most noticeably 15A, 23B and 9N. These changes were observed across all Queensland regions.

Conclusion

A reduction in Queensland IPD numbers caused by PCV13 isolates was observed post vaccine however total IPD referrals remain fairly stable due to serotype replacement.

ISPPD-0335
INDIRECT EFFECTS OF PNEUMOCOCCAL CHILDHOOD VACCINATION IN INDIVIDUALS ON IMMUNOSUPPRESSANTS: A NORWEGIAN CASE-COHORT STUDY
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Background and aims
It is unknown to which extent persons with iatrogenic immunosuppression benefit from indirect effects of childhood vaccination with pneumococcal conjugate vaccines (PCVs). We determined how the sequential introduction of PCV7 and PCV13 in the childhood immunisation programme has affected the epidemiology of invasive pneumococcal disease (IPD) in individuals on immunosuppressants.

Methods
We conducted a case-cohort study using 7926 IPD patients notified to the Norwegian Surveillance System for Communicable Diseases in 2005-2014 as cases, and 249,998 individuals randomly selected from the National Registry in 2012 as cohort. We defined four treatment groups based on dispensed prescriptions retrieved from the Norwegian Prescription Database: no immunosuppressants, chemotherapy, long-term systemic corticosteroids (>1.5 DDDs for >1 month) and other immunosuppressants.

Results
The PCV13-IPD incidence decreased by 5-12% during the study period in all groups. The non-PCV13-IPD incidence increased by 4-10% for all groups, most so in the chemotherapy group (not significant). In the PCV13 era, the age-adjusted relative risk for IPD was highest (significant) and the percentage of PPV23-type cases was lowest (numerical, not tested) in individuals on chemotherapy (RR=20.4, PPV23=52%), followed by individuals on corticosteroids (RR=6.2, PPV23=64%), other immunosuppressants (RR=5.6, PPV23=68%), and no immunosuppressants (RR=reference, PPV23=74%).
Conclusions
The IPD incidence declined in both immunocompetent and iatrogenically immunosuppressed individuals following the introduction of PCV in children, underscoring the benefit of childhood vaccination for the entire population. Non-PCV13-IPD incidence increased in all groups, but most in those on chemotherapy (not significant). The potential for IPD prevention through vaccination has reduced but PPV23 types still cause the majority of cases.

Background and Aims:
Australia introduced infant 7-valent pneumococcal conjugate vaccine (7vPCV) from 2005, replaced by 13vPCV in 2011. The 23-valent pneumococcal polysaccharide vaccine (23vPPV) was subsidised for adults >65 in 1997, with full funding progressively expanded to include all 65+ adults from 2005. This study examines the impact of vaccination on invasive pneumococcal disease (IPD) serotypes in 65+ adults.

Methods:
Analyses were performed on IPD notifications in the 65+ population collected through National Notifiable Diseases Surveillance System from 2002 to 2016. Serotype data was available for 92.6% of 8,298 notifications in this population.

Results:
The Figure highlights the combined herd immunity and replacement impact of the childhood PCV programs. The direct impact of 23vPPV is evident in the significantly lower rate of growth in IPD attributable to its 11 exclusive serotypes compared to non-vaccine serotypes from 2005, resulting in higher incidence of the latter from 2009. There were no changes in incidence of serotype 3 IPD. In 2016, serotype 3 was the most common in this population.

Conclusion
Infant and adult pneumococcal vaccination programs have shaped the serotype-specific epidemiology of IPD in the 65+ population. Herd immunity impact is clear for PCV serotypes excluding 3. An increasing proportion of IPD is due to non-vaccine serotypes.
ISPPD-0228
LIMITED VACCINE-INDUCED CONTROL OF PNEUMOCOCCAL CARRIAGE AMONGST CHILDREN SIX YEARS POST-INTRODUCTION OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN MALAWI: IMPACT OF FORCE-OF-INFECTION AND NATURAL IMMUNITY
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Background and Aims:

In 2011, Malawi introduced the 13-valent pneumococcal conjugate vaccine (PCV13; 3+0 schedule; coverage >90%). With persistent high vaccine serotype (VT) carriage amongst PCV13-vaccinated and age-ineligible children, we hypothesised high force-of-infection (FOI) and waning vaccine-induced immunity limits pneumococcal carriage control and, therefore, indirect herd protection.

Methods:

Cross-sectional nasopharyngeal carriage surveys over 2 years using random sampling of PCV13-vaccinated and age-ineligible healthy Malawian children. Serotyping was by 13-valent latex agglutination kit and DNA microarray. Age-/time-dependent VT carriage decay was assessed using deterministic-transmission mathematical (population-level) and non-linear statistical (individual-level) models.

Results:

1,382 PCV13-vaccinated (3-6yrs) and 889 PCV13-unvaccinated (5-10yrs) children were recruited June 2015 - April 2017. By latex, VT carriage prevalence decreased since study-start, from 23% to 17% amongst vaccinated (Adjusted Odds Ratio:0.69, p=0.05) and 27% to 15% amongst unvaccinated (AOR:0.56, p=0.03) children. Microarray detection of low-abundance VT pneumococci amongst multiple-serotype-carriage samples increased estimates of VT carriage by 36%, offsetting latex-based evidence of herd protection. Mathematical modelling projected ongoing VT carriage, suggesting high FoI, and highlighting importance of naturally-acquired immunity in augmenting waning vaccine-induced control. Statistical modelling supported this with a 5.3yr VT-carriage half-life after 6-months of age, irrespective of vaccination status.

Conclusion

A 3+0 schedule in Malawi has not achieved the sustained colonisation control required to generate robust herd protection. To optimise PCV population impact, it will be important to assess alternative strategies, including a booster dose in the 2nd year of life and/or maximising colonisation reduction/ minimising recolonisation by primary immunisation. Further understanding how naturally-acquired immunity augments vaccine-induced immunity may lead to novel interventions.
Methods:

Retrospective cohort study NCT02742753 analysed OM diagnoses from children ≤5 living in Skåne or Västra Götalandsregionen (VGR) between 1/1/2005 and 31/12/2013. PCV cohorts grouped subjects according to vaccine for which they were eligible.

Two different statistical approaches were used: 1) Time-series analyses (TSA) of monthly incidence rates (IRs) among children ≤2 described differences between pre-PCV, PCV7, and PHiD-CV/PCV13 vaccination time periods; and 2) among children ≤5, adjusted Age-Period-Cohort (APC) predictive models estimated VE and IR ratios of OM between PCV cohorts.

Results:

TSA showed the OM IR declined 42% (Skåne) and 25% (VGR) after PHiD-CV/PCV13 vs pre-PCV. Declines after PCV7 vs pre-PCV were 23% (Skåne) and 4% (VGR), but baseline IR and duration of PCV7 use differed between counties. Adjusted APC models, taking into account previous periods and vaccination status, showed that OM IR did not change significantly with PCV7 introduction in Skåne or VGR. The IR decreased after PHiD-CV vs pre-PCV by 9.9% (95%CI: 4.4, 15.1; p<0.001) and PCV13 vs pre-PCV by 2.3% (95%CI: -3.2, 7.6; p=0.401).

Conclusion

Descriptive TSA showed the IR of OM declined following introduction of both PHiD-CV and PCV13, while adjusted APC models suggest that only PHiD-CV was associated with a significant reduction of OM IR.

Funding: GlaxoSmithKline Biologicals SA

Background and Aims:

Mass vaccination of children with pneumococcal conjugate vaccines (PCVs) reduces the occurrence of pneumococci and potentially other organisms colonizing the upper respiratory tract, leading to a reduction in the risk of acute otitis media/otitis media (AOM/OM). PCV7 was introduced in Sweden in 2009 and replaced by the pneumococcal polysaccharide protein D-conjugate vaccine (PHiD-CV) or PCV13 in 2010. We assessed changes in time-to-first AOM/OM diagnosis in children aged ≤2 years separately for 2 Swedish counties, Skåne and Västra Götalandsregionen (VGR) using PHiD-CV and PCV13, respectively.

Methods:

This retrospective cohort study was conducted in Sweden and covered the period between 01/01/2005 and 31/12/2013, using data from regional and national databases (PASiS, Vega,
Time-to-first AOM/OM diagnosis was estimated by survival analysis using a confounder-adjusted right-censored Cox proportional hazards model.

**Results:**

Adjusted time-to-event analyses showed that both PHiD-CV and PCV13 decreased the risk of first AOM/OM diagnosis for children aged ≤2 years versus PCV7 and pre-PCV cohorts, with reductions relative to PCV7 being similar (Table). Adjusted hazard rates were significantly lower for the PCV7 cohort than the pre-PCV cohort in Skåne, but not in VGR.

Table. Adjusted hazard ratios (HR) of time-to-first AOM/OM diagnosis between study cohorts

<table>
<thead>
<tr>
<th>PCV cohorts</th>
<th>Skåne</th>
<th>VGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV7 relative to pre-PCV</td>
<td>0.792</td>
<td>0.997</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.771–0.814</td>
<td>0.969–1.025</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>0.821</td>
</tr>
<tr>
<td>PHiD-CV/PCV13 relative to pre-PCV</td>
<td>0.673</td>
<td>0.867</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.654–0.692</td>
<td>0.849–0.886</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PHiD-CV/PCV13 relative to PCV7</td>
<td>0.849</td>
<td>0.870</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.820–0.879</td>
<td>0.843–0.898</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AOM/OM, acute otitis media/otitis media; VGR, Västra Götalandsregionen; PCV, pneumococcal conjugate vaccine; CI, confidence interval; PCV7, 7-valent PCV; PCV13, 13-valent PCV; PHiD-CV, pneumococcal polysaccharide protein D-conjugate vaccine.

Note: The model was adjusted for sex, maternal age, smoking at pre-conception, smoking at 30 weeks gestation and health condition at birth.

**Conclusion**

Adjusted HRs for time-to-first AOM/OM diagnosis were consistently lower for PCV13 and PHiD-CV versus either PCV7 or pre-PCV, across both Skåne and VGR. Both PHiD-CV and PCV13 appear to decrease the risk of first AOM/OM in young children.

**Funding:** GlaxoSmithKline Biologicals SA

**ISPPD-0609**

HEALTHCARE UTILIZATION AND DIRECT COSTS ASSOCIATED WITH OTITIS MEDIA IN CHILDREN AGED ≤2 YEARS FOLLOWING PNEUMOCOCCAL CONJUGATE VACCINE INTRODUCTION IN SWEDEN: A RETROSPECTIVE COHORT STUDY

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**Background and Aims:**

Otitis media (acute or other; AOM/OM) is a major reason for antibiotic prescriptions and one of the main drivers of healthcare utilization (HCU) and associated costs in young children. In Sweden, 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in 2009 and replaced by pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV) or 13-valent PCV (PCV13) in 2010. We analyzed AOM/OM-related HCU and direct costs in children aged ≤2 years, separately for 2 Swedish counties (Skåne, Västra Götalandsregionen [VGR]) using PHiD-CV and PCV13, respectively.

**Methods:**
In this retrospective cohort study, data were collected for children aged ≤2 years from national and regional healthcare databases (PASiS, Vega, NPR, PDR) between 01/07/2005 and 31/12/2013.

**Results:**

Annualized mean total AOM/OM-associated HCU costs decreased in PCV7 versus pre-PCV cohort and further declined in PHID-CV/PCV13 cohort, although higher at baseline in Skåne (Figure). Changes in adjusted annualized cost ratios for AOM/OM were statistically significant after PCVs introduction in both counties (Table).

**Conclusion**

Following PCVs introduction, AOM/OM-related HCU and direct costs appeared to decline in both Skåne and VGR. Cautious interpretation is warranted, since antibiotic-prescribing guidelines for AOM/OM changed when PHID-CV/PCV13 were introduced, and there are more ENTs and pediatricians in regions using PHID-CV versus PCV13.

**Funding:** GlaxoSmithKline Biologicals SA
ISPPD-0618
CROSS SECTIONAL POST-PCV13 SURVEY ON STREPTOCOCCUS PNEUMONIAE COLONIZATION AMONG CHILDREN AND THEIR IMMEDIATE FAMILY CIRCLE IN DAPONG, NORTHERN TOGO
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Background and Aims:
Because of funding and supply limitations, almost no Gavi-eligible country introducing pneumococcal conjugate vaccines (PCVs) in routine infant immunization programs have conducted catch-up campaigns. An exception was the districts of Tone and Cinkasse, Northern Togo where all children 9 months to 4 years of age (y) received one dose of PCV13 in march 2015 after vaccine introduction in june 2014. Our study aims at evaluating the impact of PCV13 on Streptococcus pneumoniae (Sp) nasopharyngeal (NP) colonization in the population of the city of Dapaong (District of Tone).

Methods:
Between january and march 2017 we conducted a cross-sectional study of Sp carriage in 10 schools of Dapaong. We evaluated healthy school children ages 3-15y (n = 338), their siblings <3y (n = 293), and persons over 15y in their immediate family circle including parents (n = 101). NP swabs were obtained and evaluated by standard microbiology at the laboratory in Dapaong.

Results:
We isolated Sp from 558 (76%) of 732 NP swabs, 344 (84%) of 408 in children <5y. Age-specific NP colonization prevalences were 84%, 84%, 71%, and 55% in <1y, 1-4y, 5-14y, and 15y+ persons respectively. PCV13 coverage based on card or history (with card only) was 79% (75%) among <1y (2+ PCV13 doses during routine immunization) and 70% (56%) among 1-4y (1+ PCV13 doses during routine immunization or catch-up).

Conclusion
NP carriage was high after PCV13 introduction. Serotyping is ongoing and will allow assessment of the impact of routine immunization combined with a catch-up campaign in vaccine serotype pneumococcal transmission within families.

ISPPD-0337
INVASIVE BACTERIAL INFECTIONS IN CHILDREN UNDER FIVE WITH RADIOLOGICALLY CONFIRMED PNEUMONIA AFTER THE INTRODUCTION OF HAEMOPHILUS INFLUENZAE TYPE B AND PNEUMOCOCCAL CONJUGATE VACCINES IN MOZAMBIQUE
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Background and Aims:

Pneumonia continues to be a major cause of morbidity and mortality worldwide. Mozambique introduced the *Haemophilus influenzae* type b (Hib) vaccine and 10-valent pneumococcal conjugate vaccine (PCV10) in 2009 and 2013, respectively. We aimed to describe the impact of these vaccines on invasive Hib and vaccine-type (VT) pneumococcal disease in patients with X-ray confirmed (XRC) pneumonia.

Methods:

We used hospital-based surveillance in Manhiça District to identify XRC pneumonia (per WHO definition) in children aged <5 years who had blood culture collected. *H. influenzae* and pneumococcus blood culture isolates were serotyped by slide agglutination and Quellung, respectively. We compared prevalence of Hib and VT-pneumococcal invasive disease among children with XRC pneumonia pre- (2006–2008) and post- (2014–2016) vaccines introduction.

