

Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019

References with abstracts cited in the position paper in the order of appearance.

O'Brien KL, et al. Report from a WHO Working Group: standard method for detecting upper respiratory carriage of *Streptococcus pneumoniae*. *Pediatr Infect Dis J*; 2003; 22(2): e1-11.

BACKGROUND:

Numerous studies evaluating the efficacy of conjugate pneumococcal vaccines are being conducted or planned throughout the world. Some of these studies are evaluating the effect of vaccine on nasopharyngeal (NP) carriage.

METHODS:

The World Health Organization established a Working Group comprised of representatives from these trials and other NP colonization experts to establish core, standardized methods for the study of pneumococcal NP colonization that could be used in these trials. The intent was to reduce or eliminate variability in key methods which themselves could contribute to variability of observed pneumococcal NP colonization. In this way variability of vaccine effects between trials on NP colonization could more easily be analyzed for population or vaccine differences without the confounding effect caused by differences in study methodology.

RESULTS:

This paper presents the evidence base supporting the need for standardized NP colonization study methods, the methods themselves (Core Consensus Methods), including collection techniques, culture media, equipment, serotyping, storage of specimens and transport of isolates agreed on by the Working Group as well as a discussion of research priorities.

CONCLUSIONS:

The Core Consensus Methods provide a common methodology to conduct pneumococcal NP colonization studies with minimum interstudy method variability. The intention is to allow more meaningful comparisons of study results from conjugate pneumococcal vaccine trials.

Johnson HL, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. *PLoS Med*. 2010;7:pil:e1000348.

BACKGROUND:

Approximately 800,000 children die each year due to pneumococcal disease and >90% of these deaths occur in developing countries where few children have access to life-saving serotype-based vaccines. Understanding the serotype epidemiology of invasive pneumococcal disease (IPD) among children is necessary for vaccine development and introduction policies. The aim of this study was to systematically estimate the global and regional distributions of serotypes causing IPD in children <5 years of age.

METHODS AND FINDINGS:

We systematically reviewed studies with IPD serotype data among children <5 years of age from the published literature and unpublished data provided by researchers. Studies conducted prior to pneumococcal conjugate vaccine (PCV) introduction, from 1980 to 2007, with ≥ 12 months of surveillance, and reporting ≥ 20 serotyped isolates were included. Serotype-specific proportions were pooled in a random effects meta-analysis and combined with PD incidence and mortality estimates to infer global and regional serotype-specific PD burden. Of 1,292, studies reviewed, 169 were included comprising 60,090 isolates from 70 countries. Globally and regionally, six to 11 serotypes accounted for $\geq 70\%$ of IPD. Seven serotypes (1, 5, 6A, 6B, 14, 19F, 23F) were the most common globally; and based on year 2000 incidence and mortality estimates these seven serotypes accounted for >300,000 deaths in Africa and 200,000 deaths in Asia. Serotypes included in both the 10- and 13-valent PCVs accounted for 10 million cases and 600,000 deaths worldwide.

CONCLUSIONS:

A limited number of serotypes cause most IPD worldwide. The serotypes included in existing PCV formulations account for 49%-88% of deaths in Africa and Asia where PD morbidity and mortality are the highest, but few children have access to these life-saving vaccines. Please see later in the article for the Editors' Summary.

Yaro S, et al. Epidemiological and molecular characteristics of a highly lethal pneumococcal meningitis epidemic in Burkina Faso. Clin Infect Dis. 2006;43:693–700.

BACKGROUND:

Public health and clinical strategies for meningitis epidemics in sub-Saharan Africa usually assume that *Neisseria meningitidis* infection causes most disease.

METHODS:

During 24 months from 2002 to 2005, we collected clinical and laboratory information for suspected acute bacterial meningitis cases from 3 districts in Burkina Faso. *Streptococcus pneumoniae* was identified by culture, polymerase chain reaction, or antigen detection in cerebrospinal fluid. Pneumococcal genotyping was performed on strains using multilocus variable-number tandem repeat typing and multilocus sequence typing.

RESULTS:

Samples of cerebrospinal fluid were collected from 1686 persons; 249 (15%) had *S. pneumoniae* identified (annual incidence, 14 cases per 100,000 persons). Of these patients, 115 (46%) died, making *S. pneumoniae* the most commonly identified organism and responsible for two-thirds of deaths due to bacterial meningitis. During the meningitis epidemic season, an average of 38 cases of *S. pneumoniae* infection were identified each month, compared with an average of 8.7 cases during other months. Of 48 pneumococci that were tested, 21 (44%) were identified as serotype 1, and the remaining 27 (56%) were identified as 15 different serogroups and/or serotypes. Both serotype 1 and other serogroups and/or serotypes were seasonal. The genotypes of serotype 1 isolates were closely related but diversified over the study period and were similar to, but not identical to, the predominant genotypes found previously in Ghana.

CONCLUSIONS:

Intervention strategies during the epidemic season in Burkina Faso (and perhaps elsewhere) must now account for pneumococcal meningitis occurring in an epidemic pattern similar to

meningococcal meningitis. Although a serotype 1 clone was commonly isolated, over half of the cases were caused by other serogroups and/or serotypes, and genetic diversification increased over a relatively short period.

Kwambana-Adams BA, et al. An outbreak of pneumococcal meningitis among older children (≥ 5 years) and adults after the implementation of an infant vaccination programme with the 13-valent pneumococcal conjugate vaccine in Ghana. BMC Infect Dis. 2016;16(1):575.

BACKGROUND:

An outbreak of pneumococcal meningitis among non-infant children and adults occurred in the Brong-Ahafo region of Ghana between December 2015 and April 2016 despite the recent nationwide implementation of a vaccination programme for infants with the 13-valent pneumococcal conjugate vaccine (PCV13).

METHODS:

Cerebrospinal fluid (CSF) specimens were collected from patients with suspected meningitis in the Brong-Ahafo region. CSF specimens were subjected to Gram staining, culture and rapid antigen testing. Quantitative PCR was performed to identify pneumococcus, meningococcus and Haemophilus influenzae. Latex agglutination and molecular serotyping were performed on samples. Antibiogram and whole genome sequencing were performed on pneumococcal isolates.

RESULTS:

Eight hundred eighty six patients were reported with suspected meningitis in the Brong-Ahafo region during the period of the outbreak. In the epicenter district, the prevalence was as high as 363 suspected cases per 100,000 people. Over 95 % of suspected cases occurred in non-infant children and adults, with a median age of 20 years. Bacterial meningitis was confirmed in just under a quarter of CSF specimens tested. Pneumococcus, meningococcus and Group B Streptococcus accounted for 77 %, 22 % and 1 % of confirmed cases respectively. The vast majority of serotyped pneumococci (80 %) belonged to serotype 1. Most of the pneumococcal isolates tested were susceptible to a broad range of antibiotics, with the exception of two pneumococcal serotype 1 strains that were resistant to both penicillin and trimethoprim-sulfamethoxazole. All sequenced pneumococcal serotype 1 strains belong to Sequence Type (ST) 303 in the hypervirulent ST217 clonal complex.

CONCLUSION:

The occurrence of a pneumococcal serotype 1 meningitis outbreak three years after the introduction of PCV13 is alarming and calls for strengthening of meningitis surveillance and a re-evaluation of the current vaccination programme in high risk countries.

Leimkugel J, et al. An outbreak of serotype 1 Streptococcus pneumoniae meningitis in northern Ghana with features that are characteristic of Neisseria meningitidis meningitis epidemics. J Infect Dis. 2005 Jul 15;192(2):192-9.

BACKGROUND:

The Kassena-Nankana District (KND) of northern Ghana lies in the African meningitis belt, where epidemics of bacterial meningitis have been reoccurring every 8-12 years. These

epidemics are generally caused by *Neisseria meningitidis*, an organism that is considered to be uniquely capable of causing meningitis epidemics.

METHODS:

We recruited all patients with suspected meningitis in the KND between 1998 and 2003. Cerebrospinal fluid samples were collected and analyzed by standard microbiological techniques. Bacterial isolates were subjected to serotyping, multilocus sequence typing (MLST), and antibiotic-resistance testing.

RESULTS:

A continual increase in the incidence of pneumococcal meningitis was observed from 2000 to 2003. This outbreak exhibited strong seasonality, a broad host age range, and clonal dominance, all of which are characteristic of meningococcal meningitis epidemics in the African meningitis belt. The case-fatality rate for pneumococcal meningitis was 44.4%; the majority of pneumococcal isolates were antibiotic sensitive and expressed the serotype 1 capsule. MLST revealed that these isolates belonged to a clonal complex dominated by sequence type (ST) 217 and its 2 single-locus variants, ST303 and ST612.

CONCLUSIONS:

The *S. pneumoniae* ST217 clonal complex represents a hypervirulent lineage with a high propensity to cause meningitis, and our results suggest that this lineage might have the potential to cause an epidemic. Serotype 1 is not included in the currently licensed pediatric heptavalent pneumococcal vaccine. Mass vaccination with a less complex conjugate vaccine that targets hypervirulent serotypes should, therefore, be considered.

