References with summaries


Study to assess the overall effectiveness of PCV7 against IPD in Navarra, Spain. All children aged <5 years who were diagnosed with IPD during the period 2001–2005 (n = 85) and 5 control subjects per case patient (n = 425), individually matched by birth date and birth hospital, were analyzed. Vaccination records were obtained from the regional immunization registry. Conditional logistic regression was used to estimate odds ratios. Eighteen case patients (21%) and 114 control subjects (27%) had received ≥1 dose of PCV7. PCV7 serotypes were responsible for 34 (51%) of the cases in unvaccinated children. The overall effectiveness for case prevention was 31% (odds ratio, 0.69; 95% confidence interval, 0.37–1.27). In a separate analysis, vaccination with PCV7 was 88% effective in preventing IPD due to vaccine serotypes (odds ratio, 0.12; 95% confidence interval, 0.02–0.91) and was associated with a higher risk of IPD due to nonvaccine serogroups (odds ratio, 6.16; 95% confidence interval, 1.63–23.3). These data reveal a higher risk of IPD caused by non-PCV7 serogroups among vaccinated children. Consequently, the overall effectiveness of PCV7 for IPD prevention may be greatly reduced.


BACKGROUND: Immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D-conjugate vaccine (PHiD-CV) was evaluated when coadministered with DTPw-HBV/Hib and OPV at 6, 10, and 14 weeks of age in the Philippines, or with DTPw-HBV/Hib and IPV at 2, 4, and 6 months of age in Poland.

METHODS: In this double-blind, controlled study (107007/NCT00344318), 400 Filipino and 406 Polish infants 6 to 12 weeks of age were randomized (3:1) to receive either PHiD-CV or the 7-valent pneumococcal conjugate vaccine (7vCRM). Immune responses were assessed 1 month post-dose III.

RESULTS: Percentages of infants with anti-pneumococcal antibody concentrations >or=0.2 microg/mL (GSK's 22F-inhibition ELISA) were within the same range for both pneumococcal conjugate vaccine groups, with the exception of serotypes 6B and 23F for which lower percentages were observed in the PHiD-CV group in Poland. At least 98.2% of PHiD-CV vaccinees had antibody concentrations >or=0.2 microg/mL against pneumococcal
serotypes 1, 5, and 7F. In both countries, anti-pneumococcal antibody geometric mean concentrations against serotypes 18C and 19F were higher in the PHiD-CV group than in the 7vCRM group. Antibody geometric mean concentrations for most of the other common serotypes were within the same range for both groups in the Philippines and were lower in the PHiD-CV group in Poland. Functional responses (opsonophagocytic activity [OPA]) were observed for all vaccine serotypes in both countries.

CONCLUSIONS: PHiD-CV was immunogenic against each of the 10 pneumococcal vaccine serotypes when coadministered with DTPw-HBV/Hib and poliovirus vaccines.


We review 15 economic analyses of pneumococcal conjugate vaccines, published between 2002 and 2006, in terms of methodology, assumptions, results and conclusions. We found a great diversity in assumptions (eg, vaccine efficacy parameters, incidence rates for both invasive and non-invasive disease) mainly due to local variation in data and opinions. Accordingly, the results varied greatly, from total net savings to over euro 100,000 per discounted QALY gained. The cost of the vaccination program (determined by price per dose and schedule (4 or 3 doses, or fewer)), and likely herd immunity impacts are highly influential though rarely explored in these published studies. If the net long-term impact (determined by a mixture of effects related to herd immunity, serotype replacement, antibiotic resistance and cross reactivity) remains beneficial and if a 3-dose schedule confers near-equivalent protection to a 4-dose schedule, the cost-effectiveness of PCV7 vaccination programs can be viewed as attractive in developed countries.