Results:

A total of 367 (24.7%) and 224 (34.9%) had XRC pneumonia pre- and post-vaccine, respectively. Among children with XRC pneumonia and blood culture collected, Hib was isolated from 2.7% (10/367) versus 0% (0/221; P=0.008) in pre- and post-vaccine periods, and pneumococcus was isolated from 10.3% (38/367) versus. 8.5% (19/221; P=0.49). The prevalence of VT-pneumococcus among those with invasive pneumococcal disease decreased from 54% (20/38) to 27.8% (5/18) (P=0.07) after PCV10 introduction, whereas prevalence of 13-valent PCV (PCV13) unique serotypes (3, 6A 19A) increased from 10.8% (4/37) to 33.3% (6/17; P=0.06).

Conclusion

Declines in Hib and VT-pneumococcal disease in children with XRC pneumonia were observed. Mozambique is switching to PCV13 in November 2017 and it will be important to monitor if this change will control the additional serotypes.
The Belgian infant pneumococcal conjugate vaccine (PCV) programme changed from PCV13 to PCV10 in 2015-2016. In 2016-2017 (year 2), we monitored for the second year *S. pneumoniae* colonization in healthy infants, using the methodology as for the earlier study in March-June 2016 (year 1).

**Methods:**

In infants (6-30 months) residing in one of 112 randomly selected day-care centres (DCC), a single nasopharyngeal swab was taken in November-March and transported in STGG medium to the pneumococcal reference laboratory. *S. pneumoniae* were cultured with and without BHI enrichment, screened for antibiotic resistance (5 antibiotics), and serotyped (Quellung). Demographic and clinical characteristics and vaccination status were collected via a questionnaire.

**Results:**

In 1096 infants included *per protocol*, pneumococcal carriage was frequent (68.2%), as in year 1 (60.8%). Among carriers, PCV13 serotypes were identified at low frequency (3.5%, 95%CI=2.3%-5.1%), and dominated by 19F and 19A. Prevalence of PCV13-non-PCV10 serotypes (3, 6A, 19A) altogether (1.6%, 95%CI=0.9%-2.9%) was not significantly different from year 1 (0.9%, 95%CI=0.3%-2.4%). Predominant non-vaccine serotypes were 23B (17.8%) and 15B (8.3%). Among detected strains, 41.4% and 11.3% were resistant against at least one or at least two antibiotics, respectively. Pneumococcal carriage was related to having siblings, AOM-history, signs of common cold and antibiotic treatment within 3 months prior to sampling (P-value Chi²<0.05).

**Conclusion**

One year after the PCV13-to-PCV10 switch in Belgium, culture-based PCV13 serotype carriage in infants remained low and the increase of PCV13-non-PCV10 serotypes was not significant. Since half of the infants were vaccinated before the switch, further monitoring is necessary.

**ISPPD-0282**

**GENOMIC EPIDEMIOLOGY AND ANTIMICROBIAL RESISTANCE IN INVASIVE SEROTYPE 19A PNEUMOCOCCI BEFORE AND AFTER INTRODUCTION OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) IN FINLAND**

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**Background and Aims:**

Following introduction of 10-valent pneumococcal conjugate vaccine (PCV10) into infant National Vaccination Program in 2010, the incidence of serotype 19A invasive pneumococcal disease (IPD) has increased in adults, particularly among older age groups. We studied changes in genomic epidemiology and antimicrobial resistance in invasive 19A isolates from Finnish children during 2007–2015.

**Methods:**

Clinical microbiology laboratories routinely submit IPD isolates to the national reference laboratory for species confirmation and typing. All 19A pneumococci (n=67) isolated from
children <5 years of age before (2007–2010, n=26) and after (2011–2015, n=41) PCV10 introduction were evaluated. Antimicrobial susceptibility was determined by agar dilution method using EUCAST breakpoints. Whole genome sequencing (WGS) data was generated using Illumina MiSeq platform. A core-genome MLST (cgMLST) scheme based on 1234 genes was used for genome-wide comparisons. Classical seven-locus MLST sequence types were determined using Ridom SeqSphere+ and/or Streptococcus pneumoniae MLST Database (PubMLST) tools.

Results:

Before PCV10-introduction, ST193, resistant to erythromycin, clindamycin and tetracycline, and antimicrobial susceptible ST482 were most prevalent clones. During PCV10 period, a previously undetected, antimicrobial susceptible ST994 strain and an erythromycin-resistant, penicillin-nonsusceptible single locus variant of ST671 have become the predominant clones.

Conclusion

The genomic structure of 19A IPD isolates from children shifted rapidly after PCV10-introduction, suggesting selective pressure from vaccination program. Future studies should also evaluate changes in the genomic epidemiology and antimicrobial resistance among older age groups.

ISPPD-0757
STREPTOCOCCI PNEUMONIA EMPYEMA IN A FULLY IMMUNISED TODDLER WITH THE 13-VALENT PNEUMONOCOCCAL VACCINE
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Background and Aims:
Streptococcus pneumoniae is one of the main pathogens in community acquired pneumonia in children. Serious complications include parapneumonic effusion and/or empyema. We present a case of pleural empyema in a fully vaccinated child in order to discuss streptococcal pneumonia serotypes that are not included in available pneumococcal 13-valent vaccine and raise a public health issue in paediatric population.

Methods:

A 26 months old boy presented in poor general condition with grunting, respiratory distress, tachypnea, hyperpyrexia 40°C, difficulty with feeding and an eight day history of fever and coughing. He was on treatment with oral amoxicillin-clavulanic acid (60mg/kg/d). Left hemithorax air entry was reduced. Chest x-Ray and ultrasound revealed left sided pleural effusion and CRP was 117mg/l. He was started on intravenous antibiotics with Ceftriaxone and Vancomycin. 24 hours later he deteriorated further, repeated chest ultrasound showed increased pleural effusion >1/2 of the left hemithorax, and he underwent surgical chest drainage and fibrinolysis. Pleural fluid PCR isolated Streptococcus Pneumoniae, with a serotype not present in 13-valent pneumococcal vaccine. Child was fully immunized with 13-valent pneumococcal vaccine

Results:

The course of the disease since was uncomplicated although total recovery was noted after 2 months period

Conclusion

Although 13-valent pneumococcal vaccine thought to diminish the incidence of pneumococcal effusions after the use of 7-valent vaccine, it seems that new or old serotypes not included in the 13-valent vaccine continue to complicate community acquired pneumonia in children with serious conditions such as parapneumonic effusion and empyema and pose the vaccination program in children for pneumococcal disease under discussion.

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ISPPD-0041

BURDEN OF PAEDIATRIC BACTERIAL MENINGITIS AMONG CHILDREN PRE AND POST INTRODUCTION OF PCV13 IN TOGO

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Background and Aims:

Prior to new vaccines introducing in the immunization schedule in Togo it was necessary to monitor invasive bacterial diseases. Hib-vaccine was introduced in July 2008 and PCV₁₃ vaccine in June 2014.

Methods:
Paediatric bacterial meningitis (PBM) surveillance started in June 2005 at CHU Sylvanus Olympio in Lome using the WHO’s generic protocol. We compared data during the PCV$_{13}$ pre-vaccine period (2010-2014) to two years post-vaccine data (2015-2016).

**Results:**

An early post-vaccine significant 40-50% reduction was observed for suspected meningitis cases, and 86-100% reduction for pneumococcal meningitis cases during the first two post-vaccine years (p<0.001). We observed an emergence of *Haemophilus influenzae* six years after anti *Haemophilus influenzae* type b vaccine introduction into EPI (table 1).

**Table 1: Annual distribution of meningitis cases from 2010 to 2016**

<table>
<thead>
<tr>
<th>Year</th>
<th>Suspected cases</th>
<th>Lumbar puncture</th>
<th>Probable meningitis</th>
<th>Confirmed cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spn</td>
</tr>
<tr>
<td>2010</td>
<td>518</td>
<td>477</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>2011</td>
<td>631</td>
<td>626</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td><strong>PCV$_{13}$ pre-vaccine period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>770</td>
<td>760</td>
<td>51</td>
<td>4</td>
</tr>
<tr>
<td>2013</td>
<td>623</td>
<td>616</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>2014</td>
<td>535</td>
<td>530</td>
<td>44</td>
<td>6</td>
</tr>
<tr>
<td>Annual mean</td>
<td>615</td>
<td>601</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td><strong>PCV$_{13}$ post-vaccine period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>308</td>
<td>306</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>2016</td>
<td>375</td>
<td>373</td>
<td>28</td>
<td>0</td>
</tr>
</tbody>
</table>

Spn = *Streptococcus pneumoniae*, Hi = *Haemophilus influenzae*, Nm = *Neisseria meningitidis*

**Conclusion**

We report impact of PCV13 vaccine through PBM sentinel surveillance in Togo. It will be necessary to continue the surveillance to monitor change in bacterial strains.

**Acknowledgements:** the authors acknowledge GAVI, the WHO/AFRO and the Ministry of Health in Togo.

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**ISPPD-0348**

**TRENDS IN STREPTOCOCCUS PNEUMONIAE (SP) SEROTYPES ISOLATED FROM NASOPHARYNGEAL (NP) CARRIAGE IN CHILDREN, ATLANTA, USA 2010-2017**

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Background and Aims:

Introduction of 13-valent pneumococcal conjugate vaccine (PCV13) in 2010 decreased pediatric invasive pneumococcal disease (IPD) due to vaccine serotypes (VT). Trends in NP carriage of SP were analyzed to describe carriage serotypes.

Methods:

NP swabs collected from children ages 6-59 months in an emergency department in Atlanta from 2010-17 were broth-enriched and cultured for SP. Isolates were serotyped and susceptibility testing performed. Patient characteristics, health history, and immunization records were collected. Trends over time were assessed.

Results:

NP swabs from 4,765 children grew SP at similar rates throughout the study period (mean 30.5/100 children enrolled [CE]). Mean age of carriers was 25 months and 53% were males. Carriage rates were higher among younger children (6-23months), black race, daycare attendees, and those presenting with upper respiratory infections (URI; P<0.05). VT rates declined from 4.9/100CE in 2010-11 to 0.8/100CE in 2016-17. Non-VT carriage serotypes included 15B/C(5.0/100CE), 35B(4.5/100CE), 23A/B(3.4/100CE), 11A(2.5/100CE), 21(2.0/100CE) and 15A(1.8/100CE). No single dominant non-VT has emerged. Antibiotic nonsusceptibility (NS) to ceftriaxone, penicillin, and clindamycin dropped significantly (p<0.01) over time, but was unchanged to erythromycin (36%). Children up-to-date (UTD) for PCV13 increased from 47.9% in 2010-11 to 92.3% in 2016-17 (p<0.01). VT carriage was higher in those not UTD (5.7 vs 1.8).

Conclusion

SP carriage was highest among children age 6-23months, of black race, daycare attendees and those with URI. Erythromycin NS remains significant among SP isolates. The overall rate of pediatric NP carriage was stable but VT carriage declined significantly, most notably in those UTD for PCV13.

ISPPD-0177

SEROTYPE 15A (S15A) INVASIVE PNEUMOCOCCAL INFECTIONS (IPIs) IN CHILDREN FROM EL SALVADOR (ES): THE NEED FOR CONTINUOUS SURVEILLANCE

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Background and Aims:

S15A non-invasive and IPIs have emerged in some countries following universal PCV introduction, and multi-drug resistance among these patients(pts) has been a concern. However, multicenter studies involving significant number of pts to determine the overall prevalence are needed. In ES, universal PCV7(3+1) and PCV13(2+1) were introduced for infants in Jan-2010 and Jan-2011, respectively. We describe the first Central American report of pts who developed a serotype 15A-IPI at the only national pediatric tertiary referral hospital of ES.
Methods:

Retrospective chart and laboratory review of all pts <13 years hospitalized with a culture-confirmed S15A IPI at our center: Jan-01-2007 to Sep-30-2017.

Results:

Among 149 pts with an IPI during this specific period, serogroup determination was available in 144 (96.6%) pts. Of these, 10/144 (6.9%) had a serogroup 15 infection as follows: serotype 15A (6pts), serotype 15C (2pts), serotype 15B (1pt), and undetermined, 1 pt. Among the six S15A pts analyzed, all infections occurred during the last 3 years: 2015 (2), 2016 (2) and 2017-Sep 30th (2). Ages were 4, 5, 6, 72, 96 and 108 months, respectively. 3 (50%) pts were male. Primary clinical diagnosis was: sepsis/septic shock (3pts), pneumonia (2pts), and endophthalmitis/intraocular abscess (1pt). 3 (50%) died (all sepsis/septic shock pts). 5/6 (83.3%) pts required PICU admission and all were mechanically ventilated. Penicillin/cefotaxime resistance was 0% and 16.7%, respectively.

Conclusion

Following universal PCV7/PCV13 introduction, a slight increase of S15A has been observed at our hospital. Of interest, most isolates were penicillin/cefotaxime susceptible. The morbidity and mortality rates of pediatric S15A IPIs were high.

ISPPD-0190
SEROTYPE 10A (S10A) INVASIVE PNEUMOCOCCAL INFECTIONS (IPIs) ASSOCIATED WITH HIGH FATALITY RATES IN CHILDREN FROM EL SALVADOR (ES)
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², San Salvador, El Salvador

Background and Aims:

The overall prevalence of S10A IPIs in children prior to universal PCVs introduction was very low, and even after, very few reports have addressed its clinical and microbiological importance. In ES, universal PCV7 (3+1) and PCV13 (2+1) were introduced for infants in Jan-2010 and Jan-2011, respectively. We describe the first cases of S10A IPIs at the only national pediatric tertiary referral academic hospital in ES.

Methods:

Retrospective chart and laboratory review of pts <13 years hospitalized with a culture-confirmed S10A IPI at our center: Jan-01-2007 to Sep-30-2017.

Results:

Among 149 pts with an IPI during this specific period, serogroup determination was available in 144 (96.6%) pts. Of these, 11/144 (7.6%) had a serogroup 10 infection as follows: serotype 10A (5pts), serotype 10B (1pt), serotype 10F (1pt), and undetermined (4pts). Month ages were 2, 7, 24, and 132 (2 pts), respectively. 3 (60%) pts were male. Primary clinical diagnosis was: sepsis/septic shock (2pts), pneumonia (1pt), meningitis (1pt), and primary peritonitis (1pt). Underlying medical conditions were documented in 3 pts: 32-week prematurity (1pt), Down syndrome + Hypothyroidism (1pt) and ALL (1 pt).
Penicillin/cefotaxime resistance was detected in 2 (40%) and 1 (20%), respectively. All 5 (100%) pts developed septic shock, required PICU admission, and mechanical ventilation; 1 pt (meningitis) developed neurological death. All 5 (100%) pts died.

**Conclusion**

Although the prevalence of pediatric S10A IPIs is low, surprisingly all of our patients died. Continuous surveillance of S10A and other emerging serotypes should be continued in ES following PCV introduction.