Wahl B, et al. Burden of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. *Lancet Global Health*. 2018;6(7):e744–57.

BACKGROUND:

Pneumococcal conjugate vaccine (PCV) and *Haemophilus influenzae* type b (Hib) vaccine are now used in most countries. To monitor global and regional progress towards improving child health and to inform national policies for disease prevention and treatment, we prepared global, regional, and national disease burden estimates for these pathogens in children from 2000 to 2015.

METHODS:

Using WHO and Maternal and Child Epidemiology Estimation collaboration country-specific estimates of pneumonia and meningitis mortality and pneumonia morbidity from 2000 to 2015, we applied pneumococcal and Hib cause-specific proportions to estimate pathogen-specific deaths and cases. Summary estimates of the proportion of pneumonia deaths and cases attributable to these pathogens were derived from four Hib vaccine and six PCV efficacy and effectiveness study values. The proportion of meningitis deaths due to each pathogen was derived from bacterial meningitis aetiology and adjusted pathogen-specific meningitis case-fatality data. Pneumococcal and Hib meningitis cases were inferred from modelled pathogen-specific meningitis deaths and literature-derived case-fatality estimates. Cases of pneumococcal and Hib syndromes other than pneumonia and meningitis were estimated using the ratio of pathogen-specific non-pneumonia, non-meningitis cases to pathogen-specific meningitis cases

from the literature. We accounted for annual HIV infection prevalence, access to care, and vaccine use.

FINDINGS:

We estimated that there were 294 000 pneumococcal deaths (uncertainty range [UR] 192 000-366 000) and 29 500 Hib deaths (18 400-40 700) in HIV-uninfected children aged 1-59 months in 2015. An additional 23 300 deaths (15 300-28 700) associated with pneumococcus and fewer than 1000 deaths associated Hib were estimated to have occurred in children infected with HIV. We estimate that pneumococcal deaths declined by 51% (7-74) and Hib deaths by 90% (78-96) from 2000 to 2015. Most children who died of pneumococcus (81%) and Hib (76%) presented with pneumonia. Less conservative assumptions result in pneumococcccal death estimates that could be as high as 515 000 deaths (302 000-609 000) in 2015. Approximately 50% of all pneumococcal deaths in 2015 occurred in four countries in Africa and Asia: India (68 700 deaths, UR 44 600-86 100), Nigeria (49 000 deaths, 32 400-59 000), the Democratic Republic of the Congo (14 500 deaths, 9300-18 700), and Pakistan (14 400 deaths, 9700-17 000)]. India (15 600 deaths, 9800-21 500), Nigeria (3600 deaths, 2200-5100), China (3400 deaths, 2300-4600), and South Sudan (1000 deaths, 600-1400) had the greatest number of Hib deaths in 2015. We estimated 3·7 million episodes (UR 2·7 million-4·3 million) of severe pneumococcus and 340 000 episodes (196 000-669 000) of severe Hib globally in children in 2015.

INTERPRETATION:

The widespread use of Hib vaccine and the recent introduction of PCV in countries with high child mortality is associated with reductions in Hib and pneumococcal cases and deaths. Uncertainties in the burden of pneumococcal disease are largely driven by the fraction of pneumonia deaths attributable to pneumococcus. Progress towards further reducing the global burden of Hib and pneumococcal disease burden will depend on the efforts of a few large countries in Africa and Asia.

Isaacman DJ, et al. Burden of invasive pneumococcal disease and serotype distribution among *Streptococcus pneumoniae* isolates in young children in Europe: impact of the 7-valent pneumococcal conjugate vaccine and considerations for future conjugate vaccines. *Int J Infect Dis.* 2010;14:e197–209.

OBJECTIVES:

The overall reported burden of invasive pneumococcal disease (IPD) varies among countries in Europe. This review describes the epidemiology and serotype distribution of IPD in European children from studies published from 1990 to 2008.

METHODS:

Averages were derived from all studies from all countries that had available data.

RESULTS:

Before widespread immunization with 7-valent pneumococcal conjugate vaccine (PCV7), the overall mean annual incidence of IPD in children aged <2 years was 44·4/100 000. The mean case fatality rate for IPD was 3·5%, and resistant rates were approximately 23% for penicillin G (minimum inhibitory concentration > or =2mg/l), 41% for erythromycin, and 9% (< or =5 years) for third-generation cephalosporins. The most common serotypes causing IPD were 14, 6B, 19F, and 23F, all of which are included in PCV7. Vaccine serotype coverage ranged from 37% to

100% for PCV7, with mean increases in coverage of 7% and 16% for investigational 10- and 13-valent pneumococcal conjugate vaccines, respectively. The most common IPD isolates since PCV7 introduction in Belgium, France, Germany, Greece, Norway, Portugal, Spain, and the UK were serotypes 1, 19A, 3, 6A, and 7F.

CONCLUSIONS:

With routine effective use of PCV7, a general decline in IPD, antibiotic non-susceptibility, and vaccine serotypes has been observed. The most common IPD isolates since PCV7 introduction are serotypes 1, 19A, 3, 6A, and 7F, highlighting the need for inclusion of these serotypes in future vaccine formulations.

Black S, et al. Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In: Plotkin SA, Orenstein WA, Offit P, editors. Vaccines. 5th ed. Philadelphia (PA): WB Saunders Co; 2008:531–67.

(No abstract available)

Roca A, et al. Invasive pneumococcal disease in children < 5 years of age in rural Mozambique. Trop Med Int Health. 2006;11:1422–31.

(No abstract available)

Karstaedt AS, et al. Pneumococcal bacteremia during a decade in children in Soweto, South Africa. Pediatr Infect Dis J. 2000;9:454–7.

OBJECTIVES:

To monitor for a decade the incidence and the clinical and microbiologic characteristics of pneumococcal bacteremia in children in Soweto and to assess the influence of HIV infection on any changes.

METHODS:

Case records of children with pneumococcal bacteremia at Chris Hani Baragwanath Hospital from July, 1986, to June, 1987 (1986/ 1987), and from July, 1996, to June, 1997 (1996/ 1997), were retrospectively reviewed.

RESULTS:

There were 194 episodes, 62 in 1986/1987 and 132 in 1996/1997. The minimum annual incidence for children younger than 5 years of age increased from 61 per 100000 (179 per 100000 for those <12 months old) in 1986/1987 to 130 per 100000 (349 per 100000 for those <12 months old) in 1996/1997. Sixty-seven (60%) of 111 patients tested in 1996/1997 were HIV-seropositive; none were tested in 1986/1987. The HIV-infected compared with HIV-noninfected were more likely to be malnourished (61% vs. 36%, $P = 0.02$), less likely to have other underlying disease (12% vs. 50%, $P = 0.00001$) and more frequently used antibiotics recently (69% vs. 43%, $P = 0.008$). Penicillin-nonsusceptible isolates were found in 22 (35%) patients in 1986/1987 and 52 (39%) in 1996/1997. There was no significant change in antimicrobial susceptibility during the decade or by HIV serostatus.

CONCLUSIONS:

Children in Soweto had a high incidence of pneumococcal bacteremia which doubled during the decade mainly as a result of the impact of the HIV epidemic. There has been no significant change in antimicrobial susceptibility for the decade.

Cutts FT, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet*. 2005;365:1139–46.

BACKGROUND:

Pneumonia is estimated to cause 2 million deaths every year in children. *Streptococcus pneumoniae* is the most important cause of severe pneumonia. We aimed to assess the efficacy of a nine-valent pneumococcal conjugate vaccine in children.

METHODS:

We undertook a randomised, placebo-controlled, double-blind trial in eastern Gambia. Children age 6-51 weeks were randomly allocated three doses of either pneumococcal conjugate vaccine (n=8718) or placebo (8719), with intervals of at least 25 days between doses. Our primary outcome was first episode of radiological pneumonia. Secondary endpoints were clinical or severe clinical pneumonia, invasive pneumococcal disease, and all-cause admissions. Analyses were per protocol and intention to treat.

FINDINGS:

529 children assigned vaccine and 568 allocated placebo were not included in the per-protocol analysis. Results of per-protocol and intention-to-treat analyses were similar. By per-protocol analysis, 333 of 8189 children given vaccine had an episode of radiological pneumonia compared with 513 of 8151 who received placebo. Pneumococcal vaccine efficacy was 37% (95% CI 27-45) against first episode of radiological pneumonia. First episodes of clinical pneumonia were reduced overall by 7% (95% CI 1-12). Efficacy of the conjugate vaccine was 77% (51-90) against invasive pneumococcal disease caused by vaccine serotypes, 50% (21-69) against disease caused by all serotypes, and 15% (7-21) against all-cause admissions. We also found an efficacy of 16% (3-28) against mortality. 110 serious adverse events arose in children given the pneumococcal vaccine compared with 131 in those who received placebo.