RCT to determine the efficacy, safety and immunogenicity of the heptavalent CRM197 pneumococcal conjugate vaccine against invasive disease caused by vaccine serotypes and to determine the effectiveness of this vaccine against clinical episodes of otitis media. The Wyeth Lederle Heptavalent CRM197 (PCV) was given to infants at 2, 4, 6 and 12 to 15 months of age in a double blind trial; 37,868 children were randomly assigned 1:1 to receive either the pneumococcal conjugate vaccine or meningococcus type C CRM197 conjugate. The primary study outcome was invasive disease caused by vaccine serotype. Other outcomes included overall impact on invasive disease regardless of serotype, effectiveness against clinical otitis media visits and episodes, impact against frequent and severe otitis media and ventilatory tube placement. In addition the serotype-specific efficacy against otitis media was estimated in an analysis of spontaneously draining ears. In the interim analysis in August, 1998, 17 of the 17 cases of invasive disease caused by vaccine serotype in fully vaccinated children and 5 of 5 of partially vaccinated cases occurred in the control group for a vaccine efficacy of 100%. Blinded case ascertainment was continued until April, 1999. As of that time 40 fully vaccinated cases of invasive disease caused by vaccine serotype had been identified, all but 1 in controls for an efficacy of 97.4% (95% confidence interval, 82.7 to 99.9%), and 52
cases, all but 3 in controls in the intent-to-treat analysis for an efficacy of 93.9% (95% confidence interval, 79.6 to 98.5%). There was no evidence of any increase of disease caused by nonvaccine serotypes. Efficacy for otitis media against visits, episodes, frequent otitis and ventilatory tube placement was 8.9, 7.0, 9.3 and 20.1% with P < 0.04 for all. In the analysis of spontaneously draining ears, serotype-specific effectiveness was 66.7%.


Routine use of the 7-valent pneumococcal conjugate vaccine (PCV7), available since 2000, has resulted in a dramatic reduction in the incidence of invasive pneumococcal disease (IPD) attributable to serotypes of Streptococcus pneumoniae contained in the vaccine. However, IPD caused by nonvaccine pneumococcal serotypes has increased, and nonvaccine serotypes are now responsible for the majority of the remaining cases of IPD occurring in children. A 13-valent pneumococcal conjugate vaccine has been licensed by the US Food and Drug Administration, which, in addition to the 7 serotypes included in the original PCV7, contains the 6 pneumococcal serotypes responsible for 63% of IPD cases now occurring in children younger than 5 years. Because of the expanded coverage provided by PCV13, it will replace PCV7. This statement provides recommendations for (1) the transition from PCV7 to PCV13; (2) the routine use of PCV13 for healthy children and children with an underlying medical condition that increases the risk of IPD; (3) a supplemental dose of PCV13 for (a) healthy children 14 through 59 months of age who have completed the PCV7 series and (b) children 14 through 71 months of age with an underlying medical condition that increases the risk of IPD who have completed the PCV7 series; (4) "catch-up" immunization for children behind schedule; and (5) PCV13 for certain children at high risk from 6 through 18 years of age. In addition, recommendations for the use of pneumococcal polysaccharide vaccine for children at high risk of IPD are also updated.


Related citations OBJECTIVE: Since the 10-valent pneumococcal conjugate vaccine (PCV-10) and 13-valent pneumococcal conjugate vaccine (PCV-13) were recently licensed for use in Argentina, both vaccines were evaluated to estimate the costs, health benefits and cost-effectiveness of adding a PCV to the routine child immunization schedule.

METHODOLOGY: The integrated TRIVAC vaccine cost-effectiveness model from Pan American Health Organization's ProVac Initiative (Version 1.0.65) was used to assess the health outcomes of 20 successive cohorts from birth to 5 years of age. PCV-10 and PCV-13 were each compared to a scenario assuming no PCV vaccination. A 3+1 (three doses+booster) schedule and a vaccination price of US$ 20.75 per dose was assumed in the base case for both vaccines.
RESULTS: Introduction of PCV-13 rather than PCV-10 would increase the number of life years gained (LYG) by at least 10%. The number of LYG (and LYG after adjustment for DALY morbidity weights) was 56,882 (64,252) for PCV-10 compared to 65,038 (71,628) for PCV-13. From the health system perspective, the cost per DALY averted was US$ 8973 and US$ 10,948 for PCV-10 and PCV-13 respectively, and US$ 8546 and US$ 10,510 respectively, after incorporating costs saved by households. When PCV13 was compared to PCV10 directly, the additional benefits of PCV-13 was conferred at a cost of US$ 28,147 per DALY averted. Cost-effectiveness was influenced mainly by vaccine price, serotype replacement, pneumonia mortality and discount rate.

CONCLUSION: Routine vaccination against S. pneumoniae in Argentina would be cost-effective with either PCV-10 or PCV-13. PCV-13, with higher coverage of local serotypes, would prevent more cases of pneumonia, invasive pneumococcal disease, sequelae and deaths with a higher number of LYG and DALYs averted, but PCV-10, due its higher impact in the prevention of AOM, would save more costs to the healthcare system.