**ISPPD-0414**

**A TWO-YEAR ASSESSMENT OF PPV23-VACCINE EFFECTIVENESS AGAINST INVASIVE PNEUMOCOCCAL DISEASE IN THE DANISH ELDERLY POPULATION USING THE INDIRECT COHORT METHOD**

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²Statens Serum Institut, Department of Bacteria-Parasites and Fungi, København S, Denmark

**Background and Aims:**

PPV23 (Pneumovax) will prevent approximately 70% of Invasive pneumococcal disease (IPD) in immunocompetent adults. We wanted to study the vaccine effectiveness (VE) in the elderly population (≥65 years), where chronic conditions and immunosenescence play a role. These groups are eligible for pneumococcal vaccination with PPV23 and/or PCV13, some with limited subsidy. In 2014 the estimated coverage in 65 year olds was 13% for PPV23 and 2% for PCV13

**Methods:**

We assessed the vaccination status of all IPD cases aged ≥65 years in 2015 and 2016 by contacting their general practitioners. Pneumococcal isolates from cases of IPD were submitted to the National Reference Laboratory for serotyping as part of the mandatory surveillance. To estimate vaccine effectiveness (VE) of PPV23 and of PCV13, we used the indirect cohort method, a case-control type design, which uses non-vaccine type (NVT) cases as controls and vaccine types (VT) as cases

**Results:**

We obtained information about vaccination status for 741 (75%) out of the 979 cases. Serotyping was available for 97%, and 74 and 22 had received PPV23 or PCV13 at least 14 days prior to the episode of IPD, respectively. We found 205 NVT and 524 (74%) VT cases with information about PPV23 vaccination status. The results showed a PPV23 VE of 58% (95% CI: 31-75), adjusted for age, gender and year of notification. The study was not powered to investigate the outcome VE for PCV13

**Conclusion**

PPV23 vaccination is effective in reducing the burden of IPD in an elderly population where PPV23 VT are very frequent.
LONG-TERM IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN KENYA: NASOPHARYNGEAL CARRIAGE AMONG CHILDREN AND ADULTS WITH SEVERE ACUTE RESPIRATORY INFECTION SIX YEARS AFTER INTRODUCTION

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Background and Aims:

Kenya introduced the 10-valent pneumococcal conjugate vaccine (PCV10) in 2011, using 3 primary doses and catch-up campaigns in select areas. Carriage of PCV10 serotypes soon declined, yet it is unknown to what extent vaccine-types continue to circulate.

Methods:

We assessed pneumococcal carriage among patients with severe acute respiratory infection (SARI) from ongoing surveillance in Kibera (Nairobi urban slum, no catch-up) and Asembo (rural western Kenya, 2-dose catch-up for children 1-4 years). SARI criteria were: for <5 years, cough or difficulty breathing plus indrawing, danger sign, or hypoxemia (saturation <90%); for ≥5 years, cough or difficulty breathing or chest pain plus temperature >38.0 °C or hypoxemia. Nasopharyngeal swabs were frozen in STGG within 4 hours and underwent broth enrichment before culturing. Isolates were serotyped by Quellung.

Results:

From 1/2017 to 9/2017, we enrolled 892 SARI patients; 737 (83%) were swabbed, and 689 (93%) cultured to date. Pneumococcus was detected in 30/41 (73%) and 64/131 (49%) cases aged <5 and ≥5 years respectively in Kibera, and 94/141 (67%) and 109/376 (29%) respectively in Asembo. Among 261 (88%) isolates serotyped to date, 35 (13%) are vaccine-type, including 8% and 19% from cases aged <5 and ≥5 years respectively in Kibera, and 14% and 12% respectively in Asembo. PCV10 serotypes in Kibera were 5 (n=3), 23F (n=3), 1 (n=2), 19F (n=2), 14 (n=1), and in Asembo 19F (n=14), 23F (n=5), 14 (n=3), 4 (n=1), 9V (n=1).

Conclusion

Six years post-PCV10 introduction, vaccine serotypes persist in Kenya, including in areas with a catch-up campaign.

INCREASED CARRIAGE OF NON-VACCINE SEROTYPES WITH LOW INVASIVE DISEASE POTENTIAL FOUR YEARS AFTER SWITCHING TO THE 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN THE NETHERLANDS

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⁴University Medical Centre Utrecht, Utrecht, The Netherlands
⁵Stichting Erasmus Medical Centre, Rotterdam, The Netherlands

Background and Aims:

The Netherlands switched from a 7- to a 10-valent pneumococcal conjugate vaccine (PCV10) in 2012, with no catch-up campaign. We assessed whether the introduction of PCV10 was associated with increased carriage of vaccine-escape serotypes in children.
Background and Aims:

The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in The Netherlands in 2006 and was replaced by the 10-valent PHiD-CV10 in 2011. Data on carriage prevalence of *S. pneumoniae* serotypes in children and invasive pneumococcal disease (IPD) in children and elderly were collected to examine the impact of PCVs on carriage and IPD in The Netherlands from 2004 until 2016.

Methods:

Data from the 2015/2016 carriage study were compared with data from previous studies in 2005, 2009, 2010/11 and 2012/13.

Results:

The overall pneumococcal carriage rate in children was 48% in 2015/2016 and lower as compared to pre-PHiD-CV10 in 2010/2011 (64%) and pre-vaccination in 2005 (66%). Carriage of the previously dominant non-vaccine serotypes 19A and 11A declined from 14.2% to 4.6% and 4.2% to 2.7% since 2010/2011, while carriage of serotypes 6C and 23B increased (4.2% to 6.7% and 3.9% to 7.3%). Serotypes 6C and 23B are therefore now the most prevalent carriage serotypes. The dominant carriage serotypes 6C, 23B and 11A show low invasive disease potential. IPD incidence declined in children (20/100,000 cases in 2004/2006 to 6/100,000 cases in 2015/2016) as well as in elderly (63/100,000 cases to 51/100,000 cases). Serotype 8 is the main causative agent for IPD in elderly (11.3%).

Conclusion

In conclusion, 4 years after the switch to PHiD-CV10 in The Netherlands shifts in carriage and disease serotypes are still ongoing. Surveillance of both carriage and IPD is important to assess PCV impact and to predict necessary future vaccination strategies in both children and elderly.

__ISPPD-0151__

IDENTIFYING AGE GROUPS ASSOCIATED WITH INDIRECT PROTECTION OF PCVS

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²Ben-Gurion University of the Negev, Faculty of Health Sciences, Be’er Sheva, Israel
Background and Aims:

To predict and understand the effectiveness of alternative dosing strategies for pneumococcal conjugate vaccines, it is important to determine which age groups contribute most to indirect protection. We evaluated this question using comprehensive data on vaccine uptake, carriage, and disease from Israel.

Methods:

We used data from Israel on nasopharyngeal carriage and otitis media in children and invasive pneumococcal disease (IPD) adults 65+ years of age. Data on vaccine uptake were obtained from children visiting the emergency department. We calculated uptake of PCV7/13 in each month post-PCV introduction in age bands that varied in width and ages included. For each of the three outcomes, we fit a series of logistic regression models to test the association between population-level vaccine uptake in the different age bands and the odds of isolating a PCV7-targeted serotype. Models of carriage and otitis media also controlled for the vaccine status of the individual. AIC scores were used to determine the importance of vaccine uptake in each age band.

Results:

The temporal pattern of decline of PCV7-targeted serotypes in carriage in children, otitis media in children, IPD in adults was most closely correlated with uptake of PCV7/13 in toddlers and early school-aged children rather than infants (Figure).

Conclusion

The vaccine status of children age 1-4y could be more important in driving indirect protection than that of infants.

ISPPD-0596
THE IMPACT OF THE 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE ON RECURRENT ACUTE OTITIS MEDIA EPISODES AND PRESSURE-EQUALIZING TUBE INSERTIONS AMONG YOUNG CHILDREN IN TENNESSEE
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Background and Aims:

The impact of early pneumococcal acute otitis media (AOM) prevention through vaccination, on subsequent AOM episodes, remains unclear due to the challenge of accounting for recurrent episodes in traditional survival analyses. We assessed whether the transition from PCV7 to PCV13 changed the risk of AOM or pressure-equalizing tube (PET) insertions among children <2 years accounting for the dependence between recurrent events.

Methods:

We identified consecutive annual (July-June) birth cohorts of children enrolled in the Tennessee Medicaid program (2006-2014) from date of birth through age two years or loss of enrollment. We identified AOM episodes using coded diagnoses and considered episodes <21 days apart to be the same episode. We modeled adjusted hazard ratios (aHR) and compared the average cumulative incidence of AOM episodes and pressure-equalizing tube (PET) insertions between birth cohorts while accounting for risk factors (e.g., birth weight, gender, maternal tobacco use, among others) and the dependence between recurrent events.

Results:

We observed 692,092 AOM episodes and 27,831 PET insertions among 414,134 children. The adjusted average incidence of AOM and PET insertions increased during the pre-PCV13 years and declined following PCV13 introduction (Figure 1). Compared to the 2008-2009 cohort, the adjusted hazards of AOM and PET insertions were lower in the 2013-2014 cohort [aHR:0.95 (95% CI:0.94-0.96) and aHR:0.76 (95% CI:0.73-0.80), respectively].

![Figure 1. Average cumulative incidence of acute otitis media (AOM) and pressure-equalizing tube (PET) insertions at 2 years for each birth cohort accounting for risk factors (i.e., child gender and birthweight, maternal tobacco use and history of poor pregnancy outcomes, prenatal care, gestational diabetes/hypertension and maternal age) and the dependence between recurrent events. Estimates for the 2009-2010 birth cohort are not included as PCV13 was introduced in the US in early-2010 (vertical dashed-line). Locally-weighted scatter-plot smoothing used to create curves for AOM and PET insertions. Adjusted hazard ratios (with 95% CI) compare the last observed cohort (2013-2014) to the last pre-PCV13 cohort (2008-2009) accounting for risk factors and dependence between recurrent events.](image)
Conclusion

Transition to PCV13 was associated with reductions in AOM and PET insertions among young children.

ISPPD-0086

CHANGES OF SEROTYPE IN STREPTOCOCCUS PNUMONIAE SEROTYPES BETWEEN PRE AND POST OF THE 13-VALENT PNEUMOCOCCAL VACCINATION IN A HOMOGENOUS POPULATION IN THE SOUTH KOREA

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Background and Aims:

To assess whether changing of the molecular types of Streptococcus pneumoniae (S. Pneumoniae) after 13-valent pneumococcal vaccine (PCV 13) was introduced in a homogenous population of South Korea and whether these associations varied with age.

Methods:

We compared the molecular types of S. pneumoniae between prevaccinal period (2009~2010) with postvaccinal period (2014~2015) of in a single tertiary hospital.

Results:

A total of 307 S. pneumoniae strains were isolated during the periods. Most of the S. pneumoniae isolates were obtained from all ages. Of all isolates, 119 (38.7%) were obtained from elderly ≥ 65 years and 112 (36.4%) from children < 5 years old. The common set specimen was sputum and transtracheal aspirates (n=224, 77.1%), followed by nasopharyngeal fluid (n= 51, 16.2%), ear discharge (n=9, 2.9%), blood (n=8, 2.5%), and others (n=14, 4.4%). The most frequent serotypes were 19A/F, 23A, 15A/F, and 3. In pre-vaccination period, 4 serotypes were identified and the serotypes were 19A/F, 15A/F, 19B, and 23A. In post-vaccination period, 15 serotypes were identified and the major serotypes were 23A, 15A/F, and 3. PCV 13 serotype coverage was 80.0% and 30.5% in pre and post vaccination periods, respectively.

Conclusion

After post vaccination period, PCV 13 serotype coverage was decreased compared with heterogenous population studies. 19A/F serotype including PCV 13 serotype was significantly lower prevalence, but the proportion of non-PCV 13 serotypes showed an increasing trend in homogenous population after PCV 13 introduction. It will be useful when considering pneumococcal vaccination strategies in our area.

ISPPD-0120

NATIONAL TRENDS IN AMBULATORY CARE VISITS FOR OTITIS MEDIA IN CHILDREN UNDER THE AGE OF FIVE IN THE UNITED STATES

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²Pfizer Inc, Statistical Research and Consultation Center, New York City, USA
³Biostatistician Consultant, Biostatistician Consultant, Pittsboro, USA
⁴Pfizer Inc, Vaccine Research, Collegeville, USA
Background and Aims:

The 7 and 13-valent pneumococcal conjugate vaccines (PCV7 and PCV13) were approved in the US in 2000 and 2010 respectively for active immunization against invasive disease and otitis media (OM) caused by 7 serotypes common to both vaccines starting at ≥6 weeks of age. This study assessed the impact of PCV13 on OM by evaluating changes in US ambulatory care visit rates between the period before (pre-) PCV7 (1997–1999), during PCV7 (2001–2009) and after the introduction of PCV13 (2011-2013) among US children <5 years.

Methods:

This ecologic study used US National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey data. Trend analyses using weighted least-squares regression and mean visit rates over comparison periods were calculated for OM and control endpoints unrelated to vaccinations, skin rash and trauma.

Results:

Among children <2, 2-<5, and <5 years, statistically significant reductions in OM visits per 100 children were 24% (21 visits), 16% (6 visits), and 22% (13 visits) comparing PCV13 to PCV7 periods and 48% (59 visits), 29% (14 visits), and 41% (32 visits) comparing PCV13 to pre-PCV7 periods. Visit rates for skin rash and trauma remained stable during PCV13 and PCV7 periods.

Conclusion

Significant reductions in US ambulatory care visit rates for OM were observed among children aged <5 years after introduction of PCV13 compared to before and during PCV7 periods, and were greatest among children <2 years. The additional reductions beyond PCV7 period are likely due to the 6 additional serotypes in PCV13.

Background and Aims:

Invasive bacterial infections cause significant morbidity and mortality in sub-Saharan African. Many are vaccine preventable although the impact of new vaccines and vaccine policies on disease patterns in communities and populations is rarely documented. We retrospectively compared disease trends in relation to the vaccines introduced in order to detect changes in the pathogens responsible for disease.

Methods:

ISPPD-0063
ABSTRACT:COMMUNITY ACQUIRED INVASIVE BACTERIAL INFECTIONS IN THE GAMBIA: A 10 YEAR RETROSPECTIVE ANALYSIS
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Data for all patients with positive blood and cerebrospinal fluid (CSF) cultures between January 2005 and December 2015 were analysed. Surveillance periods were determined over the following three time periods: pre-PCV introduction (January 2005-December 2009), PCVs introduction (January 2010 - December 2011) and post-PCV introduction (January 2012 - December 2015). We compared disease prevalence between pre-PCV and post-PCV introduction.