INTERPRETATION:

In this rural African setting, pneumococcal conjugate vaccine has high efficacy against radiological pneumonia and invasive pneumococcal disease, and can substantially reduce admissions and improve child survival. Pneumococcal conjugate vaccines should be made available to African infants.

Benavides JA, et al. Population-based surveillance for invasive pneumococcal disease and pneumonia in infants and young children in Bogotá, Colombia. *Vaccine*. 2012;30(40):5886–92.

BACKGROUND:

In children <5 years of age, *Streptococcus pneumoniae* (SP) is, globally, the leading cause of vaccine-preventable death. Surveillance conducted in Bogotá, Colombia estimated incidence

rates of invasive pneumococcal disease (IPD), clinical and chest radiograph-confirmed pneumonia (CXR+Pn); SP serotype distribution and antimicrobial susceptibility.

METHODS:

This prospective population-based surveillance was conducted from 2006 to 2008 in children 28 days to <36 months of age seeking care at SaludCoop centers. We determined incidence rates of IPD and pneumonia (clinical and CXR+Pn). Eligibility criteria included: temperature $\geq 39.0^{\circ}\text{C}$ within 24h and/or clinical suspicion of IPD or pneumonia. Blood was obtained for culture in all children. Other sterile site specimens were obtained per routine practice.

RESULTS:

Of 8261 subjects enrolled, a total of 64 had invasive pneumococcal disease detected by isolation of SP from nonduplicative cultures (62) or detected solely by PCR and a clinical picture consistent with IPD (2). The overall IPD incidence rates for culture-positive only cases for children aged 28 days to <36 months was 76.4/100,000 per year for years 1 and 2 combined. Age stratification found the highest rates in children 6-12 and 12 to <24 months of age. IPD incidence rates were assessed for bacteremic pneumonia (54.2/100,000), bacteremia (17.2/100,000), meningitis (3.7/100,000), and sepsis (1.2/100,000). Most common serotypes causing IPD were: 14 (51.6%), 6B (9.7%), and 19F (9.7%). Coverage of IPD cases by pneumococcal conjugate vaccine (PCV) 7, PCV10, and PCV13 was 77.4%, 85.5%, and 91.9%, respectively. Twenty-eight isolates (45.2%) were penicillin-nonsusceptible; PCV7 covered 96.3% of these; PCV10 covered 96.3% and PCV13 covered 100%. The overall incidence of clinical pneumonia and CXR+Pn was 6276/100,000 and 2120/100,000, respectively.

CONCLUSION:

Pneumococcal disease and pneumonia burden is considerable in children in Bogotá, Colombia. Vaccination with pneumococcal conjugate vaccines has the potential to decrease this burden. Epidemiologic data are critical in assessing the potential impact of introduction of PCVs into national immunization schedules.

Arguedas A, et al. Prospective epidemiologic surveillance of invasive pneumococcal disease and pneumonia in children in San José, Costa Rica. *Vaccine*. 2012;30(13):2342–8.

BACKGROUND:

Streptococcus pneumoniae (SP) is the leading cause of vaccine-preventable death in children <5 years of age, globally. This surveillance determined incidence rates of invasive pneumococcal disease (IPD), clinical and chest radiograph-confirmed pneumonia (CXR+Pn); and SP serotype distribution and antimicrobial susceptibility in children in San José, Costa Rica.

METHODS:

This was a 2-year prospective, population-based surveillance conducted in 2007-2009 in children aged 28 days to 36 months presenting to participating healthcare centers. Eligibility criteria for study inclusion were as follows: temperature $\geq 39.0^{\circ}\text{C}$ within 24h and/or clinical suspicion of IPD or pneumonia.

RESULTS:

8801 subjects were enrolled. Median age: 14.5 months. A total of 25 children had invasive pneumococcal disease with *S. pneumoniae* isolated from nonduplicative cultures (22) or detected solely by PCR and a clinical picture consistent with IPD (3). Sources of positive cultures

(some children had >1 positive culture) were: blood (20), pleural fluid (4), and cerebrospinal fluid (3). Of the 3 cases detected solely by PCR, 2 were from cerebrospinal fluid and 1 from pleural fluid. The overall IPD incidence rates for culture-positive only cases for children aged 28 days to <3 years was 33.7/100,000 per year for years 1 and 2 combined. Age stratification of culture-positive only subjects showed a peak during year 1 (106.8/100,000) in children 28 days to <6 months of age group, and in year 2 (45.5/100,000) in children 12 months to <24 months of age group. Most common serotypes were 14 (28.6%), followed by 3, 4, 6A, 19A, and 22F (9.5% each). Of 22 nonduplicative IPD isolates, 42.9% were penicillin- and trimethoprim/sulfamethoxazole nonsusceptible isolates. Consideration of PCR-positive cases increases the incidence of IPD for children aged 28 days to <3 years to 46.0/100,000. Overall incidence of clinical pneumonia and CXR+Pn was 1968/100,000 and 551/100,000, respectively.

CONCLUSIONS:

There is a considerable burden of IPD and pneumonia in children in San José. These epidemiologic data serve as a baseline to evaluate the effectiveness of the incorporation of new conjugate pneumococcal vaccines into the National Immunization Program in Costa Rican children.

Andrade AL, et al. Population-based surveillance for invasive pneumococcal disease and pneumonia in infants and young children in Goiânia, Brazil. Vaccine. 2012;30(10):1901–9.

BACKGROUND:

Streptococcus pneumoniae is the leading cause of vaccine-preventable death in children <5 years of age globally. We determined incidence rates of invasive pneumococcal disease (IPD), clinical and chest X-ray-confirmed pneumonia (CXR+Pn), *S. pneumoniae* serotype distribution, and antimicrobial susceptibility in children in Goiânia, Brazil.

METHODS:

Prospective, population-based surveillance was conducted from May 2007 to May 2009 in children 28 days to <36 months of age presenting to all 33 pediatric healthcare services (outpatient departments, emergency rooms, hospitals) in Goiânia. Eligibility criteria were temperature ≥ 39.0 °C in the previous 24h and/or clinical suspicion of pneumonia or IPD.

RESULTS:

14,509 subjects were enrolled. Median age was 14.0 months. *S. pneumoniae* was detected in 64 samples from 62 subjects: 58 (90.6%) blood; 4 (6.3%) cerebrospinal fluid; and 2 (3.1%) pleural fluid. Incidence rate of IPD (culture- and polymerase chain reaction-positive) for all children aged 28 days to <36 months was 57.5/100,000; overall incidence for culture-positive only was 54.9/100,000. Age stratification of culture-positive-only subjects found the highest rates were, 114.6/100,000 and 69.8/100,000, respectively, for the 6 months to <12 months and 12 months to <24 months age groups. The overall incidence of invasive pneumonia and pneumococcal meningitis was 37.2/100,000 and 5.3/100,000, respectively. The most common IPD serotypes were 14 (45.0%), 6B (13.3%), 18C (6.7%), and 23F (5.0%). Eight isolates (13.3%) were penicillin nonsusceptible. The cumulative percentages of serotypes included in 7-valent, 10-valent, and 13-valent pneumococcal conjugate vaccines were 78.3%, 80.0%, and 88.3%, respectively. The overall incidence of clinical pneumonia and CXR+Pn was, 9598/100,000 and

3428/100,000, respectively. CXR+Pn rates for hospitalized and non-hospitalized subjects were 1751/100,000 and 1677/100,000, respectively.

Howidi M, et al. The burden of pneumococcal disease in children less than 5 years of age in Abu Dhabi, United Arab Emirates. *Ann Saudi Med.* 2011;31(4):356–9.

BACKGROUND AND OBJECTIVE:

Streptococcus pneumoniae is a major cause of mortality and morbidity in both developing and industrialized countries, especially among young children and in both immunocompromised and immunocompetent individuals. It is implicated in both invasive (e.g. meningitis and septicemia) as well as noninvasive disease (community-acquired pneumonia and otitis media). The objective of the current study was to describe the overall epidemiology of both invasive and noninvasive pneumococcal disease in Abu Dhabi over a 5-year period.

DESIGN AND SETTING:

Retrospective review of all pediatric (≤ 5 year old) pneumococcal disease admissions to Shaikh Khalifa Medical City (SKMC) and Mafraq Hospital in Abu Dhabi from 1 January 2001 till 31 December 2005.

METHODS:

We retrieved computerized data from the health information management systems (International Classification of Diseases, 9th Revision (ICD9) diagnosis codes) as well as manual surveillance in the laboratory record of pneumococcal isolates.

RESULTS:

The incidence of invasive pneumococcal disease was 13.6/100,000 per year (95% CI, 6.5–24.9) and the incidence of noninvasive pneumococcal disease was 172.5/100,000 per year (95% CI, 143.8–205.2). The total incidence rate was 186.0/100,000 per year (95% CI, 156.2–219.9).

CONCLUSION:

This epidemiological survey indicates that the incidence rates in the United Arab Emirate are higher than in Western countries where conjugate pneumococcal vaccine has been introduced. This study is important as it documents the incidence of pneumococcal disease in the era before introduction of the conjugate pneumococcal vaccine and allows for future research to document the impact of a new vaccine considering the geographic variation of pneumococcal serotypes.