BACKGROUND: Licensed pneumococcal conjugate vaccine (7vCRM) is usually coadministered with combination vaccines in pediatric immunization programs. Reactogenicity and safety after primary and booster vaccination with a novel 10-valent pneumococcal non-typeable Haemophilus influenzae protein D-conjugate vaccine (PHiD-CV) in comparison with 7vCRM, both coadministered with commonly used pediatric vaccines, was evaluated in 5 clinical studies.

METHODS: Five randomized, controlled studies in which PHiD-CV or licensed 7vCRM vaccines coadministered with various DTPa-based combination vaccines, Neisseria meningitidis serogroup C conjugate vaccines and DTPw-HBV/Hib were conducted. Local and general symptoms were solicited for 4 days after each vaccine dose, using diary cards. All adverse events were recorded for 31 days after each dose and serious adverse events throughout the entire study periods.

RESULTS: A total of 4004 subjects contributed to the safety data analyzed in this review. Fever >or=38.0 degrees C (rectal temperature) was reported after about one-third of primary or booster vaccine doses coadministered with DTPa-based vaccines and after approximately 60% of primary doses with DTPw coadministration in both PHiD-CV and 7vCRM groups. Fever >40.0 degrees C was reported after <or=1.1% of PHiD-CV doses and <or=2.2% of 7vCRM doses. The incidences and intensity of general reactions were generally within the same ranges in the PHiD-CV and 7vCRM groups. Drowsiness and irritability in the study with MenC-conjugates coadministration and irritability and loss of appetite in the study with DTPw-combined vaccines coadministration tended to be slightly higher in PHiD-CV groups. No such trend was observed for solicited general symptoms with grade 3 intensity.
CONCLUSIONS: The safety and reactogenicity profiles of PHiD-CV and 7vCRM were within the same range when administered for primary and booster vaccination in coadministration with other routinely used pediatric vaccines.


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.


To analyze the efficacy of heptavalent conjugate vaccine against Streptococcus pneumoniae (VPn7) in children with cochlear implant, in relation with the eradication of nasopharyngeal carriers and the prevention of complications. Analysis of the antimicrobial resistance and sensitivity of the different pneumococci strains isolated in cochlear implant nasopharyngeal carriers and healthy non-vaccinated children. Pneumococcal nasopharyngeal carriers were analyzed in this prospective study including two groups of children aged between 2 and 5
years, from 2005 to 2006. The first group included 55 cochlear implant recipients and all of them were vaccinated with VPn7. The second group included 60 non-vaccinated healthy children. Nasopharyngeal swabs for culture were obtained from each child in order to detect the pneumococcus, its serotypes and the sensitivity to antibiotics. In the control group of non-vaccinated children, 25% of them were found to be pharyngeal pneumococcus carriers, whereas this figure fell to 11% in the vaccinated group. The non-vaccine serotypes (83.3%) isolated in vaccinated children showed high or moderate sensitivity to penicillin. There were no complications due to S pneumoniae infections in any of the patients with cochlear implant who were vaccinated.

VPn7 contributes to a decrease in pharyngeal colonization by pneumococci in general and, in particular, by the pneumococcal serotypes included in the vaccine, although there is a replacement phenomenon involving non-vaccine serotypes.


A 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7) was licensed in the United States of America in 2000, but no comprehensive postmarketing review of safety has been carried out. We conducted a systematic review of the safety of PCV7 and other pneumococcal conjugate vaccines. A total of 42 studies were included in the review. Reactogenicity data from some randomized trials suggest that PCV7 may result in more local reactions and fever than certain comparison vaccines. However, the reactions were mild and self-limited, and PCV7 did not carry an increased risk of severe injection-site reactions or high fever. Some, although not all, of the randomized trials in children found that mild local and systemic reactions associated with PCV7 may increase with the number of doses, at least over the three-dose primary series. In addition, PCV7 and other pneumococcal conjugate vaccines were found to have tolerable reactogenicity in Native American and African populations and in medically high-risk groups for which pneumococcal vaccination is recommended. Two of the largest studies of PCVs, one involving PCV7 and the other, PCV9, found a statistically significant increased risk of hospitalization for reactive airway disease, including asthma. Another large trial of PCV9, however, did not find an increased risk of asthma. In conclusion, this review of the evidence did not identify any major safety problems with PCV7 or any other pneumococcal conjugate vaccine, with the possible exception of reactive airway disease, which may bear further scrutiny as additional data become available.