Results:

We evaluated 15203 blood and 1246 CSF cultures and analysed 982 pathogens respectively from 957 patients. The most common organisms were *S. pneumoniae* (261/982; 26.6%), *S. aureus* (210/982; 21.4%), *E. coli* (103/982; 10.5%) and NTS (94/982; 9.6%). *S. pneumoniae* prevalence dropped across all age groups post-PCV and inversely, *S. aureus* proportionally increased across all age groups. A decrease in vaccine serotypes was noted from 59.8% to 43.1% with a concurrent increase in non-vaccine serotypes from 17.9% to 39.7%, 12F being the more prominent.

Conclusion

*S. aureus* has emerged as the leading cause of invasive disease after introduction of PCV vaccine. This apparent replacement by another pathogen suggests that multiple approaches to tackling invasive bacterial disease in sub-Saharan Africa is warranted.

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VACCINE STUDIES FROM THE ASIA/PACIFIC

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ISPPD-0469

PROTEIN D IgG POST PRIMARY SERIES AND POST-BOOSTER FOLLOWING ALTERNATIVE PNEUMOCOCCAL VACCINATION STRATEGIES IN VIETNAM

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5University of Melbourne, Pathology, Melbourne, Australia
6London School of Hygiene and Tropical Medicine, Child Health and Vaccinology, London, United Kingdom

Background and Aims:

*Streptococcus pneumoniae* and non-typeable *Haemophilus influenzae* (NTHi) cause severe infant infections. The PCV10 vaccine (Synflorix) contains eight of ten polysaccharide serotypes conjugated to Protein D of NTHi. Our recent trial in Ho Chi Minh City, Vietnam compared Protein D IgG responses following four unique PCV10 schedules.

Methods:

Infants were randomised to receive 2 to 4 doses of PCV10 – refer table. Protein D IgG was measured in blood samples collected one month post-primary series and one month post-booster. Protein D immunogenicity is presented for 364 paired samples.
Results:

There was a significant increase in Protein D IgG for Groups A, C and D post-booster (p<0.0001). There was a significant decrease (p<0.0001) in Protein D IgG in Group B at 10 months following the primary series, 3 X PCV10. Refer table.

<table>
<thead>
<tr>
<th>Group</th>
<th>3 X PCV10</th>
<th>3+1 PCV10</th>
<th>3 X PCV10</th>
<th>3+0 PCV10</th>
<th>2 X PCV10</th>
<th>2+1 PCV10</th>
<th>1 X PCV10</th>
<th>1+1 PCV10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number pairs</td>
<td>72</td>
<td>72</td>
<td>122</td>
<td>98</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine (months)</td>
<td>2,3,4</td>
<td>9</td>
<td>2,3,4</td>
<td>-</td>
<td>2,4</td>
<td>9</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Bloods (months)</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>GMC, 95% CI</td>
<td>89 (75-107)</td>
<td>138 (114-168)</td>
<td>91 (73-115)</td>
<td>40 (32-49)</td>
<td>51 (44-60)</td>
<td>105 (88-125)</td>
<td>7 (6.8)</td>
<td>53 (44-63)</td>
</tr>
</tbody>
</table>

Conclusion

Specific IgG to Protein D reflects the number of doses in the primary series. The IgG to Protein D increases significantly post a booster dose and wanes rapidly when no booster dose is given. The functional capacity of this IgG is still to be determined.

Background and Aims:

Pneumococcal conjugate vaccines (PCV) are yet to be introduced to many countries in Asia due to the scarcity of local data and the high cost of vaccination. The Vietnam Pneumococcal Trial II is designed to evaluate if 1 or 2 doses of PCV are likely to be sufficient to maintain herd immunity.

Methods:

The trial involves 2500 infants from 3 sites in Ho Chi Minh City, randomised to 1 of 5 vaccination schedules: PCV10 or PCV13 at 2 and 12 months (1+1) or 12 months (0+1), or no infant PCV (with a dose at 24 months). Participants are enrolled at 2 months and followed-up to 24 months of age. Participants provide 4 nasopharyngeal swabs at 6, 12, 18 and 24
months. 200 participants per group contribute to an immunology sub-study and provide up to 3 blood samples.

Results:

Recruitment commenced in March 2017 and is expected to finish in June 2018. To 9 November we have enrolled 1058 participants with a consent rate of 87.8%. 630 participants have completed their infant vaccinations and 194 6m NP swabs have been collected. Participant retention has been good; 10 participants have been withdrawn to date, giving a withdrawal rate of 0.9%. There have been 20 SAEs.

Conclusion

This trial will provide a critical evidence base on simplified and more affordable PCV schedules. It aims to open the way to the future use of reduced-dose schedules for countries with established PCV programs that have already achieved herd immunity.

ISPPD-0451
DETERMINING THE PNEUMOCOCCAL VACCINATION COVERAGE REQUIRED FOR INDIRECT IMMUNITY AGAINST INVASIVE PNEUMOCOCCAL DISEASE IN AUSTRALIA
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Background and Aims:

The introduction of pneumococcal conjugate vaccines (PCV) in Australia resulted in significant declines in invasive pneumococcal disease (IPD) through both direct protection of vaccinated individuals, and indirect protection of under-vaccinated individuals. While the indirect effects of PCV vaccination are well described, the PCV coverage required to achieve these effects, using a 3+0 schedule, is unknown. We used a linked dataset to investigate the PCV7 and PCV13 coverage required to achieve substantial declines in vaccine-type (VT) IPD among under-vaccinated children.

Methods:

Vaccination records and IPD notifications were individually linked for a cohort of 1.37 million children born from 2001-2012, in two Australian states, followed up to 2013. We calculated rates of IPD among under-vaccinated children up to 5 years of age, at 3-month intervals. We
defined a child as under-vaccinated, and therefore contributing person-time at-risk, up until they received 2 doses or one dose at ≥12 months of age.

Results:

PCV7-type IPD rates among under-vaccinated children (indirect effects) decreased rapidly as PCV7 coverage increased. Smaller absolute reductions in VT IPD occurred following the introduction of PCV13 in 2011.

![Graph showing PCV7 and PCV13 coverage and IPD rates](image)

* Coverage calculated among children 12-23m of age, vaccinated defined as receiving at least 2 doses at any age or at least 1 dose ≥12m of age

Conclusion

There are rapid and substantial indirect effects following PCV vaccine introduction. Further analysis is planned to more precisely estimate a threshold for PCV coverage where indirect effects of PCV are first seen. These findings would be relevant to low- and middle-income countries, many of whom use the 3+0 schedule.

ISPPD-0456

USING NASOPHARYNGEAL CARRIAGE SURVEILLANCE IN CHILDREN HOSPITALISED WITH ACUTE RESPIRATORY INFECTION TO DETERMINE THE PNEUMOCOCCAL CONJUGATE VACCINE COVERAGE REQUIRED FOR INDIRECT IMMUNITY

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Background and Aims:

Pneumococcal conjugate vaccines (PCVs) prevent disease through both direct protection of vaccinated individuals, and indirect protection of under-vaccinated individuals through reduction of nasopharyngeal (NP) carriage and transmission of vaccine-type pneumococci. While the indirect effects of PCV vaccination are well described, the PCV coverage required to achieve the indirect effects is unknown. We will determine this using hospital-based NP pneumococcal carriage surveillance at three sites.

Methods:

Surveillance includes children aged 2-59 months of age, admitted to participating hospitals with acute respiratory tract infection in Lao People’s Democratic Republic (Lao PDR), Mongolia and Papua New Guinea (PNG). NP swabs are collected according to guidelines. Pneumococci are detected using lytA qPCR and serotyped by microarray. We will compare risk of PCV13 carriage among under-vaccinated cases by village/subdistrict-level PCV13 coverage, determined using administrative data or community survey.

Results:

As of August 2017, we have recruited 1122, 3847 and 530 cases from Lao PDR, Mongolia and PNG respectively. Overall pneumococcal carriage varies by site.

<table>
<thead>
<tr>
<th>Lao PDR</th>
<th>Mongolia</th>
<th>PNG</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV13 introduction</td>
<td>2013</td>
<td>2016</td>
</tr>
<tr>
<td>Vaccine schedule</td>
<td>6,10,14 weeks</td>
<td>2,4,9 months</td>
</tr>
<tr>
<td>Catch-up program</td>
<td>3 doses, up to 12m old</td>
<td>2 doses, up to 24m old</td>
</tr>
<tr>
<td>Samples tested-to-date</td>
<td>1099</td>
<td>285</td>
</tr>
<tr>
<td>Pneumococcal carriage</td>
<td>409 (37%)</td>
<td>150 (53%)</td>
</tr>
</tbody>
</table>

Conclusion


The inclusion of three sites, which have contrasting vaccine schedules and pneumococcal epidemiology, will enable us to explore factors which may modify the vaccine coverage required to achieve indirect effects.

ISPPD-0734
IMMUNOGENICITY OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE ADMINISTERED IN DIFFERENT SCHEDULES AND IMPACT ON NASOPHARYNGEAL CARRIAGE IN CHILDREN
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Background and Aims:
In Taiwan, the 13-valent pneumococcal conjugate vaccine (PCV13) catch-up immunization program was implemented to children < 5 years old in 2013–2014. Universal PCV13 immunization with 2+1 schedule was implemented in 2015.

Methods:
In 2016-2017, 500 healthy children aged < 10 years with different doses of PCV13 immunization were enrolled for analysis of serotype-specific antibodies by ELISA and nasopharyngeal carriage. The immunogenicity was evaluated based the doses of each capsular polysaccharide antigen given, irrespective of PCV7 or PCV13 received. Opsonophagocytic activity (OPA) was determined for serotypes 1, 3, 5, and 19A in 50 out of the 500 children.

Results:
Figure 1: (A) Serotype-specific IgG of 500 children receiving different schedules of PCV: Catch-up (n=257), PCV13 2+1 (n= 60), PCV13 3+1 (n= 164) and those without vaccination (n=19). (B) The correlation between log-transformed IgG levels and OPA titers ranged from 0.309 (serotype 5), 0.718 (serotype 1), 0.877 (serotype 3) to 0.915 (serotype 19A).

Conclusion
Serotype 3 showed the poorest immunogenicity among vaccine serotypes. Both 2+1 and 3+1 schedules induced antibody titers >0.35 µg/mL for 4-5 years in Taiwanese children. Vaccine serotypes 19A, 19F, 23F and 14 are still persisting at a low rate of nasopharyngeal carriage in the post-PCV13 era. Higher 19A-specific antibody is required to reduce serotype 19A carriage than other serotypes.
Figure 2: The 90th percentile of 19A-specific IgG was 8.33 µg/mL; the predicted acquisition rate was 0.98%. The rate was higher than other persisting vaccine serotypes, namely 14, 19F and 23F.

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COST-OF-ILLNESS FOR PNEUMONIA AMONG CHILDREN <5 YEARS OF AGE IN SELECTED FACILITIES IN BANGLADESH: PRELIMINARY ANALYSIS FROM HOUSEHOLD PERSPECTIVE

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Background and Aims:

Despite pneumonia is the leading cause of morbidity and mortality in children under-five in Bangladesh, treatment costs of this disease are unknown. We estimate the cost associated with the management of pneumonia in this population from the household perspective to understand the economic impact of this disease.

Methods:

This is part of a larger cost of illness study conducted in Bangladesh. A total of 347 under five children with pneumonia were reported during August-October 2017 from public, private and NGO facilities in Sylhet (low performing region; n=172) and Rajshahi (high performing region; n=175). Data on healthcare utilization, costs of treatment, productivity losses, income, and household assets are collected from exit interviews and follow-up interviews performed within 2 weeks after the initial interviews.

Results:
The average per-patient household cost for pneumonia treatment was US$99 (95% CI: 84-113) of which direct and indirect costs constitute 56.0% (US$55) and 44.0% (US$44) respectively. The average cost for seeking outpatient care was US$25 and for inpatient care US$176. The costs were highest in private facilities (US$214), as compared to public (US$54) and NGO facilities (US$16). The cost was higher in Sylhet region (US$135) compared to Rajshahi region (US$63). Medicine was the largest cost (US$20.2) driver followed by dietary cost (US$8.1) and hospital bed charges (US$6.0). For pneumonia-related out-of-pocket health expenses, 52.7% households spent more than 10% of their monthly income, leading households to face catastrophic payments.

Conclusion

Results indicate high treatment cost of pneumonia in Bangladesh. Prevention of pneumonia through vaccination is necessary to avert this treatment cost.

ISPPD-0366
DEMONSTRATING THE ECONOMIC CONSEQUENCES OF PNEUMONIA IN BANGLADESH AND UGANDA: METHODOLOGICAL APPROACH OF A COST OF ILLNESS STUDY*

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²International Centre for Diarrheal Disease Research, iced-b, Dhaka, Bangladesh
³Makerere University, School of Public Health, Kampala, Uganda

Background and Aims:

The economic consequences of pneumonia are not well known. This limitation is compounded by the lack of guidelines on best practices for costing out diseases like pneumonia in low-resource settings. We conduct a cost of illness study to understand the economic consequences of pneumonia in Bangladesh and Uganda.

Methods:

This is a micro-costing study of the amount of resources used to treat children with suspected pneumonia and associated costs and expenditures at different healthcare facility levels and households during 2017-18. This study will be conducted in 2 Bangladesh districts (Sylhet and Rajshahi) and 4 Ugandan districts (Gulu, Jinja, Mbarara, and Wakiso). Cost generating events will be estimated in different organizational levels (healthcare facilities, district health offices, pharmacies) and from primary caregivers. Resource use, cost and expenditure data will be collected through facility records review from 72 facilities across the two countries and face-to-face interviews with caretakers of 1,660 children under 5 years with pneumonia. Follow-up surveys will be conducted 7-14 days after initial survey to collect additional out-of-pocket payments.

Results:

Initial results about the cost of pneumonia in Bangladesh and Uganda will be presented and variance between the costs of care by socio-economic status and location of care will be discussed. In addition, risk of experiencing catastrophic expenditures due to pneumonia will be presented and analytic issues will be discussed.

Conclusion
Evidence of the economic consequences of pneumonia is critical to informing policy decisions and securing financial support for PCV vaccination.

* This is a BMGF funded DOVE IV study.

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**ISPPD-0368**

**ASSESSING LONG-TERM BENEFITS OF PCV INTRODUCTION IN NEPAL: MOVING BEYOND TRADITIONAL METHODS**

_D. Constenla¹, C. Garcia¹_

¹_Johns Hopkins Bloomberg School of Public Health, International Health, Baltimore, USA_

**Background and Aims:**

When children become ill, their families may have to use savings, sell property, or take out loans to pay for their care. Additionally, their time spent away from work may impact negatively on their income. By preventing diseases, vaccines have the potential to improve labor force participation, education attainment, productivity and wages. We plan to design a methodology to measure the impact of pneumococcal conjugate vaccine (PCV) investment on lifetime returns.

**Methods:**

We will develop a life course modeling approach to evaluate investments of PCV on labor force participation, education attainment, productivity and wages. The model will replicate the average life course for a cohort of 100,000 Nepalese children using a range of clinical, economic and social parameters. We will use data from a recent study that looked at household health expenditures and lost productivity due to pneumonia in Nepal [1]. Within the model vaccine purchasing and delivery costs will be considered investments with future economic consequences attributed to changes in pneumonia morbidity and mortality.