Lin TY, et al. Summary of invasive pneumococcal disease burden among children in the Asia–Pacific region. *Vaccine.* 2010;28(48):7589–605.

Invasive pneumococcal disease (IPD) burden is significant in the Asia-Pacific region. This review describes the epidemiology and *Streptococcus pneumoniae* (SP) serotype distribution of IPD in children in the Asia-Pacific region from studies published from 1999 to 2010. IPD incidence varies widely in Asia-Pacific countries depending on the method of surveillance, the population studied, and the time period. Incidences are highest for younger children, with rates near 100–200 cases per 100,000 children aged <1 or 2 years. Incidences of preventable disease are estimated to be 6–200 cases per 100,000. Heptavalent pneumococcal conjugate vaccine (PCV7) serotype coverage shows a very wide range over the Asia-Pacific region. Ten countries have high vaccine serotype coverage ($>70\%$), and six countries have low vaccine serotype coverage

(<50%). The majority of SP serotypes in children with IPD in most countries in the Asia-Pacific region are susceptible to penicillin (intermediate and resistant <50%); a few countries have SP serotypes with high level resistance to penicillin (intermediate and resistant >50%). Japan, Taiwan, and Thailand have high PCV7 serotype coverage. Countries with low pneumococcal resistance to antimicrobials have shown increasingly higher nonsusceptibility with time. National vaccination programmes that include PCV7, 10-valent pneumococcal conjugate vaccine (PCV), or 13-valent PCV would significantly affect IPD burden in children aged <5 years in the Asia-Pacific region, as well as the burden of penicillin-nonsusceptible IPD.

Owais A, et al. Incidence of pneumonia, bacteremia, and invasive pneumococcal disease in Pakistani children. Trop Med Int Health. 2010;15(9):1029–36.

OBJECTIVE:

To determine the incidence of pneumonia, bacteremia, and invasive pneumococcal disease (IPD) in Pakistani children <5 years old.

METHODS:

Household surveillance from 1st February 2007 to 12th May 2008 was conducted in two low-income, coastal communities of Karachi. Community health workers referred each sick child <5 years old to the local clinic. Blood culture was obtained whenever possible from children meeting inclusion criteria.

RESULTS:

Overall, 5570 children contributed 3949 observation years. There were 1039 clinical cases of pneumonia, of which 54 were severe pneumonia and four cases of very severe disease according to WHO criteria. The overall pneumonia incidence was 0.26 (95% CI: 0.25-0.28) episodes per child-year. A pathogen was isolated from the blood of 29 (2.8%) pneumonia cases. Bacteremia incidence was 912 (95% CI: 648-1248) episodes per 100,000 child-years with a case fatality rate of 8%. The detected IPD incidence was 25 (95% CI: 1-125) episodes per 100,000 child-years. The under-five mortality rate was 55 per 1000 live births, with pneumonia causing 12 (22%) deaths among children <5 years old.

CONCLUSION:

Clinical pneumonia is common in Pakistani children, with one in four deaths attributable to the disease. Bacteremia occurs at a high rate but surveillance for pneumococcus underestimates the burden of IPD.

Memish ZA, et al. Epidemiology of invasive pneumococcal infection in children aged five years and under in Saudi Arabia: a five-year retrospective surveillance study. Int J Infect Dis. 2010;14(8):e708–12.

(No abstract available)

Russell FM, et al. Invasive pneumococcal disease in Fiji: clinical syndromes, epidemiology, and the potential impact of pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2010;29(9):870–2.

Invasive pneumococcal disease (IPD) epidemiology and the potential impact of the pneumococcal conjugate vaccine in Fiji are documented. The annual incidence was 26.5 and

10.9 in those aged <5 and > or =55 years per 100,000, respectively. The case fatality rate was 9.4% and 67% in <5 and >65 year olds, respectively. One pneumococcal death and case would be prevented in <5 years olds for every 1930 and 128 infants vaccinated with 7vPCV, respectively.

Arifeen SE, et al. Invasive pneumococcal disease among children in rural Bangladesh: results from a population-based surveillance. Clin Infect Dis. 2009;48 Suppl 2:S103–13.

BACKGROUND:

Streptococcus pneumoniae infection is recognized as a global priority public health problem, and conjugate vaccines have been shown to prevent vaccine-type invasive pneumococcal disease (IPD) in children. However, better estimates of the disease burden and reliable population-based data on serotype composition are needed for vaccine development and implementation in developing countries.

METHODS:

We initiated a population-based surveillance in the rural Bangladesh community of Mirzapur, covering a population of approximately 144,000. Village health care workers made weekly visits to approximately 12,000 children 1-59 months of age in the study area. Children with reported fever, cough, or difficulty breathing were assessed by the village health care workers using a clinical algorithm and were referred to the hospital if required. Children from the study area who were seen in the hospital underwent clinical examination and laboratory testing if they met standardized case definitions. IPD was confirmed by blood and/or cerebrospinal fluid culture results. Isolates were identified, tested for susceptibility to antibiotics, and serotyped in accordance with standard laboratory methods. We present here the results from the first 3 years of the surveillance (July 2004-June 2007).

RESULTS:

Village health care workers identified 5020 cases of possible severe pneumonia and/or very severe disease (165 cases per 1000 child-years) and 9411 cases of possible pneumonia (310 cases per 1000 child-years) as well as 2029 cases of suspected meningitis and/or very severe disease (67 cases per 1000 child-years) and 8967 cases of high fever and/or possible bacteremia (295 cases per 1000 child-years). Pneumonia was the single most common form of illness observed among 2596 hospitalizations (found in 977 [38%] of cases). We recovered 26 *S. pneumoniae* isolates (25 isolates from 6925 blood cultures and 1 isolate from 41 cerebrospinal fluid cultures), which gave an overall IPD incidence of 86 cases per 100,000 child-years. Invasive pneumococcal infection was common during infancy (with infants accounting for 23 of the 26 cases), and 50% of the total isolates were obtained from nonhospitalized patients who received a diagnosis of upper respiratory tract infection and fever. The most prevalent pneumococcal serotypes were serotypes 1, 5, 14, 18C, 19A, and 38. Ten of the 26 isolates were completely resistant to trimethoprim-sulfamethoxazole, and another 10 isolates had intermediate resistance.

CONCLUSIONS:

IPD contributes substantially to childhood morbidity in rural Bangladesh. *S. pneumoniae* can cause invasive but nonsevere disease in children, and IPD incidence can be seriously under reported if such cases are overlooked. The emerging high resistance to trimethoprim-

sulfamethoxazole should be addressed. Data on serotype distribution would help to guide appropriate pneumococcal conjugate vaccine formulation.

Vuori-Holopainen E, et al. Reappraisal of lung tap: review of an old method for better etiologic diagnosis of childhood pneumonia. Clin Infect Dis. 2001;32:715–26.

Identification of the etiology of childhood pneumonia is difficult, even in the cases that most likely have bacterial origins. A positive blood culture result is diagnostic but rare (< 10% of cases), and other noninvasive microbiological methods are nonspecific or are at least shadowed by interpretation problems. However, lung tap (or aspiration), a method developed a century ago, warrants reappraisal, especially since the prevalence of pneumococcal resistance to penicillin is increasing. An analysis of 59 studies that were published in 6 languages led us to conclude that (1) bacterial etiology is disclosed in approximately 50% of cases (virological tests were rarely done); (2) lung tap is safer than is generally considered; (3) potential pneumothorax is mostly symptomless and resolves spontaneously without impairing recovery; and (4) in comparison with routine diagnostic tools, lung tap offers so many advantages that it warrants reconsideration at centers where personnel have experience in handling potential pneumothorax.

Lucero MG et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database Systemic Review, 2009, 7:CD004977.

BACKGROUND:

Pneumonia, caused by *Streptococcus pneumoniae*, is a major cause of morbidity and mortality among children in low-income countries. The effectiveness of pneumococcal conjugate vaccines (PCVs) against invasive pneumococcal disease (IPD), pneumonia, and mortality needs to be evaluated.

OBJECTIVES:

To update the 2004 review on the efficacy of PCVs in preventing vaccine-serotypes IPD (VT-IPD), X-ray defined pneumonia among HIV-1 negative children, and other new outcomes.

SEARCH STRATEGY:

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 1), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1990 to Week 4 February 2009); and EMBASE (1974 to March 2009).

SELECTION CRITERIA:

Randomised controlled trials (RCTs) comparing PCV with placebo, or another vaccine, in children under two with IPD and clinical / radiographic pneumonia as outcomes.

DATA COLLECTION AND ANALYSIS:

Two review authors independently identified studies, extracted data, and evaluated their corresponding risks of bias. Differences were resolved by discussion. Meta-analysis used the inverse variance method.