RCT to assess potential of new conjugate vaccines to prevent a substantial portion of cases of acute otitis media caused by Streptococcus pneumoniae. 1662 infants were enrolled in a randomized, double-blind efficacy trial of a heptavalent pneumococcal polysaccharide conjugate vaccine in which the carrier protein is the nontoxic diphtheria-toxin analogue CRM197. The children received either the study vaccine or a hepatitis B vaccine as a control
at 2, 4, 6, and 12 months of age. The clinical diagnosis of acute otitis media was based on predefined criteria, and the bacteriologic diagnosis was based on a culture of middle-ear fluid obtained by myringotomy.

Of the children who were enrolled, 95.1 percent completed the trial. With the pneumococcal vaccine, there were more local reactions than with the hepatitis B vaccine but fewer than with the combined whole-cell diphtheria-tetanus-pertussis and Haemophilus influenzae type b vaccine that was administered simultaneously. There were 2596 episodes of acute otitis media during the follow-up period between 6.5 and 24 months of age. The vaccine reduced the number of episodes of acute otitis media from any cause by 6 percent (95 percent confidence interval, -4 to 16 percent [the negative number indicates a possible increase in the number of episodes]), culture-confirmed pneumococcal episodes by 34 percent (95 percent confidence interval, 21 to 45 percent), and the number of episodes due to the serotypes contained in the vaccine by 57 percent (95 percent confidence interval, 44 to 67 percent). The number of episodes attributed to serotypes that are cross-reactive with those in the vaccine was reduced by 51 percent, whereas the number of episodes due to all other serotypes increased by 33 percent.


A prospective cohort trial to evaluate the impact of PCV-7 administered at 3, 5 and 11 months of age on respiratory tract infections in very young children. A total of 1,571 healthy infants (910 males) aged 75–105 days (median 82 days) were enrolled to receive a hexavalent vaccine (DTaP/IPV/HBV/Hib) and PCV-7 (n = 819) or the hexavalent vaccine alone (n = 752) at 3, 5 and 11 months of age. Morbidity was recorded for the 24 months following the second dose by monthly telephone interviews conducted by investigators blinded to the study treatment assignment using standardised questionnaires. During these interviews, the caregivers and the children's pediatricians were questioned about illnesses and the use of antibiotics since the previous telephone call. All of the data were analysed using SAS Windows v.12. Among the 1,555 subjects (98.9%) who completed the study, analysis of the data by the periods of follow-up demonstrated that radiologically confirmed community-acquired pneumonia (CAP) was significantly less frequent in the PCV-7 group during the follow-up as a whole and during the last period of follow-up. Moreover, there were statistically significant between-group differences in the incidence of acute otitis media (AOM) in each half-year period of follow-up except the first, with significantly lower number of episodes in children receiving PCV-7 than in controls. Furthermore, the antibiotic prescription data showed that the probability of receiving an antibiotic course was significantly lower in the PCV-7 group than in the control group.


7
The 7-valent pneumococcal polysaccharide-protein (CRM(197)) conjugate vaccine (PCV-7) was licensed based on clinical efficacy trials using the four-dose schedule of three infant doses and a booster dose in the second year of life (3 + 1). An assessment of PCV-7 immunogenicity in studies evaluating two infant doses with a booster (2 + 1) showed similar immunogenicity for the 2 + 1 and 3 + 1 schedules, with the exception of lower post-dose two responses for serotypes 6B and 23F, compared with a three-dose primary series. The 2 + 1 PCV-7 schedule has been shown to be effective in controlling pneumococcal disease in several countries, as used in national immunization programs that are marked in particular by good uptake, compliance with the booster dose and application of a catch-up program.


BACKGROUND: The 7-valent CRM197 pneumococcal conjugated vaccine (PCV7) was originally licensed using 3 primary doses during infancy and a booster in the second year of life. We compared the originally licensed regimen to 2 widely used alternative regimens.

METHODS: Five hundred forty-three infants were randomized to receive PCV7 at 2, 4, 6, and 12 months (3 + 1), at 4, 6, and 12 months (2 + 1), or at 2, 4, and 6 months (3 + 0). Blood was drawn at 2, 7, 13, and 19 months. Serotype-specific IgG concentrations were determined by ELISA.