**Results:**

Preliminary findings of the life course analysis will be presented, including an approach to measure the impact of PCV on labor force participation, education attainment, productivity and wages.

**Conclusion**

Measuring the impact of PCV investment on lifetime returns helps to inform policies geared to improving health and economic outcomes over many generations.


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**ISPPD-0753**

**EMERGING PENICILLIN RESISTANT INVASIVE PNEUMOCOCCAL DISEASE UNDER FIVE CHILDREN WITH ITS IMPACT ON VACCINE INTRODUCTION IN INDIAN SCENERIO**

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²_Maulana Azad Medical College, Department of Microbiology, New Delhi, India_

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Background and Aims:

Invasive pneumococcal disease (IPD) remains a major medical problem associated with high morbidity and mortality among children younger than 59 months especially in developing nations like India. The study was aimed to determine clinical outcomes, serotype distribution, vaccine coverage of serotypes and antimicrobial resistance patterns in children with IPD aged 2-59 months.

Methods:

In this prospective study (September 2015 through September 2017), children with suspected IPD were included and their sterile site samples like Blood, CSF and pleural fluid were collected and investigated. Bacterial identification and antimicrobial susceptibility was determined using Vitek2C. Serotyping was performed using Quellung reaction.

Results:

Among a total of 1042 patients 90 pneumococci were isolated, with 79 strains from blood, 13 from pleural fluid, 6 from CSF and 1 isolate from ascitic fluid. Among culture proven IPD cases, 56% were aged <2 years. Overall case fatality was 94 (9%) and 16 (18%) in proven IPD cases. An average length of stay (ALOS) was 8.7 days and was longer among culture positive cases. Of 22 serotypes (70% of all), the predominant included 14 (30%), 5 (8.8%), 19A (7.7%), 1 (6.6%), 19F (6.6%), 6B (6.6%). Serotypes 14 (17 cases), 19A (8 cases) and 6B (6 cases) were predominant in <2 years whereas 14 (10 cases), 5 (6 cases) and 1 (5 cases) were prevalent among children ≥2. Penicillin non-susceptibility was 6.6%. Most common serotypes among penicillin non-susceptible isolates were 14 (3), 6B (2) and 6A (1). Among the fatal cases, serotype 14 (4 cases) was predominant followed by 6B (3 cases) and 19F (2 cases). Pneumococcal Conjugate vaccine 13 (PCV13) has vaccine coverage of 79% of serotypes.

Conclusion

There is high mortality due to IPD. Most prevalent Serotypes were 14, 5 and 19A. Penicillin resistance is emerging in pneumococcal strains and is currently restricted to vaccine serotypes only.

ISPPD-0545
IMPACT OF THE 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV-10) ON NASOPHARYNGEAL CARRIAGE IN HEALTHY BANGLADESHI CHILDREN

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⁴The University of Edinburgh, Paediatric Infectious Diseases and Global Health, Edinburgh,
Background and Aims:

Nasopharyngeal (NP) carriage is the first step of invasive pneumococcal disease and assessment of dynamics of *Streptococcus pneumoniae* (Spn) in the nasopharynx is important to evaluate the impact of pneumococcal conjugate vaccine (PCV). We conducted a NP carriage study before and after PCV-10 introduction (March 2015) to understand the impact of the vaccine on pneumococcal carriage in Bangladeshi children.

Methods:

We collected 127 NP specimens in the pre-vaccine era and 189 NP specimens in the post-vaccine era from 18 weeks old children. Spn was detected using culture and serotyped using quelling reaction.

Results:

Spn was detected in 68% (86/127) of pre-vaccine and 63% (119/189) of post-vaccine specimens. Accounting for cross-protection against 6A, in the pre-vaccine era, predominant vaccine-serotypes (VTs) were 19F (14%), 6B (9%) and 6A (9%), and non-vaccine-serotypes (NVTs) were 35B (7%) and 6C (6%) and in the post-vaccine era primary VTs were 23F (6%), 19F (5%), 6B (5%) and NVTs were 35B (9%), 15B (6%), and 19A (6%). Overall, VT coverage decreased from 45% to 29% (p=0.013) from pre- to post-vaccine era, whereas NVTs increased from 55% to 71% (p=0.013).

Conclusion

These findings suggest that PCV-10 leads to significant reductions in VTs in the nasopharynx. Carriage of NVTs increased, particularly serotypes 35B and 15B. Continued surveillance and further investigation are required to monitor trends and determine whether increasing proportions of NVTs in the nasopharynx are associated with significant invasive potential to cause replacement disease.

ISPPD-0507

CHANGES OF SPECTRUM OF DISEASES IN HOSPITAL ADMISSION AFTER INTRODUCTION OF PCV10 IN NEPAL

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Background and Aims:

Two major earthquakes struck Nepal in April/May 2015. To prevent outbreaks of infectious diseases, personal hygiene and sanitation were emphasized in the affected communities. In
October 2015 the Government of Nepal, with GAVI assistance, introduced Pneumococcal Conjugate Vaccine (PCV10) as part of routine childhood immunisation.

Methods:

We conducted a retrospective study of children admitted to Siddhi Memorial Hospital (SMH) in Bhaktapur. Bhaktapur was a severely earthquake affected district in the Kathmandu valley. SMH is the only children's hospital in the district. Inpatient data collected between 1st January 2014 and 31st December 2016 were analysed.

Results:

A total of 3,873 children were admitted. The median age was 18 months (IQR: 6-42) and 62.1% were male. Acute respiratory infections (ARI) (n=882, 22.8%), x-ray confirmed pneumonia (n=656, 16.9%), acute gastroenteritis (n=368, 9.5%), febrile seizure (n=361, 9.3%), neonatal sepsis (n=246, 6.4%), typhoid (n=231, 6.0%), and urinary tract infections (n=210, 5.4%) were the main causes of hospital admission. In post vaccine period, the proportion of children with x-ray confirmed pneumonia decreased from 17.9% (n=422) to 15.4% (n=234) (P =0.04). The proportion of children with neonatal sepsis (7.3%, n=172 to 4.8%, n=74; P =0.002), and typhoid (6.8%, n=161 to 4.6%, n=70; P =0.004) also decreased, whereas proportion of children with ARI increased (from 21.1%, n=497 to 25.5%, n=387; P =0.002).

Conclusion

The introduction of PCV10 and improved hygiene and sanitation after the earthquake may have played major roles in the decrease of the admissions due to pneumonia, neonatal sepsis and typhoid. Incidence of pneumonia before and after PCV10 introduction needs to be evaluated.

ISPPD-0522
SUBJECT RECRUITMENT AND RETENTION: EXPERIENCE FROM A VACCINE TRIAL IN INFANTS IN HO CHI MINH CITY, VIETNAM
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1Pasteur Institute in HCMC, Control and prevention disease, Ho Chi Minh, Vietnam
2Murdoch Childrens Research Institute, Pneumococcal research, Melbourne, Australia
3Charles Darwin University, Global Health, Darwin, Australia

Background and Aims:

Subject recruitment and retention are crucial factors contributing to the success of clinical trials. We describe the experience from a clinical trial of pneumococcal conjugate vaccines carried out in Ho Chi Minh City between 2013 and 2016, involving 1201 infants recruited at 2 months of age and 199 additional control group participants recruited at 18 months of age.

Methods:

Potential subjects were identified from birth records. Subjects were identified and followed up by health clinic staff. Phone calls and home visits were used to enhance the timeliness of visits and subject retention.

Results:
The overall consent rate among infants was 84.0%. 97.3% of subjects were followed up beyond the primary endpoint visit at 5 months, and 91% were followed up to 18 months. Of these, 87.4% consented to extend follow up to 24 months, and 83.4% completed the study.

Conclusion

We experienced excellent subject retention, despite this being the first trial involving infants to take place within Ho Chi Minh City. Moving away and fear of blood sampling were main factor affects retention rate.

ISPPD-0463
PNEUMOCOCCAL CARRIAGE IN HEALTHY CHILDREN IN THREE ASIA-PACIFIC COUNTRIES PRIOR TO THE INTRODUCTION OF PCV

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Background and Aims:

Pneumococcal carriage underpins pneumococcal disease and transmission. Pneumococcal carriage characteristics vary by geographic region. Here, we describe pneumococcal carriage in healthy children in Fiji, Lao PDR, and Mongolia prior to PCV introduction.

Methods:

Carriage surveys were conducted in infants aged 5–8 weeks and children aged 12–23 months. Nasopharyngeal swabs were collected according to WHO recommendations. Pneumococci were detected by lytA qPCR, and molecular serotyping and antimicrobial resistance gene detection conducted by microarray.

Results:

Carriage prevalence and data on serotype diversity, density, and antimicrobial resistance genes are shown in the Table.

<table>
<thead>
<tr>
<th></th>
<th>Fiji</th>
<th>Lao PDR</th>
<th>Mongolia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-8wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pneumococcal carriage, %</td>
<td>30.2</td>
<td>14.3</td>
<td>28.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCV13 serotype carriage, %</td>
<td>9.6</td>
<td>6.5</td>
<td>12.3</td>
<td>0.004</td>
</tr>
<tr>
<td>non-PCV13 serotype carriage, %</td>
<td>20.8</td>
<td>7.7</td>
<td>17.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>multiserotype carriage, %</td>
<td>4.6</td>
<td>0.6</td>
<td>2.8</td>
<td>0.001</td>
</tr>
<tr>
<td>serotypes, n</td>
<td>40</td>
<td>29</td>
<td>37</td>
<td>0.022</td>
</tr>
<tr>
<td>median density (log_{10})</td>
<td>5.13</td>
<td>5.35</td>
<td>4.88</td>
<td>0.002</td>
</tr>
<tr>
<td>antimicrobial resistance gene, %*</td>
<td>16.5</td>
<td>70.4</td>
<td>77.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12-23mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pneumococcal carriage, %</td>
<td>48.6</td>
<td>55.8</td>
<td>60.8</td>
<td>0.001</td>
</tr>
<tr>
<td>PCV13 serotype carriage, %</td>
<td>26.6</td>
<td>32.9</td>
<td>42.6</td>
<td>&lt;0.001</td>
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<tr>
<td>non-PCV13 serotype carriage, %</td>
<td>26.4</td>
<td>26.9</td>
<td>26.9</td>
<td>0.974</td>
</tr>
<tr>
<td>multiserotype carriage, %</td>
<td>9.6</td>
<td>8.2</td>
<td>13.3</td>
<td>0.027</td>
</tr>
<tr>
<td>serotypes, n</td>
<td>38</td>
<td>30</td>
<td>36</td>
<td>0.273</td>
</tr>
<tr>
<td>median density (log_{10})</td>
<td>5.03</td>
<td>5.56</td>
<td>5.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>antimicrobial resistance gene, %*</td>
<td>12.1</td>
<td>71.0</td>
<td>84.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*detection in samples containing a single pneumococcal serotype
Conclusion

The use of sensitive molecular methods enables thorough investigation of pneumococcal carriage. Carriage prevalence, serotype distribution, and density varied by country and age. Antimicrobial resistance genes were much more common in Lao PDR and Mongolia than in Fiji.

ISPPD-0475
IMPACT OF PCV13 INTRODUCTION ON PNEUMOCOCCAL CARRIAGE IN LAO PDR: RESULTS FROM PRE- AND POST-PCV CROSS-SECTIONAL CARRIAGE STUDIES
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6London Bioscience Innovation Centre, BUGS Bioscience, London, United Kingdom
7Laos-Oxford-Mahosot Wellcome Trust Research Unit, Laos-Oxford-Mahosot Wellcome Trust Research Unit, Vientiane, Lao PDR
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Background and Aims:

In 2013, Lao PDR introduced PCV13 with 3 doses for children up to 12 months old. Direct effects and indirect effects on infants too young to be vaccinated on pneumococcal carriage were investigated using cross-sectional community carriage surveys.

Methods:

Carriage surveys were conducted in 2013 (pre-PCV13) and 2015 (post-PCV13) in children aged 12–23 months (toddlers) and unvaccinated infants aged 5–8 weeks. Nasopharyngeal swabs were collected according to WHO recommendations. Pneumococci were detected by lytA qPCR and molecular serotyping and antimicrobial resistance gene detection conducted by microarray.

Results:

In 2013, PCV13 serotype carriage prevalence was 32.9% (95%CI 28.8–37.2) in toddlers (n=503) and 6.5% (95%CI 4.5–9.0) in young infants (n=498). In 2015, carriage of PCV13 serotypes declined in toddlers (n=507) to 19.8% (95%CI 16.4–23.6; p<0.001) with 90.2 % of age-eligible participants receiving PCV13. 70.3% of pneumococcal-positive samples had an antimicrobial resistance gene detected in 2012 compared with 71.9% in 2015.

There was no change in PCV13 serotype carriage prevalence in young infants (n=502) (5.2% [95%CI 3.4–7.5]). However, the proportion of pneumococci belonging to PCV13 serotypes declined from 32/71 (45%) in 2013 to 26/90 (29%) in 2015 (p=0.034).
Conclusion

Two years following PCV13 introduction in Lao PDR, there was evidence of direct protection, which is likely to translate to reductions in pneumococcal disease. Indirect effects in infants too young to be vaccinated were not apparent, but a lower proportion of pneumococci belonged to PCV13 serotypes. Antibiotic resistance is very common and warrants further investigation as additional selective pressure on pneumococci.

ISPPD-0489
DIRECT AND INDIRECT EFFECTS OF PCV10 INTRODUCTION ON PNEUMOCOCCAL CARRIAGE IN FIJI: RESULTS FROM FOUR ANNUAL CROSS-SECTIONAL CARRIAGE SURVEYS

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6Telethon Kids Institute, Infection and Vaccines, Subiaco, Australia
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9London School of Hygiene and Tropical Medicine, Department of Infectious Disease Epidemiology, London, United Kingdom

Background and Aims:

Fiji introduced PCV10 in 2012 using a 3+0 schedule. We investigated direct and indirect effects of PCV10 introduction using four annual cross-sectional nasopharyngeal carriage surveys conducted in four age groups.

Methods:

Carriage surveys were conducted on 5-8 week old infants, 12-23 month old children, 2-6 year old children, and adults (n ≈ 500/age group/year). Pneumococci were detected by qPCR and molecular serotyping performed by microarray.

Results:

By 2015, PCV10 serotype carriage prevalence declined in all age groups (Table). Carriage prevalence of non-PCV10 serotypes, particularly 35B, 21, and 19A, increased in infants and 12-23 mo children. Density of PCV10 serotypes was lower in vaccinated compared to unvaccinated 12-23 mo children (mean difference 0.54 log10 genome equivalents/ml, 95%CI 0.26 – 0.83), with this effect more pronounced in Fijians of Indian Descent than in indigenous Fijians (iTakuei). No reduction in H. influenzae carriage was observed in 12-23 mo children.
Conclusion

Indirect effects were observed three years post PCV10 introduction, with serotype replacement beginning to emerge. This is the first study to show indirect effects on carriage in infants too young to be vaccinated.