MAIN RESULTS:

We identified 11 publications from six RCTs conducted in Africa, US, Philippines and Finland where 57,015 children received PCV; while 56,029 received placebo or another vaccine. Seven publications provided high quality evidence on PCV efficacy against IPD and four provided moderate quality evidence against pneumonia. None of the five trials with all-cause mortality data were powered to investigate this outcome. Only two trials have data on all-cause admissions. The main analysis for this review involved HIV-1 negative children and used the pooled results of random-effects model, intent-to-treat analysis (ITT). Pooled vaccine efficacy (VE) for VT-IPD was 80% (95% confidence interval (CI) 58% to 90%, $P < 0.0001$); all serotypes-IPD, 58% (95% CI 29% to 75%, $P = 0.001$); World Health Organization X-ray defined pneumonia was 27% (95% CI 15% to 36%, $P < 0.0001$); clinical pneumonia, 6% (95% CI 2% to 9%, $P = 0.0006$); and all-cause mortality, 11% (95% CI -1% to 21%, $P = 0.08$). Analysis involving HIV-1 positive children had similar findings.

AUTHORS' CONCLUSIONS:

PCV is effective in preventing IPD, X-ray defined pneumonia, and clinical pneumonia among HIV-1 negative and HIV-1 positive children under two years. The impact was greater for VT-IPD than for all serotypes-IPD, and for X-ray defined pneumonia than for clinical pneumonia. An 11% reduction with a 95% CI of -1% to 21% and a $P = 0.08$ is compatible with reduction in all-cause mortality.

Cilloniz C, et al. Seasonality of pathogens causing community-acquired pneumonia.

Respirology. 2017;22(4):778–85.

BACKGROUND AND OBJECTIVE:

Seasonal distribution of microbial aetiology in patients with community-acquired pneumonia (CAP) may add important information both for epidemiologists and clinicians. We investigate the seasonal distribution of microbial aetiology in CAP.

METHODS:

This prospective observational study was carried out in the Hospital Clinic of Barcelona, Spain (January 2003-December 2014).

RESULTS:

We studied 4431 patients with CAP, of whom 2689 (61%) were males. Microbial aetiology was identified in 1756 patients (40%). CAP was most frequent in winter (34%) but two-third of patients with CAP presented in other seasons. Seasonal variations included *Streptococcus pneumoniae* (winter 21% vs spring 17% vs summer 14% vs autumn 13%, overall $P < 0.001$). Influenza viruses were most prevalent in autumn (6%) and winter (5%) compared with spring (3%) and summer (1%) (overall $P < 0.001$). *Legionella pneumophila* was most frequent in autumn (4%) and summer (4%) compared with spring (2%) and winter (1%) (overall $P < 0.001$). Incidence of polymicrobial pneumonia also differed between seasons (winter 7% vs spring 5% vs summer 3% vs autumn 6%, overall $P = 0.001$). We observed a significant correlation between the lowest seasonal average temperature and polymicrobial pneumonia, pneumococcal pneumonia, and influenza viruses; conversely, *L. pneumophila* was more common when temperatures were higher.

CONCLUSION:

CAP should not be regarded as a seasonal disease but occurs throughout all seasons. However, *S. pneumoniae*, influenza viruses, polymicrobial pneumonia and *L. pneumophila* are clearly subject to seasonal variations.

Numminen E, et al. Climate induces seasonality in pneumococcal transmission. *Sci Rep.* 2015;5:11344.

Streptococcus pneumoniae is a significant human pathogen and a leading cause of infant mortality in developing countries. Considerable global variation in the pneumococcal carriage prevalence has been observed and the ecological factors contributing to it are not yet fully understood. We use data from a cohort of infants in Asia to study the effects of climatic conditions on both acquisition and clearance rates of the bacterium, finding significantly higher transmissibility during the cooler and drier months. Conversely, the length of a colonization period is unaffected by the season. Independent carriage data from studies conducted on the African and North American continents suggest similar effects of the climate on the prevalence of this bacterium, which further validates the obtained results. Further studies could be important to replicate the findings and explain the mechanistic role of cooler and dry air in the physiological response to nasopharyngeal acquisition of the pneumococcus.

Ben-Shimol S, et al. Seasonality of both bacteremic and nonbacteremic pneumonia coincides with viral lower respiratory tract infections in early childhood, in contrast to nonpneumonia invasive pneumococcal disease, in the pre-pneumococcal conjugate vaccine era. *Clin Infect Dis.* 2015;60(9):1384–7.

We assessed the seasonality of viral lower respiratory tract infections (V-LRI), bacteremic pneumonia, nonbacteremic pneumonia and nonpneumonia invasive pneumococcal diseases (IPD) in the pre-PCV era. Both bacteremic and nonbacteremic pneumonia seasonality peaked in winter, coinciding with V-LRI seasonality, whereas non-pneumonia IPD peaked in autumn before V-LRI increase, suggesting different pathogenesis.

Dangor Z, et al. Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children. *PLoS One.* 2014;9(3):e91464.

INTRODUCTION:

The seasonal variability in hospitalization for tuberculosis may in part relate to super-imposed bacterial or predisposing respiratory viral infections. We aimed to study the temporal association between hospitalization for culture-confirmed pulmonary tuberculosis (PTB), invasive pneumococcal disease (IPD) and influenza virus epidemics in South African children.

METHODS:

We undertook a retrospective analysis which examined seasonal trends, from 2005 to 2008, for hospitalization for culture-confirmed PTB and IPD among children in relation to the influenza epidemics in Soweto, South Africa. Original time-series of the influenza virus epidemics and hospitalization rates for PTB and IPD were decomposed into three components: a trend cycle component, a seasonal component and an irregular component using the X-11 seasonal

adjustment method. To compare the seasonality amongst the three series, the trend and irregular components were removed and only seasonal components examined.

RESULTS:

Across the study period, the influenza virus epidemics peaked during May to July (winter) months, which was closely followed by an increase in the incidence of hospitalization for IPD (August to October) and PTB (August to November).

DISCUSSION:

Within- and between-year temporal changes associated with childhood TB hospitalization may in part be driven by factors which influence temporal changes in pneumococcal disease, including potential variability in the severity of influenza virus epidemics in temperate climates. The dynamics of the interplay between the host and these infectious agents appears to be complex and multifactorial.

Kyaw MH, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. N Engl J Med. 2006;354:1455–63.

BACKGROUND:

Five of seven serotypes in the pneumococcal conjugate vaccine, introduced for infants in the United States in 2000, are responsible for most penicillin-resistant infections. We examined the effect of this vaccine on invasive disease caused by resistant strains.

METHODS:

We used laboratory-based data from Active Bacterial Core surveillance to measure disease caused by antibiotic-nonsusceptible pneumococci from 1996 through 2004. Cases of invasive disease, defined as disease caused by pneumococci isolated from a normally sterile site, were identified in eight surveillance areas. Isolates underwent serotyping and susceptibility testing.

RESULTS:

Rates of invasive disease caused by penicillin-nonsusceptible strains and strains not susceptible to multiple antibiotics peaked in 1999 and decreased by 2004, from 6.3 to 2.7 cases per 100,000 (a decline of 57 percent; 95 percent confidence interval, 55 to 58 percent) and from 4.1 to 1.7 cases per 100,000 (a decline of 59 percent; 95 percent confidence interval, 58 to 60 percent), respectively. Among children under two years of age, disease caused by penicillin-nonsusceptible strains decreased from 70.3 to 13.1 cases per 100,000 (a decline of 81 percent; 95 percent confidence interval, 80 to 82 percent). Among persons 65 years of age or older, disease caused by penicillin-nonsusceptible strains decreased from 16.4 to 8.4 cases per 100,000 (a decline of 49 percent). Rates of resistant disease caused by vaccine serotypes fell 87 percent. An increase was seen in disease caused by serotype 19A, a serotype not included in the vaccine (from 2.0 to 8.3 per 100,000 among children under two years of age).

CONCLUSIONS:

The rate of antibiotic-resistant invasive pneumococcal infections decreased in young children and older persons after the introduction of the conjugate vaccine. There was an increase in infections caused by serotypes not included in the vaccine.

Edmond K, et al. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(5):317–28.

Few data sources are available to assess the global and regional risk of sequelae from bacterial meningitis. We aimed to estimate the risks of major and minor sequelae caused by bacterial meningitis, estimate the distribution of the different types of sequelae, and compare risk by region and income. We systematically reviewed published papers from 1980 to 2008. Standard global burden of disease categories (cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment, hydrocephalus) were labelled as major sequelae. Less severe, minor sequelae (behavioural problems, learning difficulties, unilateral hearing loss, hypotonia, diplopia), and multiple impairments were also included. 132 papers were selected for inclusion. The median (IQR) risk of at least one major or minor sequela after hospital discharge was 19.9% (12.3-35.3%). The risk of at least one major sequela was 12.8% (7.2-21.1%) and of at least one minor sequela was 8.6% (4.4-15.3%). The median (IQR) risk of at least one major sequela was 24.7% (16.2-35.3%) in pneumococcal meningitis; 9.5% (7.1-15.3%) in Haemophilus influenzae type b (Hib), and 7.2% (4.3-11.2%) in meningococcal meningitis. The most common major sequela was hearing loss (33.9%), and 19.7% had multiple impairments. In the random-effects meta-analysis, all-cause risk of a major sequela was twice as high in the African (pooled risk estimate 25.1% [95% CI 18.9-32.0%]) and southeast Asian regions (21.6% [95% CI 13.1-31.5%]) as in the European region (9.4% [95% CI 7.0-12.3%]; overall $I(2)=89.5\%$, $p<0.0001$). Risks of long-term disabling sequelae were highest in low-income countries, where the burden of bacterial meningitis is greatest. Most reported sequelae could have been averted by vaccination with Hib, pneumococcal, and meningococcal vaccines.