RESULTS: In the 2 + 1 group, postprimary IgG concentrations against serotypes 6B, 14, 18C, and 23F were reduced compared with the 3 + 1 or 3 + 0 groups. Both 3 + 1 and 2 + 1 groups showed marked booster response, but the 2 + 1 group had reduced concentrations against serotypes 6B, 18C, 23F. At 19 months, IgG antibodies decreased in both 3 + 1 and 2 + 1 groups but the 2 + 1 group had significantly lower concentrations against serotypes 6B, 18C, and 23F. IgG concentrations decreased in the 3 + 0 group during the second year and were significantly lower than those of 3 + 1 and 2 + 1 for all serotypes at 13 and 19 months.
CONCLUSIONS: Significant differences in immunogenicity were documented between the reduced and the licensed regimens. The clinical implications of these differences require further studies.

Glaxo SmithKline Inc. A phase IIIb open, controlled study to evaluate the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine when given as a catch-up immunization in children older than 7 months of age or given as a 3-dose primary immunization in children before 6 months of age. 10Pn-PD-DiT: GSK Biologicals' 10-valent pneumococcal conjugate vaccine (10Pn). 2011.

Glaxo SmithKline Inc. A phase IIIa, open, multicentre study to evaluate the immunological memory induced in healthy children following a 3-dose primary vaccination with either GSK Biologicals' 10-valent pneumococcal conjugate vaccine or Prevenar TM in study 10PN-PD-DiT-003 (105554), via the administration of a single booster dose of a 23-valent pneumococcal plain polysaccharide vaccine. 2009; 106623 (10PN-PD-DiT-008 BST:003).


In developing countries, endemic childhood meningitis is a severe disease caused most commonly by Streptococcus pneumoniae or Haemophilus influenzae type b (Hib). Although many studies have shown that fatality rates associated with meningitis caused by these organisms are high in developing countries, little is known about the long-term outcome of survivors. The purpose of this study was to assess the importance of disabilities following pneumococcal and Hib meningitis in The Gambia. 257 children aged 0-12 years hospitalized between 1990 and 1995 with culture-proven S. pneumoniae (n = 134) or Hib (n = 123) meningitis were included retrospectively in the study. 48% of children with pneumococcal meningitis and 27% of children with Hib meningitis died whilst in hospital. Of the 160 survivors, 89 (55%) were followed up between September 1996 and October 1997. Of the children with pneumococcal meningitis that were traced, 58% had clinical sequelae; half of them had major disabilities preventing normal adaptation to social life. 38% of survivors of Hib meningitis had clinical sequelae, a quarter of whom had major disabilities. Major handicaps found were hearing loss, mental retardation, motor abnormalities and seizures. These data show that despite treatment with effective antibiotics, pneumococcal and Hib meningitis kill many Gambian children and leave many survivors with severe sequelae. Hib vaccination is now given routinely in The Gambia; an effective pneumococcal vaccine is needed.

BACKGROUND: Pneumococcal conjugate vaccine (PCV) was introduced in the United Kingdom immunization schedule in September 2006. This study was conducted to establish the immunogenicity of licensed PCV (Prevenar) at a reduced, 2 priming dose schedule (2+1) and to evaluate functional responses in the context of vaccine effectiveness.

METHODS: Infants were randomized to receive PCV at 2 and 3 months or 2 and 4 months of age. Boosters were administered at the same time as Haemophilus influenzae type B/meningococcal C conjugate and Measles, Mumps and Rubella or with Measles, Mumps and Rubella alone (www.ClinicalTrials.gov NCT00197808).

RESULTS: PCV at 2/3 months of age was poorly immunogenic and recruitment to this arm was terminated. PCV at 2/4 months of age resulted in lower than expected responses to serotypes 6B and 23F. Functional analysis of serotype 6B by OPA revealed that an enzyme-linked immunosorbent assay cutoff of 0.2 microg/mL was a better predictor of OPA positivity than a cut off of 0.35 microg/mL. PCV booster responses were excellent and no interference from concomitant vaccines was noted.

CONCLUSIONS: An interval of at least 8 weeks is required when starting PCV vaccination at 2 months of age although not all serotypes are equally immunogenic. Correlates of protection derived from enzyme-linked immunosorbent assay values may not be equally appropriate for all serotypes as illustrated by results for 6B in this study.


BACKGROUND: The minimum number of doses of pneumococcal conjugate vaccine required for protection is not known. We studied the immunogenicity of a reduced schedule in infants and toddlers.