### Table 1: PCV10 serotypes prevalence and transmission

<table>
<thead>
<tr>
<th>PCV10 serotypes</th>
<th>2012 Prevalence (%) (95%CI)</th>
<th>2015 Prevalence (%) (95%CI)</th>
<th>Unadj. prev. ratio (95%CI)</th>
<th>Adj. prev. ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-8 wk</td>
<td>9.6 (7.1 - 12.6)</td>
<td>5.8 (3.9 - 8.3)</td>
<td>0.61 (0.39 - 0.95)</td>
<td>0.59 (0.37 - 0.93)</td>
</tr>
<tr>
<td>12-23 mo</td>
<td>22.3 (18.7 - 26.2)</td>
<td>7.3 (5.2 - 9.9)</td>
<td>0.33 (0.23 - 0.47)</td>
<td>0.34 (0.23 - 0.48)</td>
</tr>
<tr>
<td>2-6 y</td>
<td>21.7 (18.2 - 25.6)</td>
<td>9.1 (6.7 - 11.9)</td>
<td>0.42 (0.30 - 0.58)</td>
<td>0.43 (0.31 - 0.60)</td>
</tr>
<tr>
<td>adult</td>
<td>2.4 (1.2 - 4.1)</td>
<td>0.8 (0.2 - 2.0)</td>
<td>0.33 (0.11 - 1.02)</td>
<td>0.34 (0.11 - 1.04)</td>
</tr>
</tbody>
</table>

### ISPPD-0408

**ASSESSING THE POTENTIAL FOR SPILL-OVER EFFECTS IN A CLUSTER-RANDOMISED TRIAL IN NHA TRANG, VIETNAM**

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²Nagasaki University, Department of Pediatric Infectious Diseases, Nagasaki, Japan
³National Institute of Hygiene and Epidemiology, Department of Bacteriology, Hanoi, Vietnam

**Background and Aims:**

Understanding routes of pneumococcal transmission to infants is key to the success of reduced priming-dose schedules. We conducted a pilot study to assess the contact pattern of infants, a proxy for transmission routes, and the risk for spill over transmission in a cluster-randomised trial in Nha Trang, Vietnam.

**Methods:**

We randomly enrolled 100 infants 2-12 months old from an urban and a rural commune. On the first visit, local health commune staff sought informed consent. On the consecutive visit, the interviewer together with the caretaker filled in a background questionnaire and a contact diary for the previous day on the infant’s behalf.

**Results:**

In total 100 infants, equally split into rural and urban communes, were enrolled. Overall, 430 physical contacts were recorded. Most households had four or fewer members and the average household size was 4.3 (SD=1.77). The majority of contacts (92%) occurred at the infant’s home and with household members (78%). Five infants (5%) reported contact with other infants, exactly those attending nursery. Almost all (92%) caretakers had access to a motorbike and many (46%) have transported their infant with it. However, only nineteen (4.41%) contacts occurred outside of the infant’s commune.

**Conclusion**

Infants in this setting have few direct contacts across commune borders, which gives little indication for cross-cluster contamination; however, mobility of caretakers is high. Further, infant contact with young children is rare unless they attend nursery. Nursery settings may
play a critical role in transmission to older infants and is inadequately captured by common contact survey designs.

ISPPD-0479
HIGH RATES OF MULTIPLE SEROTYPE CARRIAGE DETECTED BY MICROARRAY IN HOSPITALISED CHILDREN WITH PNEUMONIA IN THE EASTERN HIGHLANDS OF PAPUA NEW GUINEA


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7Centre for International Child Health- The University of Melbourne, Department of Paediatrics, Melbourne, Australia
8London School of Hygiene and Tropical Medicine, Department of Infectious Disease Epidemiology, London, United Kingdom
9Telethon Kids Institute- The University of Western Australia, Wesfarmers Centre for Vaccines and Infectious Diseases, Perth, Australia
10Princess Margaret Hospital for Children, Department of Infectious Diseases and PathWest Department of Microbiology, Perth, Australia
11The University of Western Australia- Princess Margaret Hospital for Children, School of Paediatrics and Child Health, Perth, Australia

Background and Aims:

Pneumonia is the most common cause of childhood hospitalisation and death in Papua New Guinea (PNG), and pneumococcal carriage rates in children in PNG are among the highest in the world. The 13-valent pneumococcal conjugate vaccine (PCV13) was introduced in PNG in 2014. Following PCV13 introduction, it is essential to continue aetiological surveillance as well as monitor the direct and indirect effects of vaccine introduction.

Methods:

As part of the ongoing multicentre PneuCAPTIVE study in PNG, Laos and Mongolia, we enrol children aged <5 years presenting at Eastern Highlands Provincial Hospital or urban clinics in Goroka town with moderate to severe pneumonia. Blood and nasopharyngeal swabs (NPS) are collected. Pneumococci were identified and quantified by lytA qPCR and molecular serotyping by microarray were performed in Melbourne, Australia.

Results:

Of the 376 NPS collected from clinical pneumonia cases between April 2016 and April 2017, 88% contained pneumococci with a median density of 3.37x10^6 copies/ml. Of the 326
samples assessed to date, 39% (n=128) contained PCV13 serotypes, and 54% (n=176) had multiple serotype carriage. 61 different serotypes have been identified, the most common being acapsular lineage NT2>15B/C>19A>14>23F. Of children carrying a PCV13 serotype, 29% (n=37) were vaccinated. Invasive pneumococcal disease was confirmed in three pneumonia cases (serotypes: 29, 6B, 23A).

Conclusion

As PCV13 coverage increases, a sustained decline in PCV13 serotype carriage and disease is anticipated. However, PNG children in the highlands have diverse pneumococcal carriage from early infancy, which may limit the effectiveness of the vaccine.

ISPPD-0652
ESTIMATING THE HOUSEHOLD IMPACT FROM HOSPITALIZED PNEUMONIA, MENINGITIS, AND SEPSIS IN NEPAL: PNEUMOCOCCAL IMPACT ECONOMIC STUDY (PIES)
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²Nepal Pediatric Society, Department of Pediatric Medicine, Kathmandu, Nepal

Background and Aims:

Out-of-pocket expenditures (OOPE) for healthcare can be catastrophic to households. Families may use savings, sell property, or borrow money to pay for healthcare. We estimated the proportion of households experiencing catastrophic health expenditures (CHE) and impoverishment impact from hospitalized pneumonia, meningitis, and sepsis.

Methods:

We collected OOPE from children 1-59 months with hospitalized pneumonia, meningitis, and sepsis in 5 Nepal hospitals. OOPE included medical and non-medical costs paid by households less amounts paid third-party. Expenditures were catastrophic when OOPE exceeded 40% of a household’s non-food expenditure monthly and annually. Variable thresholds based on food expenditure ratios of poorer to wealthiest quintiles were used to estimate the impact on poorer households with fewer resources to cope. Poverty headcount post-OOPE was estimated using standard methods.

Results:

Average meningitis OOPE was highest ($263; SD $166) compared to sepsis ($157; SD $207) and pneumonia ($111; SD $115). Expenditures were catastrophic annually in 7% pneumonia, 8% meningitis, 10% sepsis households. Burden was highest amongst the 2 poorest quintiles with 43% households experiencing CHE. Lowering the catastrophic threshold in these quintiles increased the proportion experiencing CHE to 64%. Households financed health expenditures with existing income (66%), savings (31%), and borrowing (20%). Catastrophic impact was most severe immediately with post-OOPE household monthly and annual income falling below the poverty line in 23% and 3% households, respectively.

Conclusion
Pneumonia, meningitis, and sepsis can push households into poverty. Applying a uniform threshold underestimates the true impact amongst the poorest households. Understanding household impact is important for policy decisions.

ISPPD-0668
ESTIMATING THE IMPACT OF PCV ON REDUCING CATASTROPHIC HEALTH SPENDING AMONG NEPALI CHILDREN WITH HOSPITALIZED PNEUMONIA: PNEUMOCOCCAL IMPACT ECONOMIC STUDY (PIES)
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¹Johns Hopkins Bloomberg School of Health, International Vaccine Access Center-Department of International Health, Baltimore, USA

Background and Aims:
Out-of-pocket health expenditures can be catastrophic to families and can push them into poverty. We plan to estimate the impact of PCV on reducing catastrophic health expenditures (CHE) and medical impoverishment from out-of-pocket payments.

Methods:
We will model the reduction in the proportion of households experiencing CHE from and medical impoverishment from hospitalized pneumonia by income quintile comparing PCV vaccination to no vaccination. Cost of hospitalized pneumonia and CHE incidence will be derived from the Pneumococcal Impact Economics Study [1-2]. Data on hospitalized pneumonia incidence, vaccine efficacy, and serotype distribution will be obtained from secondary sources. Households experience medical impoverishment if out-of-pocket expenditures from hospitalized pneumonia reduce household income below the national poverty line. Sensitivity analyses varying parameters and vaccination scenarios will be performed.

Results:
Initial results indicate the poorest households are at greatest risk of experiencing CHE because of high pneumonia risk factor prevalence. When adjusting for health-seeking, the majority of CHE and medical impoverishment appear to occur in the 2 poorest income quintiles. PCV immunization has the potential to avert most CHE and medical impoverishment cases with the greatest impact among the poorest households.

Conclusion
We hypothesize that PCV has the potential to reduce out-of-pocket health spending from childhood hospitalized pneumonia in Nepal. The impact may be the greatest among the poorest population with fewer resources to cope.


ISPPD-0529
IMPACT OF PCV-13 ON DUAL COLONISATION OF S. pneumoniae WITH S. aureus IN HIV AFFECTED FAMILIES
Background and Aims:

Streptococcus pneumoniae and Staphylococcus aureus are pathogens that frequently colonize the nasopharynx of children prior to causing disease. We investigated the role of HIV infection on dual colonization of pneumococcus and S. aureus in children and their unvaccinated parents before and after PCV-13 immunization.

Methods:

A prospective cohort study on the impact of pneumonia preventing vaccines in HIV-infected children was conducted from March 2012 to October 2014 in West Bengal, India. A single dose of PCV-13 was administered to children with and without HIV. A total of 1661 nasopharyngeal swabs were collected from 160 children and their parents, pre and post immunization during the study. Swabs were subjected to culture for identification of S. aureus and pneumococcus.

Results:

Of the 1661 swabs collected, 1353 were from HIV-infected families and 308 from HIV uninfected families. In HIV infected families, dual colonization was seen in 31/1147 (2.7%, 95% CI: 1.8% - 3.8%) samples before and 5/206 (2.4%, 95% CI: 0.7% - 5.6%) samples after PCV-13 immunization.

In HIV uninfected families, dual colonization was observed in 4/239 (1.6%, 95% CI: 0.4% - 4.2%) samples before vaccination and none in 69 samples after PCV-13.

HIV infected individuals were found at 1.69 (95%CI: 0.5 - 6.2) times increased risk for dual colonization compared to HIV uninfected individuals.

Conclusion

HIV infected families are at a higher risk of dual colonization with S. pneumoniae and S. aureus. Dual colonization was not seen post PCV13 in HIV uninfected families.
Methods:

We conducted surveillance to monitor IPD in four sentinel hospitals from January 2012 through September 2017. We collected blood and/or CSF samples from suspected meningitis and sepsis cases in <5y children. Pneumococcus was detected using culture, immunochromatic test and/or PCR and serotyped using quellung and/or PCR. Data from pre-vaccine (January 2012 – March 2015) and post-vaccine (April 2015 –September 2017) era were compared to determine impact of vaccine in children aged 3-23m (75% of whom were vaccine-eligible) and in all <5y children.

Results:

IPD cases in 3-23m children decreased from an average of 54 cases/year in the pre-vaccine era to 37 cases/year post-PCV ($p<0.001$). Proportion of vaccine-serotypes (VT) decreased from 56-29% ($p<0.001$); no change in the number of non-VT was observed (Fig1). Overall, IPD cases in <5 children decreased from 75-56 cases/year, and proportion of VT from 58-39%.

Figure 1: Changes of IPD cases (VT, NVT) and % of VT during, Apr 2012-Sep 2017

Conclusion

We see significant decrease of IPD and proportion of VT among <5y and vaccine-eligible children (3-23m) in Bangladesh, two-and-half years after vaccine introduction. With >20 cases/year, data from our sentinel sites most likely reflect proportionate changes in the population (Hampton et al). Continued surveillance is required to understand herd immunity and track non-VT trends.

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ISPPD-0727

REACTOGENICITY OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10) CO-ADMINISTERED WITH DPTW-HBV/HIB AMONG VIETNAMESE INFANTS


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Background and Aims:

An alternative pneumococcal conjugate vaccine (PCV) reduced dosing study in a naïve population has started in Nha Trang, Vietnam. There is always a public concern on the safety of the newly introduced vaccines. This study was conducted to assess the safety or reactogenicity of PCV10 co-administered with routine vaccines.

Methods:

The study was conducted in 6 PCV10 (Synflorix®) intervention and 6 control communes, at routine first primary vaccination (DPT-w-HBV/Hib: Quinvaxem & OPV) in Nha Trang, Vietnam. From August to December in 2017, solicited symptoms for the 4-day post vaccination period and unsolicited adverse events for 30 days after the vaccination were collected and analyzed.

Results:

Healthy infants, 203 from intervention and 200 from control groups were enrolled. Among solicited symptoms happened within 4-day post vaccination, fever >=38°C was reported 51.2% in intervention, and 53.0% in control group. Overall incidence of redness in control was higher than that in intervention group (49.5 % vs 36.0%, p<0.01). However, intensity of symptoms was comparable in two groups. Within 30 days after the vaccination, the incidence of at least one unsolicited AE was within same range in the two groups (0.9% in intervention and 0.7% in control groups, respectively). Hospitalizations were reported in 2 children in intervention group. Among them, 1 fever case was considered causally related to vaccination but both infants recovered without any sequelae.

Conclusion

PCV10 co-administered with routine vaccines for the first primary dose was clinically as safe as routine immunizations alone.
Background and Aims:

PneuCAPTIVE is a large multicentre study in the Asia-Pacific region assessing direct and indirect effects of 13-valent pneumococcal conjugate vaccination in children hospitalised with pneumonia. We report on clinical and field aspects of the first half of this 3-year study from the site in Eastern Highlands Province, Papua New Guinea.

Methods:

Between April 2016 and September 2017, children <5 years presenting to Eastern Highlands Provincial Hospital or nearby urban clinics with moderate to severe pneumonia were prospectively enrolled. Clinical data, vaccination status, blood and nasopharyngeal swabs were collected. Children living within an hour’s drive of the hospital were followed up in their communities. PCV13 coverage of well children <5 yrs old within the same communities was determined using community surveys. ‘Fully vaccinated’ was defined as having received two doses of PCV13 if age <12 months or ≥1 dose if ≥12 months of age.