Global action plan for prevention and control of pneumonia (GAPP): report of an informal consultation. Geneva: World Health Organization, 2008

(http://www.who.int/maternal_child_adolescent/documents/9789241596336/en/, accessed May 2018).

More than two million children under five die of pneumonia every year, making it the single biggest killer of children worldwide. To address pneumonia in the context of our child survival strategy, WHO and UNICEF have initiated a Global Action Plan for the Prevention and Control of Pneumonia (GAPP). Other collaborators and stakeholders are the Hib Initiative and PneumoADIP. A steering group comprising of members from WHO and UNICEF has been formed.

GAPP aims to accelerate overall pneumonia prevention and control in the context of integrated interventions for child survival, by identifying priority activities to reduce pneumonia mortality. This report describes the proceedings of a meeting in which leading experts in the field discussed the outline of comprehensive reviews in epidemiology, immunization, nutrition, indoor air pollution and case management of pneumonia. They also developed a technical consensus to achieve the prevention and control of pneumonia and outlined the next steps to move GAPP activities forward.

Malley R. Antibody and cell-mediated immunity to *Streptococcus pneumoniae*: implications for vaccine development. J Mol Med (Berl) 2010; 88(2): 135-142.

It has long been assumed that children develop natural immunity to pneumococci via the acquisition of anticapsular antibodies, which confers serotype-specific immunity to the organism. This view has been further reinforced by the recent success of capsular polysaccharide conjugate vaccines in children in reducing colonization and disease caused by vaccine-type strains. Less clear, however, is whether this mechanism is responsible for the age-related gradual increased resistance to pneumococcal carriage and disease. Recent epidemiologic and experimental evidence point to the possibility that another mechanism may be involved. Here, an alternative possibility is presented, whereby it is proposed that acquired immunity to this common human pathogen is derived not only from natural acquisition of antibodies (capsular and noncapsular) that provides protection against invasive disease but also from the development of pneumococcus-specific CD4+ T(H)17 cells that reduces the duration of carriage and may also impact mucosal disease. This review focuses on the experimental and clinical evidence in support of this hypothesis. The implications for future vaccine development against *Streptococcus pneumoniae* are also discussed.

Francis JP, et al. A longitudinal study of natural antibody development to pneumococcal surface protein A families 1 and 2 in Papua New Guinean Highland children: a cohort study. Pneumonia (Nathan Qld). 2016;8:12.

BACKGROUND:

Pneumococcal surface protein A (PspA), a conserved virulence factor essential for *Streptococcus pneumoniae* attachment to upper respiratory tract (URT) epithelia, is a potential vaccine candidate for preventing colonisation.

METHODS:

This cohort study was conducted in the Asaro Valley in the Eastern Highlands Province of Papua New Guinea, of which Goroka town is the provincial capital. The children included in the analysis were participants in a neonatal pneumococcal conjugate vaccine trial (ClinicalTrials.gov NCT00219401) that was conducted between 2005 and 2009. We investigated the development of anti-PspA antibodies in the first 18 months of life relative to URT pneumococcal carriage in Papua New Guinean infants who experience one of the earliest and highest colonisation rates in the world. Blood samples and nasopharyngeal swabs were collected from a cohort of 88 children at ages 3, 9, and 18 months to quantify immunoglobulin G (IgG) levels to PspA families 1 and 2 using an enzyme-linked immunosorbent assay and to determine URT carriage.

RESULTS:

Seventy-three per cent (64/88) of infants carried *S. pneumoniae* at age 3 months; 85 % (75/88) at 9 months, and 83 % (73/88) at 18 months. PspA-IgG levels declined between ages 3 and 9 months ($p < 0.001$), then increased between 9 and 18 months ($p < 0.001$). At age 3 months, pneumococcal carriers showed lower PspA1-IgG levels (geometric mean concentration [GMC] 602 arbitrary units [AU]/ml, 95 % confidence interval [CI] 497-728) than non-carriers (GMC 1058 AU/ml [95 % CI 732-1530]; $p = 0.008$), while at 9 months, PspA1- and PspA2-IgG levels were significantly higher in carriers (PspA1: 186 AU/ml, 95 % CI 136-256; PspA2: 284 AU/ml, 95

% CI 192-421) than in non-carriers (PspA1 87 AU/ml, 95 % CI 45-169; PspA2 74 AU/ml, 95 % CI 34-159) (PspA1: $p = 0.037$, PspA2: $p = 0.003$).

CONCLUSION:

Our findings confirm that PspA is immunogenic and indicate that natural anti-PspA immune responses are acquired through exposure and develop with age. PspA may be a useful candidate in an infant pneumococcal vaccine to prevent early URT colonisation.

Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines (WHO Technical Report Series, No. 977, Annex 3). Geneva: World Health Organization; 2013

(No abstract available)

Synflorix: pneumococcal polysaccharide conjugate vaccine (adsorbed). London: European Medicines Agency; undated

(http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000973/WC500054346.pdf, accessed May 2018).

(No abstract available)

Approved products: Prevnar 13: pneumococcal 13-valent conjugate vaccine (diphtheria CRM 197 protein). Washington DC: Food and Drug Administration; 2018

(<https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM574852.pdf>, accessed May 2018).

(No abstract available)

Prevenar 13: Annex 1: Summary of product characteristics. London: European Medicines Agency; undated (https://www.ema.europa.eu/documents/product-information/prevenar-13-epar-product-information_en.pdf, accessed December 2018)

(No abstract available)

WHO prequalified vaccines. Pneumococcal (conjugate) Prevenar 13 multidose vial. Geneva: World Health Organization

(https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=317, accessed May 2018).

(No abstract available)

WHO prequalified vaccines. Pneumococcal (conjugate) Synflorix multidose vial. Geneva: World Health Organization

(https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=341, accessed January 2019).

(No abstract available)

Pneumococcal conjugate vaccine review of impact evidence (PRIME): summary of findings from systematic review, October 2017. Geneva: World Health Organization; 2017 (http://www.who.int/immunization/sage/meetings/2017/october/3_FULL_PRIME_REPORT_2017Sep26.pdf?ua=1, accessed July 2018).

(No abstract available)

Flasche S, et al. Assessing the efficiency of catch-up campaigns for the introduction of pneumococcal conjugate vaccine: a modelling study based on data from PCV10 introduction in Kilifi, Kenya. BMC Med. 2017;15:113.

BACKGROUND:

The World Health Organisation recommends the use of catch-up campaigns as part of the introduction of pneumococcal conjugate vaccines (PCVs) to accelerate herd protection and hence PCV impact. The value of a catch-up campaign is a trade-off between the costs of vaccinating additional age groups and the benefit of additional direct and indirect protection. There is a paucity of observational data, particularly from low- and middle-income countries, to quantify the optimal breadth of such catch-up campaigns.

METHODS:

In Kilifi, Kenya, PCV10 was introduced in 2011 using the three-dose Expanded Programme on Immunisation infant schedule and a catch-up campaign in children <5 years old. We fitted a transmission dynamic model to detailed local data, including nasopharyngeal carriage and invasive pneumococcal disease (IPD), to infer the marginal impact of the PCV catch-up campaign over hypothetical routine cohort vaccination in that setting and to estimate the likely impact of alternative campaigns and their dose efficiency.

RESULTS:

We estimated that, within 10 years of introduction, the catch-up campaign among children <5 years old prevents an additional 65 (48-84) IPD cases across age groups, compared to PCV cohort introduction alone. Vaccination without any catch-up campaign prevented 155 (121-193) IPD cases and used 1321 (1058-1698) PCV doses per IPD case prevented. In the years after implementation, the PCV programme gradually accrues herd protection, and hence its dose efficiency increases: 10 years after the start of cohort vaccination alone the programme used 910 (732-1184) doses per IPD case averted. We estimated that a two-dose catch-up among children <1 year old uses an additional 910 (732-1184) doses per additional IPD case averted. Furthermore, by extending a single-dose catch-up campaign to children aged 1 to <2 years and subsequently to those aged 2 to <5 years, the campaign uses an additional 412 (296-606) and 543 (403-763) doses per additional IPD case averted. These results were not sensitive to vaccine coverage, serotype competition, the duration of vaccine protection or the relative protection of infants.