METHODS: U.K. infants were given either 2 or 3 doses (at 2 and 4 or 2/3/4 months of age) of a 9-valent pneumococcal conjugate vaccine (9VPCV) followed by boosting at 12 months of age. In a separate study, toddlers (12 months) received 1 or 2 doses (2 months apart) of 9VPCV followed by pneumococcal polysaccharide vaccine at 18 months of age.

RESULTS: For infants, serotype-specific IgG geometric mean concentrations were similar post-primary immunization between the groups with both showing avidity maturation and similar booster responses. For toddlers, the primary response to 4 of the 9 serotypes was lower in the 1- compared with the 2-dose group (type 6B, 0.77 versus 7.1; type 14, 4.67 versus 14.98; type 19F, 5.05 versus 7.75; type 23F, 2.48 versus 5.05), although for all serotypes booster responses were similar between groups, and the postprimary responses in the 1-dose group were at least as high as those after infant immunization.

CONCLUSIONS: The 2-dose infant priming schedule of 9VPCV is comparable with the 3-dose schedule and may thus be equally protective, whereas 1 dose in toddlers may suffice for a catch-up.

An open-labelled, randomised trial of investigating the immunogenicity of Pneumococcal and Haemophilus influenza type b conjugate vaccines in children with sickle cell disease. The study took place at the Sickle cell clinic of the Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana. Kumasi is the second largest city in Ghana with a population of 1.2 million and an average of twenty thousand live births annually. A total of 240 children (83 infants and 138 toddlers) were recruited into the study. Mean age at enrolment of the infants was 2.2 months (range 1.3-5.5). The mean age of the toddlers at enrolment was 13.9 months (range 11.0 –20.4 months). The 9V-Pn was highly immunogenic after three doses and titres were significantly higher than those in the control group who received three doses of HbOC. By the age of one year serotype specific IgG had dropped significantly for all serotypes although titres were still significantly higher than those in the control group, with the exception of type 19F where titres were similar. No significant natural increases in antibodies were seen in the control group between the age for 4.5 months and one year of age. At the age of one year the recipients of 9V-Pn were randomised to receive a dose of 9V-Pn, PPV-23 or HbOC control. The PPV-23 was highly immunogenic and titers increased significantly for all serotypes. Titres achieved were significantly higher than those achieved in control infants. Control infants did however respond to some serotypes when immunised with PPV-23, and small but significant increases in titre (compared to the pre-booster titres) were seen for serotypes 1, 4, 5, 9V and 18C. 9V-Pn was immunogenic following boosting and titres increased significantly for all serotypes. When comparing titres achieved after boosting with 9V-Pn compared to those after three doses of 9V-Pn as priming, titres were generally higher but only significantly so for serotype 4. The titre achieved against serotype 18C was lower after boosting compared to after priming.

Grading of scientific evidence – Table I (evidence of protection). Available at http://www.who.int/entity/immunization/pneumococcal_grad_carriage.pdf.

Grading of scientific evidence – Table II (evidence of safety). Available at http://www.who.int/entity/immunization/pneumococcal_grad_carriage.pdf.

Grading of scientific evidence – Table III (choice of schedule). Available at http://www.who.int/entity/immunization/pneumococcal_grad_carriage.pdf.

Grading of scientific evidence, PPV23 Grading tables 1–7


13-Valent pneumococcal conjugate vaccine (PCV13) administered as a 4-dose series in infants, and as a toddler dose in infants previously vaccinated with PCV7 elicited comparable vaccine serotypes IgG responses to the seven common serotypes. PCV13 elicited functional responses to the six additional serotypes in both schedules after the toddler dose. The toddler dose boosted immune responses. The two regimens had comparable safety profiles. A toddler dose of PCV13 given in children previously vaccinated with PCV7 should be effective in preventing pneumococcal disease caused by common serotypes, providing protection against the additional serotypes, and supporting the transition from PCV7 to PCV13.


We analyzed >70 recent data sets to compare the serogroups causing invasive pneumococcal disease (IPD) with those represented in conjugate vaccine formulations. Five to 8 and 10-11 serogroups comprise at least 75% of pneumococcal isolates from young children and older children/adults, respectively, in each geographic region. Serogroups in the 7-valent formulation (4, 6, 9, 14, 18, 19, and 23) cause 70%-88% of IPD in young children in the United States and Canada, Oceania, Africa, and Europe, and <65% in Latin America and Asia. Serogroups in the 9-valent formulation (7-valent+1, 5) cause 80%-90% of IPD in each region except Asia (66%). Serogroup 1 accounts for >6% of IPD in each region, including Europe, except the United States and Canada and Oceania. In contrast, several serogroups not found in 7-, 9-, and 11-valent conjugate formulations are significant causes of disease in older children/adults. Nevertheless, each conjugate formulation could prevent a substantial IPD burden in each region and age group.