Results:

604 cases (moderate pneumonia 90.4%; severe pneumonia, 9.6%) have been enrolled to date (median age 9.6 months), 20.7% requiring hospitalisation with a median stay of 3 days. Two children died in hospital. 62.7% of cases were followed-up after discharge; 97% had recovered completely. Surveys were conducted on 2014 well children; their PCV13 coverage was estimated to be 55.8%, significantly greater than that observed in cases (41.7%; p<0.001).

Conclusion

Implementation of the PCV program has resulted in more than half of children being vaccinated. The impact of this program on pneumococcal disease in the target population and others will require ongoing clinical and microbiological surveillance.
Access to pneumococcal vaccines is particularly important for individuals with HIV. Pneumococcal conjugate vaccines (PCV) prevent pneumococcal transmission in populations by decreasing vaccine type carriage. We looked at pneumococcal carriage density in children with and without HIV before and after one dose of PCV-13, using a quantitative real time PCR assay.

Methods:

We conducted a nested case control study within a larger prospective cohort study on the impact of PCV-13 in families with and without HIV in West Bengal, India. Quantitative (LytA) real time PCR for *Streptococcus pneumoniae* was run on 80 random nasopharyngeal swabs from a bank of (80) from children with and without HIV before and after PCV-13 immunization. Samples with cycle threshold (Ct) values ≤ 36 were considered positive. Colonization density of pneumococcus in copies/ml was calculated using reference standards. Median colonization densities were compared between the groups by Wilcoxon rank-sum test. Differences in densities pre and post PCV were compared for each group by two-sample t test.

Results:

The median age of children in each cohort was 3 years. Children with HIV (CLH) had higher baseline pneumococcal carriage density compared to HIV uninfected children (HUC): 6.28x10^8 copies/ml vs. 2.11x10^5 copies/ml (p=.003). Following one dose of PCV-13, median pneumococcal densities dropped in both CLH (3.77x10^7/ml,) and HUC (4.94x10^4/ml). Significant decline in pneumococcal carriage density was observed in CLH post-PCV (p=0.048), but not in HUC (p=0.292).

Conclusion

Children living with HIV carry higher densities of pneumococcus in their nasopharynx. Density of pneumococcal carriage decreased in both cohorts post PCV-13.

ISPPD-0486

USING PNEUMOCOCCAL NASOPHARYNGEAL CARRIAGE IN HOSPITALISED CHILDREN TO DETERMINE THE PNEUMOCOCCAL CONJUGATE VACCINE COVERAGE REQUIRED TO SHOW HERD IMMUNITY IN LAO PDR

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Background and Aims:

The 13-valent pneumococcal conjugate vaccine (PCV13) coverage required to achieve herd immunity is unknown. The aim of this study is to determine the PCV13 coverage needed to show evidence of herd immunity using nasopharyngeal carriage surveillance in hospitalised children in Lao PDR.

Methods:

Lao PDR introduced PCV13 in October 2013 for children up to 12 months. Children 2-59 months of age admitted to Mahosot Hospital, Vientiane with acute respiratory infection were prospectively enrolled, with a nasopharyngeal swab collected. Pneumococci were detected and quantified using *lytA* real-time quantitative PCR, with positives serotyped by microarray. PCV13 vaccination status was determined by written record, with those vaccinated defined as receiving ≥2 doses at <12months and ≥1 dose at ≥12months.

Results:

Preliminary results show the unadjusted risk of PCV13 carriage among under-vaccinated children (n=167) decreases as PCV13 coverage increases (Figure).

![Graph showing the decrease in PCV13 carriage with increasing vaccine coverage.](image)
Conclusion

As the study reaches the planned sample size of 1200, we will determine the adjusted risk of PCV13 carriage at each level of PCV coverage. The results will inform decision makers about what PCV13 coverage is required to maximize the benefits of PCV and achieve herd immunity.

ISPPD-0503
COMPARISON OF PNEUMOCOCCAL VACCINE IMMUNOGENICITY BETWEEN THE TWO MAIN ETHNIC GROUPS IN FIJI
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Background and Aims:

The Fiji Pneumococcal Project examined the immunogenicity of reduced-dose PCV7 schedules (0,1,2 or 3 PCV7 doses) in infancy followed by a 23vPPV booster at 12 months of age to half the infants. The aim of this study was to compare the immunogenicity of reduced dose PCV7 schedules among the two main ethnic groups in Fiji: iTaukei (IT) and Fijians of Indian Decent (FID).

Methods:

There were 552 Fijian infants enrolled into the study, and approximately 63% were IT. Serotype-specific IgG and opsonophagocytic (OPA) responses were measured for a number of serotypes across all timepoints

Results:

Response to PCV7 varied by ethnicity and by number of doses received. While similar IgG responses were observed following 3 doses of PCV7 (except 9V; IT>FID), IT infants had significantly higher OPA responses to most PCV7 serotypes compared to FID infants. IT infants had significantly higher IgG levels for 12/23 serotypes and 2/8 serotypes for OPA post-23vPPV. Conversely, FID infants had higher IgG levels for 6B/23F after 2 PCV7 doses, whereas IT infants had higher OPA for 9V/18C. Post-23vPPV, IT infants had higher IgG and OPA levels for serotype 9V compared to FID infants, while serotype 1, 12F and 17F IgG was higher among IT infants. After 1 PCV7 dose, FID infants had higher IgG (7F/14) and OPA (1/14) responses post-23vPPV compared to IT infants.

Conclusion
PCV immunogenicity among ethnic groups, particularly in the context of reduced-dose schedules, needs to be considered in relation to the duration of protection.

ISPPD-0512
INVASIVE PNEUMOCOCCAL DISEASE POST PCV10 INTRODUCTION IN FIJI
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Background and Aims:

In 2010 Fiji introduced the PCV10 into the infant immunization program and has since achieved >90% coverage. In 2014, an invasive bacterial vaccine preventable disease (IB-VPD) surveillance was established to monitor invasive pneumococcal disease (IPD) serotypes following the introduction of PCV10.

Methods:

Sentinel site surveillance was established. WHO guidelines were adapted and clinical and laboratory training was provided. Cases of pneumonia, suspected meningitis or sepsis had blood cultures, and cerebrospinal fluid (CSF) for meningitis cases, collected and tested. qPCR testing of CSF samples for S. pneumoniae (SPN), H. influenzae (Hi), Hib, and N. meningitidis (NM) was established. Isolates were serotyped at Melbourne reference laboratories.

Results:

Between September 2012 and October 2017 there were 105 IPD cases. Clinical syndromes were 26% (28) pneumonia, 32% (34) meningitis and 41% (43) sepsis. The median age was 18 and 22 were among vaccine eligible cases. The case fatality rate was 10%. From the 105 IPD cases 68 isolates were available for serotyping. There was one vaccine failure, serotype 14 in a two year old child who had received 3 doses of PCV10 by 14 weeks of age. There were 15 VT-IPD among non-vaccine age eligible, the most common was 7F and 1. There were 12 and 36 NVT-IPD among vaccine age eligible and non-vaccine age eligible cases.

Conclusion

Quality surveillance is vital to monitor IPD causing serotypes. One vaccine failure was detected.

ISPPD-0544
IMPACT OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV-10) ON OTITIS MEDIA AMONG BANGLADESHI CHILDREN
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Background and Aims:

Pneumococcus and nontypable *Haemophilus influenzae* (NTHi) are predominant causes of otitis media (OM). Here we report the impact of PCV-10 on OM caused by these two pathogens.

Methods:

Swabs from OM cases with otorrhea were cultured for bacterial pathogens. Serotyping of pneumococcus was performed by quellung reaction and *H. influenzae* by PCR. Impact of PCV was evaluated by comparing post-PCV data (April 2015- September 2017) with pre-PCV data (April 2014-March 2015) with OM among 3-29 old children, 92% of whom were vaccine eligible.

Results:

We identified 981 (88%) otorrhea cases from 1111 OM patients in the pre-vaccine era and 2,424 (97%) otorrhea cases from 2,493 patients in the post-PCV era. NTHi was attributed to 21% and 19% of etiology-positive cases in pre- and post-PCV era; no significant change in any age group was observed. Pneumococcus was attributed to 18% (164/892) of pre-PCV and 16% (377/2415) (p=0.05) of post-PCV cases. Amongst 3-29 months group, proportion of PCV-10(+6A) serotypes decreased from 49% to 38% (p=0.03) from pre- to post-PCV (Fig1). We observed significant reduction in 19A cases (18% to 9%; p=0.006) with the introduction of PCV-10, in this group. Similar decline (9% to 3%; P=0.074) of 19A was observed among non-vaccinated group.
Conclusion

PCV-10 significantly reduced prevalence of vaccine-serotypes among the vaccinated groups, with secular decline of 19A among all age groups. We are continuing the surveillance to monitor long-term impact of PCV-10 on all OM cases in Bangladesh.

ISPPD-0467

EFFECT OF PCV10 VACCINATION ON HAEMOPHILUS INFLUENZAE CARRIAGE AND DENSITY IN VIETNAMESE CHILDREN

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Background and Aims:

PCV10 contains Haemophilus influenzae protein D as a carrier protein, leading to speculation that it may reduce H. influenzae carriage. Previously we found a trend towards reduction in non-typeable H. influenzae carriage at 12 months of age following PCV10 vaccination in a 3+1 or 2+1 schedule, in children participating in a randomized clinical trial in Ho Chi Minh City, Vietnam. Here, we investigated the effect of PCV10 on H. influenzae carriage and density in participants six months later.

Methods:

Nasopharyngeal swabs were collected from healthy children aged 18 months, given PCV10 as a 3+1 (n=135) or 2+1 (n=219) schedule, or were unvaccinated (n=177). A duplex real-time quantitative PCR (qPCR) assay targeting the hpd (encoding H. influenzae protein D) and siaT genes was developed to detect and quantify H. influenzae.

Results:

H. influenzae was detected in 29/135 (21.5%), 35/219 (16.0%) and 23/177 (13.0%) samples for the 3+1, 2+1 and unvaccinated groups respectively, when targeting hpd. Median carriage densities of 5.3 log_{10} (95%CI 5.2-5.9), 5.6 log_{10} (95%CI 5.5-6.1) and 5.8 log_{10} (95%CI 5.4-6.1) genome equivalents/ml were observed in the 3+1, 2+1 and unvaccinated groups. No significant differences were seen in carriage prevalence or density between the vaccinated and unvaccinated groups (all p>0.05). Similar results were obtained for both gene targets.

Conclusion

A duplex qPCR assay targeting hpd and siaT was developed; both gene targets produced similar results. We found no evidence that PCV10 vaccination reduces density or rates of H. influenzae carriage at 18 months of age.
ISPPD-0550
IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINE (PCV-10) ON PNEUMOCOCCAL NASOPHARYNGEAL CARRIAGE IN CHILDREN IN PAKISTAN: RESULTS OF SERIAL SURVEYS PRE AND POST INTRODUCTION OF VACCINE
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Background and Aims:
Pakistan introduced PCV-10 vaccine in Expanded Program on Immunization (EPI) in April 2013 in Sindh province. Aim of the study was to determine if there is serial decline in carriage of PCV-10 serotypes among children of age less than five years, after introduction of PCV-10 in EPI.

Methods:
We conducted yearly cross sectional surveys over the past four years, one before and three after the introduction of PCV-10 in EPI. Nasopharyngeal swabs were obtained from representative randomly sampled healthy children in one urban and one rural district of Sindh. Swabs were collected in STGG media and Pneumococci were identified through routine microbiology. Serotypes were identified through real-time sequential multiplex PCR using Centre of Disease Control (CDC), USA scheme.

Results:
Each year 440 children of age 3-12 months were enrolled from rural and urban districts and additional 220 children of age 12-59 months were enrolled from urban district only. In rural district, nasopharyngeal carriage of PCV-10 serotypes reduced from 33% at baseline in 2013 to 16% in 2016 with a gradual decline seen in each year. Similarly, decline in carriage was observed in urban district from 39% baseline to 30% in 2016, except for 2015 when increase in carriage was observed up to 51%. Most common PCV-10 serotypes were 6B and 23F.

Conclusion
The nasopharyngeal carriage of the vaccine serotypes has gradually declined in Pakistani children post introduction of PCV-10. There is likely to see reduction in the occurrence of pneumococcal pneumonia and meningitis in the future given that vaccine continues to reach children.

ISPPD-0559
EFFECTIVENESS OF PNEUMOCOCCAL CONJUGATE VACCINE (PCV-10) AGAINST VACCINE TYPE INVASIVE PNEUMOCOCCAL DISEASE IN PAKISTAN
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Background and Aims:
Pakistan was the first country in South Asia to introduce Pneumococcal Conjugate Vaccine (PCV) in its National Expanded Program of Immunization. Objective of this study was to assess PCV-10 effectiveness on invasive pneumococcal disease (IPD) due to vaccine serotypes of Streptococcus Pneumoniae.
Methods:

A matched case-control study enrolled children <5 years (eligible to receive PCV-10) who presented with radiographic confirmed pneumonia and/or meningitis at 16 hospitals serving low and middle income population. PCR for Lyt A gene was conducted on blood (for radiographic pneumonia) and Cerebrospinal fluid (for meningitis) samples to detect S Pneumoniae. The proportion of IPD due to vaccine type serotypes was determined through serial multiplex PCR. At least five controls were enrolled for each case of vaccine type IPD, matched on age, catchment and season.

Results:

From 92 IPD cases enrolled during July 2013-March 2017, 20 cases (21.7%) were vaccine serotypes positive and 4 (4.3%) were vaccine related serogroups. 36 cases (39.1%) were non-vaccine type and 32 (34.7%) were untypeable. 24 vaccine type IPD cases (including 4 vaccine related serogroups) and 134 hospital controls were analyzed for VE. Estimated effectiveness for PCV-10 against vaccine type IPD was 72.7% (CI -7.2 — 92.6) with at least one dose of vaccine, 78.8% (CI -11.9 — 96.0) for at least two doses and 81.9% (CI -55.7 — 97.9) for all three doses using hospital controls.

Conclusion

The study provides useful insights about the likely impact with enhanced uptake of the vaccine at the population level and completion of the recommended 3-dose schedule.

ISPPD-0575
IMMUNOGENICITY AND IMMUNE MEMORY AFTER PNEUMOCOCCAL POLYSACCHARIDE BOOSTER IN PNEUMOCOCCAL CONJUGATE VACCINE-PRIMED INFANTS IN PAPUA NEW GUINEA – A RANDOMISED CONTROLLED TRIAL.

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Background and Aims:

10- and 13-valent pneumococcal conjugate vaccines (PCV10; PCV13) have been introduced in low-income countries. Protection may be improved by boosting with a 23-valent pneumococcal polysaccharide vaccine (PPV23) but limited immunogenicity data exists which we investigated.