Le Polain de Waroux O, et al. Predicting the impact of pneumococcal conjugate vaccine programme options in Vietnam. Hum Vaccin Immunother. 2018;14(8):1939–47.

Although catch-up campaigns (CCs) at the introduction of pneumococcal conjugate vaccines (PCVs) may accelerate their impact, supply constraints may limit their benefit if the need for additional PCV doses results in introduction delay. We studied the impact of PCV13

introduction with and without CC in Nha Trang, Vietnam - a country that has not yet introduced PCV - through a dynamic transmission model. We modelled the impact on carriage and invasive pneumococcal disease (IPD) of routine vaccination (RV) only and that of RV with CCs targeting <1y olds (CC1), <2y olds (CC2) and <5y olds (CC5). The model was fitted to nasopharyngeal carriage data, and post-PCV predictions were based on best estimates of parameters governing post-PCV dynamics. With RV only, elimination in carriage of vaccine-type (VT) serotypes is predicted to occur across all age groups within 10 years after introduction, with near-complete replacement by non-VT. Most of the benefit of CCs is predicted to occur within the first 3 years with the highest impact at one year, when IPD incidence is predicted to be 11% (95%CrI 9 - 14%) lower than RV with CC1, 25% (21 - 30 %) lower with CC2 and 38% (32 - 46%) lower with CC5. However, CCs would only prevent more cases of IPD insofar as such campaigns do not delay introduction by more than about 6, 12 and 18 months for CC1, CC2 and CC5. Those findings are important to help guide vaccine introduction in countries that have not yet introduced PCV, particularly in Asia.

Feikin DR, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. PLoS Med. 2013 10(9):e1001517.

BACKGROUND:

Vaccine-serotype (VT) invasive pneumococcal disease (IPD) rates declined substantially following introduction of 7-valent pneumococcal conjugate vaccine (PCV7) into national immunization programs. Increases in non-vaccine-serotype (NVT) IPD rates occurred in some sites, presumably representing serotype replacement. We used a standardized approach to describe serotype-specific IPD changes among multiple sites after PCV7 introduction.

METHODS AND FINDINGS:

Of 32 IPD surveillance datasets received, we identified 21 eligible databases with rate data ≥ 2 years before and ≥ 1 year after PCV7 introduction. Expected annual rates of IPD absent PCV7 introduction were estimated by extrapolation using either Poisson regression modeling of pre-PCV7 rates or averaging pre-PCV7 rates. To estimate whether changes in rates had occurred following PCV7 introduction, we calculated site specific rate ratios by dividing observed by expected IPD rates for each post-PCV7 year. We calculated summary rate ratios (RRs) using random effects meta-analysis. For children <5 years old, overall IPD decreased by year 1 post-PCV7 (RR 0.55, 95% CI 0.46-0.65) and remained relatively stable through year 7 (RR 0.49, 95% CI 0.35-0.68). Point estimates for VT IPD decreased annually through year 7 (RR 0.03, 95% CI 0.01-0.10), while NVT IPD increased (year 7 RR 2.81, 95% CI 2.12-3.71). Among adults, decreases in overall IPD also occurred but were smaller and more variable by site than among children. At year 7 after introduction, significant reductions were observed (18-49 year-olds [RR 0.52, 95% CI 0.29-0.91], 50-64 year-olds [RR 0.84, 95% CI 0.77-0.93], and ≥ 65 year-olds [RR 0.74, 95% CI 0.58-0.95]).

CONCLUSIONS:

Consistent and significant decreases in both overall and VT IPD in children occurred quickly and were sustained for 7 years after PCV7 introduction, supporting use of PCVs. Increases in NVT IPD occurred in most sites, with variable magnitude. These findings may not represent the

experience in low-income countries or the effects after introduction of higher valency PCVs. High-quality, population-based surveillance of serotype-specific IPD rates is needed to monitor vaccine impact as more countries, including low-income countries, introduce PCVs and as higher valency PCVs are used. Please see later in the article for the Editors' Summary.

Tseng HF, et al. Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children. *Vaccine*. 2013;31:2578–83.

Although no increased risk was detected for serious adverse events in the prelicensure trials for the 13-valent pneumococcal vaccine, Prevnar 13[®] (PCV13), continued monitoring of rare but serious adverse events is necessary. A surveillance system using cohort study design was set up to monitor safety of PCV13 immediately after it was included in the childhood immunization program in the United States. The exposed population included children of 1 month to 2 years old who received PCV13 from April, 2010 to January, 2012 from the eight managed care organizations participating in the Vaccine Safety Datalink Project in the United States. The historical unexposed population was children of the same age who received the 7-valent pneumococcal conjugate vaccine Prevnar 7[®] (PCV7) in 2007 (or 2005 depending on the outcome of interest) to 2009. The risk of pre-specified adverse events in the risk window following PCV13 was repeatedly compared to that in the historical comparison group. The number of doses included in the study was 599,229. No increased risk was found for febrile seizures, urticaria or angioneurotic edema, asthma, thrombocytopenia, or anaphylaxis. An increased risk for encephalopathy was not confirmed following the medical record review. The relative risk for Kawasaki disease in 0-28 days following vaccination was 1.94 (95% confidence interval: 0.79-4.86), comparing PCV13 to PCV7. Comparing to PCV7 vaccine, we identified no significant increased risk of pre-specified adverse events in the Vaccine Safety Datalink study cohort. The possible association between PCV13 and Kawasaki disease may deserve further investigation.

Silfverdal SA, et al. Safety profile of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV). *Expert Rev Vaccines*. 2017;16 (2):109–21.

Safety and reactogenicity data were reviewed following 10 years of experience with the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) in clinical development and from post-licensure settings. Analyses of pooled clinical trial data and post-marketing reports provided an overview of its safety profile and allowed assessment of rare adverse events that might not have been identified previously. The safety of PHiD-CV was also evaluated in children at higher risk for pneumococcal infection (preterm and HIV-infected or HIV-exposed infants), for different vaccination schedules and co-administered pediatric vaccines, and with a focus on special categories of adverse events (febrile convulsions, apnea, Kawasaki disease and sudden deaths). Following the distribution of over 235 million doses, PHiD-CV has been well tolerated when co-administered with other pediatric vaccines to children aged less than 5 years from diverse ethnic and geographic backgrounds. Detailed examination of various aspects has confirmed its favorable benefit: risk profile.

Artama M, et al. Register-based ecologic evaluation of safety signals related to pneumococcal conjugate vaccine in children. *Curr Drug Saf.* 2018;13(2):107–12.

BACKGROUND:

In clinical trials of Pneumococcal Conjugate Vaccines (PCV), some adverse events have been reported more frequently in the PCV vaccinated. Ten-valent PCV (PCV10) was introduced into the Finnish National Vaccination Programme (NVP) in September 2010.

OBJECTIVE:

We conducted an ecologic register-based study to investigate further the reported adverse events after PCV.

METHODS:

This study included data obtained from the Finnish nationwide, population-based registers. First diagnoses of febrile seizures, breath-holding, urticarial rash, asthma and Kawasaki's disease were included as outcomes obtained from the hospital discharge register. Data from Finnish Population Register during 2000-2014 for children age from 3 months to 10 years were used to estimate annual incidence rates. Incidence rate ratios of the outcomes were calculated between the target cohort of children eligible for PCV10 during 2010-2014 and a reference cohort before the NVP introduction (2004-2008).

RESULTS:

No increases in the incidence of the adverse events after PCV10 introduction were found except for urticarial rash (incidence rate 2.48 vs. 1.60/1000 pyrs; incidence rate ratio, 1.54;95% CI 1.42-1.67). This increase was seen also in the unvaccinated older age groups in the post-vaccination era. The higher incidence of urticarial rash after the PCV10 introduction was due to the inclusion of diagnoses made in general medicine specialty in the discharge register because of a concomitant administrative change.

CONCLUSION:

The results do not support public health concerns related to the previously reported adverse events. Concomitant changes in health care administration and coding introduced bias, which was controlled after further evaluation of the data. We consider this register-based approach with realworld data feasible in the signal validation process after any signal detection.

Littlejohn ES, et al. Surveillance of adverse events following the introduction of 13-valent pneumococcal conjugate vaccine in infants, and comparison with adverse events following 7-valent pneumococcal conjugate vaccine, in Victoria, Australia. *Hum Vaccin Immunother.* 2015;11(7):1828–35.