BACKGROUND: Clinical trials and meta-analyses have produced conflicting results of the efficacy of unconjugated pneumococcal polysaccharide vaccine in adults. We sought to evaluate the vaccine's efficacy on clinical outcomes as well as the methodologic quality of the trials.

METHODS: We searched several databases and all bibliographies of reviews and meta-analyses for clinical trials that compared pneumococcal polysaccharide vaccine with a control. We examined rates of pneumonia and death, taking the methodologic quality of the trials into consideration.

RESULTS: We included 22 trials involving 101 507 participants: 11 trials reported on presumptive pneumococcal pneumonia, 19 on all-cause pneumonia and 12 on all-cause mortality. The current 23-valent vaccine was used in 8 trials. The relative risk (RR) was 0.64 (95% confidence interval [CI] 0.43-0.96) for presumptive pneumococcal pneumonia and 0.73 (95% CI 0.56-0.94) for all-cause pneumonia. There was significant heterogeneity between the trials reporting on presumptive pneumonia (I(2) = 74%, p < 0.001) and between those reporting on all-cause pneumonia (I(2) = 90%, p < 0.001). The RR for all-cause mortality was 0.97 (95% CI 0.87-1.09), with moderate heterogeneity between trials (I(2) = 44%, p = 0.053). Trial quality, especially regarding double blinding, explained a substantial proportion of the heterogeneity in the trials reporting on presumptive pneumonia and all-cause pneumonia. There was little evidence of vaccine protection in trials of higher methodologic quality (RR 1.20, 95% CI 0.75-1.92, for presumptive pneumonia; and 1.19, 95% CI 0.95-1.49, for all-cause pneumonia in double-blind trials; p for heterogeneity > 0.05). The results for all-cause
mortality in double-blind trials were similar to those in all trials combined. There was little evidence of vaccine protection among elderly patients or adults with chronic illness in analyses of all trials (RR 1.04, 95% CI 0.78-1.38, for presumptive pneumococcal pneumonia; 0.89, 95% CI 0.69-1.14, for all-cause pneumonia; and 1.00, 95% CI 0.87-1.14, for all-cause mortality).

INTERPRETATION: Pneumococcal vaccination does not appear to be effective in preventing pneumonia, even in populations for whom the vaccine is currently recommended.


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 >=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.


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 ≥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.


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.


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.

13-valent pneumococcal conjugate vaccine (PCV13) was compared to PCV7 in infants administered 4 doses. For the 7 common serotypes, PCV13- and PCV7-elicited responses showed comparable percent responders achieving 0.35 µg/mL IgG threshold (exception 6B, 77.5% versus 87.1%, respectively) and OPA titers of 1:8; IgGs were lower than PCV7 but functional responses were generally comparable. For the 6 additional serotypes, PCV13-elicited IgG and functional OPA responses were notably greater than PCV7. The toddler dose boosted immune responses. Vaccines were comparable with regard to safety. PCV13 should be as effective as PCV7 in preventing pneumococcal disease caused by the common serotypes and may provide protection against the additional serotypes.


To confirm the effect of 7-valent pneumococcal conjugate vaccine (PCV7), pneumococcal nasopharyngeal (NP) carriage was compared between vaccinated (3 + 1 doses PCV7) and non-vaccinated children. Vaccinated subjects were recruited from highly vaccinated regions (60%), Seoul and Incheon whereas control subjects were recruited from Jeju Island where vaccination rates are low (15%). NP swabs were obtained from 400 children aged 18-59 months. Serotype and antibiotic susceptibility was analyzed. Pneumococcal carriage rate was 18.0% (36/200) and 31.5% (63/200) for the vaccinated and control group, respectively. Among those vaccinated, 41.7% (15/36) of the serotypes were vaccine-related type (VRT: 6A, 6C, 19A) with the most common serotype 6C. The next common type was non-typable/non-capsule 30.6% (11/36) followed by non-vaccine type 16.7% (6/36) and vaccine type (VT) serotypes were found in only 11.1% (4/36). In contrast, 52.4% (33/63) of the isolates in the control group were VT. Resistance rates for penicillin and erythromycin were lower in the vaccine group (vaccine vs control; penicillin 45.2% vs 71.4%, erythromycin 74.2% vs 90.5%, P < 0.05). Multi-drug resistance was also lower in vaccinated subjects (vaccine vs control; 45.2% vs 69.8%, P < 0.05). PCV7 reduces carriage in VT which leads to replacement of pneumococci by antibiotic susceptible VRT or non-vaccine type strains.