Methods:

200 infants primed with either PCV10 or PCV13 at 1-2-3 months of age, were randomized to receive PPV23 or no PPV at age 9 months. All children received a 1/5 PPV23 challenge dose to assess immune memory at age 23 months. Vaccine-serotype (VT) and serotype 2-specific IgG was measured by ELISA at ages 9, 10, 23 and 24 months and geometric mean concentrations (GMCs) calculated.
Results:

At age 9 months, GMCs were similar between PCV groups except 6A (PCV13>PCV10; p<0.02) and 18C (PCV10>PCV13; p<0.03). Proportions ≥0.35ug/mL ranged from 35% (serotype19A) to >95% (serotype14). Significant IgG increases post-PPV23 (3-to 7-fold GMC rises; 93-100% ≥0.35ug/mL) compared to controls were seen for all PCV10 VT & serotype 2, and was similar between PCV groups. Significantly higher 19A responses occurred in PCV13-primed infants but not for serotypes 3 or 6A. By age 23 months, antibody GMCs in PPV-vaccinated children declined to levels similar to controls for most serotypes but remained significantly higher in PCV10-primed infants for serotypes 4, 7F, 9V, 18C and 23F. Both PPV-naïve & PPV-vaccinated children responded to PPV at age 23 months. Although PPV-naïve children tended to have higher GMCs, there was no difference in proportions ≥0.35ug/mL.

Conclusion

PPV23 is immunogenic as a booster after PCV10 & PCV13 priming in high-risk infants and immune memory remains intact.

Background and Aims:

Pneumococcal pneumonia is a leading cause of childhood mortality. African studies found that pneumococcal conjugate vaccines (PCVs) reduced hypoxic pneumonia in children. However, there are no 13-valent PCV (PCV13) vaccine effectiveness (VE) studies from Asia. The aim of this study is to determine the PCV13 VE against hypoxic pneumonia and pneumonia cases requiring oxygen supplementation therapy (hypoxic pneumonia) in children in Lao PDR.

Methods:

A prospective hospital-based cohort study of children up to 59 months old admitted with pneumonia to Mahosot Hospital, Vientiane was undertaken. Each participant had a NP swab taken. Potential risk factors, including demographic and clinical data, and results for respiratory syncytial virus using polymerase chain reaction, were recorded. Pneumonia was
defined as per WHO guidelines. Hypoxic pneumonia was defined as having an oxygen saturation <90% in room air or requiring oxygen supplementation at any time during hospitalisation. PCV13 status was determined by written record. VE was calculated using logistic regression, adjusted by inverse probability weighting using propensity scores (PS). The odds ratios (OR) were converted to measures of VE using the formula: $VE = \frac{(1-OR)\times 100}{1}$.

Results:

There were 657 children with pneumonia, 54.2% had hypoxic pneumonia and 72% were PCV13 vaccinated. Preliminary unadjusted and PS adjusted VE against hypoxic pneumonia was 39.8% (95%CI:11.2,59.2, p=0.01) and 55.2% (95%CI:27.4,72.3, p=0.001), respectively.

Conclusion

These preliminary findings are consistent with two studies from Africa and are the first results to show that PCV13 is effective against hypoxic pneumonia in Asia. PCV13 is likely to contribute to reducing child mortality in this region.

Background and Aims:

Pneumococcal conjugate vaccines (PCV) have reduced the burden of pneumococcal disease, however their price has delayed PCV dissemination in low-middle income countries. Therefore, a community randomized study of PCV dosing schedules, including alternate reduced dosing, is being conducted in Nha Trang, Vietnam. We investigated baseline pneumococcal carriage among children <2 years of age and their mothers in Nha Trang, Vietnam.

Methods:

The study is being conducted in 27 communes of Nha Trang city, central Vietnam. Communes are randomized to various PCV schedules and 60 children 4-11mth and 60 children 14-23mth, and their mothers in each commune are targeted for yearly recruitment for collection of nasopharyngeal (NP) specimens and demographic/risk information.
Pneumococcal carriage was screened by lytA qPCR. Serotyping result by microarray method are described separately.

**Results:**

A total of 3148 PCV naïve children and their mothers were enrolled from the study communes in October 2016. Pneumococci were detected in 1085 (35%). In children, older age (42% vs 27%), day care attendance (45% vs 18%), history of hospitalization (26% vs 21%), and respiratory symptoms within two weeks before survey (63% vs 45%), were associated with higher carriage rate (p <0.001). Three percent of the mothers had pneumococcal carriage and it was associated with carriage in their child (p<0.001).

**Conclusion**

Baseline pneumococcal carriage before PCV introduction was detected in one third of children less than 2 years of age in Nha Trang, Vietnam. This baseline data will be useful to evaluate the different PCV dosing schedules.

**Background and Aims:**

The Vietnam Pneumococcal Project is a randomised controlled trial comprising 6 different infant vaccination schedules: PCV10 in a 3+1, 3+0, 2+1 or 2-dose schedule; PCV13 in a 2+1 schedule; and a control group. Pneumococcal and non-typeable *Haemophilus influenzae* (NTHi) carriage rates were compared between groups at 12 months of age.

**Methods:**

1118 nasopharyngeal (NP) swabs were analysed using standard microbiological methods. Capsular pneumococci were serotyped using latex agglutination, and non-encapsulated pneumococci and NTHi were identified using PCR.

**Results:**

26.6% of swabs were positive for pneumococcus, the majority (79.5%) of which contained capsular pneumococcus. Of these, two thirds contained PCV13-types, almost half of which were serotypes not shared with PCV10.
Pneumococcal carriage rates were similar among the 3+1, 3+0 and both 2+1 groups. Carriage rates in these groups across all categories were lower than those in the 2-dose group and control group, although not all these differences reached statistical significance.

The overall NTHi carriage rate was 14.8%, with a trend towards lower carriage in the 3+1/2+1 PCV10 groups compared with the 3+0 and control groups.

**Conclusion**

Provision of at least 3 doses of either PCV appears to reduce vaccine-type pneumococcal carriage at 12 months of age. The impact of PCV10 on NTHi carriage is still unclear.

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**ISPPD-0553**

**VERIFIED VACCINATION DATA COLLECTION FOR PCV IMPACT STUDIES AT SENTINEL HOSPITALS IN BANGLADESH**

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**Background and Aims:**

Verified vaccination information is important for vaccine impact studies as unverified data may affect the evaluation of vaccine effectiveness. Here, we evaluated the success of active verification of vaccination date and history among <5 Invasive Pneumococcal Diseases (IPD) from March 2015, since when PCV-10 has been rolled out in Bangladesh.

**Methods:**

Children enrolled in ongoing hospital surveillance were requested and followed up to bring the vaccination card. Travel cost was reimbursed for the IPD cases and cases where vaccination card not available at hospital, visit to home and even to the EPI center were made to capture the precise information.

**Results:**

In pre-PCV era, without any efforts, only 3% (214/8399) had verified vaccination information. However, with all the efforts in post-PCV era, vaccination information for 98% (104/106) IPD cases was successfully verified compared to 41% (5994/14612) of non-IPD cases where only counseling was applied (Table-1). When compared with vaccination card, 73% (39/128)
matched with verbal response but 82% (32/39) of concordant cases had vaccination date difference of ≥ 1 month.

**Table-1: Acquiring verified information**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>&lt;5years(N=12,311)</td>
<td>Non-IPD(N=20,612)</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>n(%)</td>
<td>n(%)</td>
</tr>
<tr>
<td>Card obtained</td>
<td>8399(68%)</td>
<td>14,612(71%)</td>
</tr>
<tr>
<td>During enrollment</td>
<td>214(100%)</td>
<td>5089(85%)</td>
</tr>
<tr>
<td>Before discharge</td>
<td>905(15%)</td>
<td>46(38%)</td>
</tr>
<tr>
<td>After discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At EPI center</td>
<td>1(1%)</td>
<td>1(1%)</td>
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</tbody>
</table>

Conclusion

Discrepancy in terms of vaccination information and exact vaccination date between verbal response and vaccination card necessitates a system to capture vaccination information accurately for vaccine impact studies.

**ISPPD-0126**

**PNEUMOCOCCAL CARRIAGE IN CHILDREN AGED 2-59 MONTHS HOSPITALIZED WITH RADIOLOGICALLY-CONFIRMED AND SEVERE PNEUMONIA IN MONGOLIA PRIOR TO PNEUMOCOCCAL CONJUGATE VACCINE INTRODUCTION**


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Background and Aims:

Pneumonia is a common cause of paediatric morbidity and mortality in Mongolia. Enhanced pneumonia surveillance was initiated prior to 13-valent Pneumococcal Conjugate Vaccine (PCV13) introduction by the Mongolian Ministry of Health in 2016. We aimed to describe pneumococcal carriage of children presenting with radiologically-confirmed and severe pneumonia prior to PCV13 introduction.

Methods:
Children aged 2-59 months, who met a predefined case definition for pneumonia were consented and enrolled. Chest x-rays and nasopharyngeal swabs were taken. Between April 2015 and May 2016 samples from all children enrolled with radiologically-confirmed pneumonia and a proportion of children with severe pneumonia were examined by lytA qPCR to detect and quantify pneumococci, and serotyped by microarray.

Results:

Nearly half of all children tested had pneumococci identified on nasopharyngeal samples (324/700, 46%) and of those with microarray results 34% (226/674) were PCV13 serotypes. Only 9% (59/674) of children were carrying multiple pneumococcal serotypes. The majority of pneumococci belonged to PCV13 serotypes (226/298, 76%). The most common serotypes were 19F, 14, 19A, 6A, 6B and 23F in both age groups. Pneumococcal carriage density differed significantly (p<0.001) between children with [5.8 (5.6-5.9) log10 colony forming units (cfu)/ml] and without radiologically-confirmed pneumonia [5.1 (4.7-5.4) log10 cfu/ml].

Conclusion

In the pre-PCV period, the majority of pneumococci present in the nasopharynx in children hospitalized with pneumonia belonged to PCV13 serotypes, indicating the vaccine is likely to be effective in this setting. There was also a higher pneumococcal carriage density in children with radiologically-confirmed pneumonia compared to children without radiologically-confirmed pneumonia.
Methods:

We used four data components: Retrospective population-based medical record review of children 2-59 months admitted with pneumonia and "control" conditions from 2011-2013 (pre-PCV13) and 2014-2016 (post-PCV13). Ongoing hospital-based carriage and pneumonia surveillance of children 0-59 months with acute respiratory infections from 2014, and invasive pneumococcal disease (IPD) surveillance from 2004. Community carriage surveys in healthy infants and toddlers pre- and two years post-PCV13.

Results:

The pre-PCV13 annual incidence of hospitalised pneumonia was 1530 (95% CI 1477-1584) per 100,000 children 2-59 months, with post-PCV13 data collection underway.

Hospital-based surveillance recruited 1099 cases from December 2013 to July 2017. A sub-analysis of hypoxic pneumonia demonstrated an adjusted PCV13 vaccine effectiveness (using odds ratios) of 55.2% (95%CI 27.4-72.3%).

IPD surveillance in children 0-59 months showed a decline in PCV13 serotype cases from 85% (11/13) (pre-PCV) to 67% (2/3) (post-PCV13), but numbers were small (p=0.98).

Community carriage data comparing pre- and post-PCV periods showed a reduction in PCV13 serotype carriage [Adjusted prevalence ratio 0.69 (95%CI 0.56 – 0.85)] in children 12-23 months.

Conclusion

Using a variety of methods we demonstrated PCV13 impact in Laos despite limited preceding baseline data. This method could augment WHO PCV evaluation guidelines to be used in other low-income countries. Final results are expected early 2018.

ISPPD-0203

A COST-EFFECTIVENESS ANALYSIS OF REVACCINATING OLDER ADULTS WITH THE 23-VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPV23) COMPARED TO A SINGLE DOSE OF PPV23 IN JAPAN

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Background and Aims:

PPV23 is publicly funded (2014-2018) for adults 65 years old and catch up cohorts aged 70, 75, 80, 85, 90 and 95. The Japan Association for Infectious Diseases recommends revaccination for older adults who received primary PPV23 vaccination 5 and more years earlier. This study compared the cost-effectiveness of: (1) vaccinating adults who turn 65 years only in 2019 (no revaccination); with (2) vaccinating adults who turn 65 years only in 2019 and revaccinating them 5 years later, as well as revaccinating the cohorts who were vaccinated in 2014 (revaccination).

Methods:
A population-based Markov model was developed that considered 5 health states: no pneumococcal disease, invasive pneumococcal disease (IPD), non-bacteremic pneumococcal pneumonia (NBPP), post-meningitis sequelae and death. Cohorts of adults aged 65, 70, 75, 80, 85, 90, and 95 were followed up to 100 years of age or until death. Model parameters were retrieved from global and Japanese sources. Costs and QALYs were discounted at 2%. An incremental cost-effectiveness ratio (ICER) was estimated.

Results:

In the base case, compared to no revaccination, revaccination was estimated to prevent an additional 172 cases of IPD, 29,708 cases of NBPP, 15 deaths due to IPD and 2,096 deaths due to NBPP. Compared to no revaccination, the ICER for revaccination was estimated to be ¥1,680,050/QALY (USD 14,873/QALY).

Conclusion

Revaccination would prevent additional pneumococcal disease cases and deaths in older adults. Revaccination compared to no revaccination is cost effective at an ICER threshold of ¥5 million per QALY gained, which is typically used in Japan.

Background and Aims:

Revaccination with PPV23 is available for older adults in the Philippines who were previously vaccinated with PPV23 at 60 years old. This study assessed the cost-effectiveness of primary vaccination at 60 years and revaccination at 65 years with PPV23 compared to no vaccination in Philippines.

Methods:

A population-based Markov model was developed. The model has five health states including no pneumococcal disease, invasive pneumococcal disease (IPD), non-bacteremic pneumococcal pneumonia (NBPP), post-meningitis sequelae and death. A cohort of 60-year-olds was followed up to 100 years of age or death. Vaccine efficacy against IPD and NBPP was obtained from a meta-analysis, a clinical trial and a population-based cohort study. Cost and utilities were discounted at a rate of 3.5% annually. Incremental cost-effectiveness ratio (ICER) expressed as additional cost per quality-adjusted life year (QALY) gained was estimated as the main outcome. The WHO definition of less than three times of GDP per capita in the Philippines (i.e. PHP 433,399 per QALY gained) was used as the threshold of cost-effectiveness.

Results:
In the base case analysis, compared to no vaccination, revaccination with PPV23 prevented 684 IPD cases, 2,839 NBPP cases, 183 deaths associated with IPD and 331 deaths associated with NBPP. Compared to no vaccination, the discounted incremental costs and incremental QALYs gained for revaccination with PPV23 were estimated at PHP 86.2 million and 369, respectively, corresponding to an ICER of PHP 233, 584/QALY.

**Conclusion**

Revaccinating adults at 65 years with PPV23 was estimated to be a cost effective strategy as compared to no vaccination in Philippines.
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Toronto, Canada

2020
21-25 June

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