The 13-valent pneumococcal vaccine (PCV13) replaced the 7-valent vaccine (PCV7) on the Australian National Immunization Program (NIP) in 2011. Post-marketing surveillance of adverse events following immunization (AEFI) is crucial for detecting potential safety signals and maintaining confidence in the NIP. This study describes all AEFI reported to Surveillance of Adverse Events following Vaccination in the Community (SAEFVIC), Melbourne, Australia, following both the primary series of PCV13 (children <7 months) and the catch-up dose (12 months-35 months) in its first year of inclusion on the NIP. AEFI reporting rates per 100,000 doses of vaccine administered were compared for the PCV13 primary series and PCV7 primary series in the previous year. SAEFVIC received 229 reports describing 406 AEFI following PCV13

vaccine in the 12 months post introduction. There was no difference in the total number of AEFI cases reported between the vaccines but 7 AEFI categories were reported at a significantly higher rate following PCV13 compared with PCV7. No difference in reporting rate was observed for serious AEFI ($p = 0.25$). Post-hoc analysis of a further 12 months of PCV13 data revealed that all 7 AEFI categories that were initially reported at a significantly higher rate following PCV13 compared to PCV7 in the first 12 months post introduction, were no longer significantly increased in the 13-24 month period. The initial high reporting rate for several common AEFI post PCV13 compared to PCV7 may be explained by heightened awareness of the new vaccine. There were no safety signals detected for rare or serious AEFI that would require further investigation at this time.

Duffy J, et al. Febrile seizure risk after vaccination in children 6 to 23 months. *Pediatrics*. 2016;138(1):e20160320.

BACKGROUND AND OBJECTIVE:

An increased risk of febrile seizure (FS) was identified with concomitant administration of trivalent inactivated influenza vaccine (IIV3) and pneumococcal conjugate vaccine (PCV) 13-valent during the 2010-2011 influenza season. Our objective was to determine whether concomitant administration of IIV3 with other vaccines affects the FS risk.

METHODS:

We examined the risk of FS 0 to 1 day postvaccination for all routinely recommended vaccines among children aged 6 through 23 months during a period encompassing 5 influenza seasons (2006-2007 through 2010-2011). We used a population-based self-controlled risk interval analysis with a control interval of 14 to 20 days postvaccination. We used multivariable regression to control for receipt of concomitant vaccines and test for interaction between vaccines.

RESULTS:

Only PCV 7-valent had an independent FS risk (incidence rate ratio [IRR], 1.98; 95% confidence interval [CI], 1.00 to 3.91). IIV3 had no independent risk (IRR, 0.46; 95% CI, 0.21 to 1.02), but risk was increased when IIV3 was given with either PCV (IRR, 3.50; 95% CI, 1.13 to 10.85) or a diphtheria-tetanus-acellular-pertussis (DTaP)-containing vaccine (IRR, 3.50; 95% CI, 1.52 to 8.07). The maximum estimated absolute excess risk due to concomitant administration of IIV3, PCV, and DTaP-containing vaccines compared with administration on separate days was 30 FS per 100 000 persons vaccinated.

CONCLUSIONS:

The administration of IIV3 on the same day as either PCV or a DTaP-containing vaccine was associated with a greater risk of FS than when IIV3 was given on a separate day. The absolute risk of postvaccination FS with these vaccine combinations was small.

Chaiyakunapruk N, et al. Cost effectiveness of pediatric pneumococcal conjugate vaccines: a comparative assessment of decision-making tools. *BMC Med*. 2011;9:53.

BACKGROUND:

Several decision support tools have been developed to aid policymaking regarding the adoption of pneumococcal conjugate vaccine (PCV) into national pediatric immunization programs. The

lack of critical appraisal of these tools makes it difficult for decision makers to understand and choose between them. With the aim to guide policymakers on their optimal use, we compared publicly available decision-making tools in relation to their methods, influential parameters and results.

METHODS:

The World Health Organization (WHO) requested access to several publicly available cost-effectiveness (CE) tools for PCV from both public and private provenance. All tools were critically assessed according to the WHO's guide for economic evaluations of immunization programs. Key attributes and characteristics were compared and a series of sensitivity analyses was performed to determine the main drivers of the results. The results were compared based on a standardized set of input parameters and assumptions.

RESULTS:

Three cost-effectiveness modeling tools were provided, including two cohort-based (Pan-American Health Organization (PAHO) ProVac Initiative TriVac, and PneumoADIP) and one population-based model (GlaxoSmithKline's SUPREMES). They all compared the introduction of PCV into national pediatric immunization program with no PCV use. The models were different in terms of model attributes, structure, and data requirement, but captured a similar range of diseases. Herd effects were estimated using different approaches in each model. The main driving parameters were vaccine efficacy against pneumococcal pneumonia, vaccine price, vaccine coverage, serotype coverage and disease burden. With a standardized set of input parameters developed for cohort modeling, TriVac and PneumoADIP produced similar incremental costs and health outcomes, and incremental cost-effectiveness ratios.

CONCLUSIONS:

Vaccine cost (dose price and number of doses), vaccine efficacy and epidemiology of critical endpoint (for example, incidence of pneumonia, distribution of serotypes causing pneumonia) were influential parameters in the models we compared. Understanding the differences and similarities of such CE tools through regular comparisons could render decision-making processes in different countries more efficient, as well as providing guiding information for further clinical and epidemiological research. A tool comparison exercise using standardized data sets can help model developers to be more transparent about their model structure and assumptions and provide analysts and decision makers with a more in-depth view behind the disease dynamics. Adherence to the WHO guide of economic evaluations of immunization programs may also facilitate this process. Please see related article: <http://www.biomedcentral.com/1741-7007/9/55>.

Saokaew S, et al. Cost effectiveness of pneumococcal vaccination in children in low- and middle-income countries: a systematic review. *Pharmacoeconomics*. 2016;34(12):1211–25.

BACKGROUND:

Although pneumococcal conjugate vaccines (PCVs) have been available for prevention of invasive pneumococcal disease (IPD) caused by *Streptococcus pneumoniae* (*S. pneumoniae*) for over a decade, their adoption into national immunization programmes in low- and middle-income countries (LMICs) is still limited. Economic evaluations (EEs) play a crucial role in support of evidence-informed decisions.

OBJECTIVE:

This systematic review aims to provide a critical summary of EEs of PCVs and identify key drivers of EE findings in LMICs.

METHODS:

We searched Scopus, ISI Web of Science, PubMed, Embase and Cochrane Central from their inception to 30 September 2015 and limited the search to LMICs. The search was undertaken using the search strings 'pneumococc* AND conjugat* AND (vaccin* OR immun*)' AND 'economic OR cost-effectiveness OR cost-benefit OR cost-utility OR cost-effectiveness OR cost-benefit OR cost-utility' in the abstract, title or keyword fields. To be included, each study had to be a full EE of a PCV and conducted for an LMIC. Studies were extracted and reviewed by two authors. The review involved standard extraction of the study overview or the characteristics of the study, key drivers or parameters of the EE, assumptions behind the analyses and major areas of uncertainty.

RESULTS:

Out of 134 records identified, 22 articles were included. Seven studies used a Markov model for analysis, while 15 studies used a decision-tree analytic model. Eighteen studies performed a cost-utility analysis (CUA), with disability-adjusted life-years, quality-adjusted life-years or life-years gained as a measure of health outcome, while four studies focused only on cost-effectiveness analysis (CEA). Both CEA and CUA findings were provided by eight studies. Herd effects and serotype replacement were considered in 10 and 13 studies, respectively. The current evidence shows that both the 10-valent and 13-valent PCVs are probably cost effective in comparison with the 7-valent PCV or no vaccination. The most influential parameters were vaccine efficacy and coverage (in 16 of 22 studies), vaccine price (in 13 of 22 studies), disease incidence (in 11 of 22 studies), mortality from IPD and pneumonia (in 8 of 22 studies) and herd effects (in 4 of 22 studies). The findings were found to be supportive of the products owned by the manufacturers.

CONCLUSION:

Our review demonstrated that an infant PCV programme was a cost-effective intervention in most LMICs (in 20 of 22 studies included). The results were sensitive to vaccine efficacy, price, burden of disease and sponsorship. Decision makers should consider EE findings and affordability before adoption of PCVs.

Evidence to recommendations table: pneumococcal conjugate vaccine (PCV), Table 1: Dosing schedule impact. Geneva: World Health Organization; 2018

(http://www.who.int/immunization/policy/position_papers/recommendation_table_PCV_dosing_schedule_impact.pdf, accessed January 2019).

(No abstract available)

Evidence to recommendations table: pneumococcal conjugate vaccine (PCV), Table 2: Product choice impact. Geneva: World Health Organization; 2018

(http://www.who.int/immunization/policy/position_papers/recommendation_table_PCV_product_choice_impact.pdf, accessed January 2019).

(No abstract available)

Vaccination in humanitarian emergencies: implementation guide. Geneva: World Health Organization; 2017

(http://www.who.int/immunization/documents/general/who_ivb_17.13/en/, accessed October 2018).

(No abstract available)

Surveillance standards for vaccine-preventable diseases, second edition. Chapter 17: Pneumococcus. Geneva: World Health Organization; 2018

(https://www.who.int/immunization/monitoring_surveillance/burden/vpd/WHO_SurveillanceVaccinePreventable_17_Pneumococcus_R2.pdf?ua=1, accessed January 2019).

(No abstract available)

Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate vaccination. Geneva: World Health Organization; 2012

(http://apps.who.int/iris/bitstream/handle/10665/75835/WHO_IVB_12.08_eng.pdf?sequence=1, accessed January 2019)

(No abstract available)