BACKGROUND: Acute respiratory tract infections caused by Streptococcus pneumoniae are a leading cause of morbidity and mortality in young children. We evaluated the efficacy of a 9-valent pneumococcal conjugate vaccine in a randomized, double-blind study in Soweto, South Africa.

METHODS: At 6, 10, and 14 weeks of age, 19,922 children received the 9-valent pneumococcal polysaccharide vaccine conjugated to a noncatalytic cross-reacting mutant of diphtheria toxin (CRM197), and 19,914 received placebo. All children received Haemophilus influenzae type b conjugate vaccine. Efficacy and safety were analyzed according to the intention-to-treat principle.

RESULTS: Among children without human immunodeficiency virus (HIV) infection, the vaccine reduced the incidence of a first episode of invasive pneumococcal disease due to serotypes included in the vaccine by 83 percent (95 percent confidence interval, 39 to 97; 17 cases among controls and 3 among vaccine recipients). Among HIV-infected children, the efficacy was 65 percent (95 percent confidence interval, 24 to 86; 26 and 9 cases,
respectively). Among children without HIV infection, the vaccine reduced the incidence of first episodes of radiologically confirmed alveolar consolidation by 20 percent (95 percent confidence interval, 2 to 35; 212 cases in the control group and 169 in the vaccinated group) in the intention-to-treat analysis and by 25 percent (95 percent confidence interval, 4 to 41; 158 and 119 cases, respectively) in the per-protocol analysis (i.e., among fully vaccinated children). The incidence of invasive pneumococcal disease caused by penicillin-resistant strains was reduced by 67 percent (95 percent confidence interval, 19 to 88; 21 cases in the control group and 7 in the vaccinated group), and that caused by strains resistant to trimethoprim-sulfamethoxazole was reduced by 56 percent (95 percent confidence interval, 16 to 78; 32 and 14 cases, respectively).

CONCLUSIONS: Vaccination with a 9-valent pneumococcal conjugate vaccine reduced the incidence of radiologically confirmed pneumonia. The vaccine also reduced the incidence of vaccine-serotype and antibiotic-resistant invasive pneumococcal disease among children with and those without HIV infection.


BACKGROUND: The choice of non-typeable Haemophilus influenzae Protein D as main carrier protein in the candidate 10-valent pneumococcal conjugate vaccine (PHiD-CV, GlaxoSmithKline Biologicals), was driven in part to avoid carrier-mediated suppression and possible bystander interference with coadministered vaccines. Immunogenicity data from 3 primary and 2 booster vaccination studies were assessed for possible impacts of PHiD-CV coadministration on immune responses to routinely administered childhood vaccines, in comparison to 7-valent pneumococcal conjugate vaccine (7vCRM) coadministration.

METHODS: Randomized, controlled studies in which PHiD-CV or 7vCRM vaccines were coadministered with DTPa-[HBV]-IPV/Hib, DTPa-[HBV]-IPV, DTPw-HBV/Hib, IPV, and OPV, combined Hib-Neisseria meningitidis serogroup C vaccine (Hib-MenC-TT), standalone MenC-TT or MenC-CRM vaccines.

RESULTS: One month after primary vaccination, >96% of PHiD-CV recipients had seroprotective antibody concentrations against diphtheria, tetanus, poliovirus types 1 and 3, Hib (>or=0.15 microg/mL), SBA-MenC (>or=1:8), and >94% were seropositive for antibodies against pertussis antigens. Somewhat lower responses against poliovirus type 2 in study A (compared with poliovirus type 1 and 2 responses) and hepatitis B in the 6-, 10-, and 14-week schedule in the Philippines (compared with hepatitis B responses in the other studies) were observed after coadministration of both PHiD-CV and 7vCRM vaccines. Antitetanus and anti-PRP antibody geometric mean concentrations (GMCs) tended to be higher after PHiD-CV coadministration, probably because of the TT carrier protein for serotype 18C in PHiD-CV. Booster vaccination induced substantial increases in antibody GMCs for all coadministered antigens. These responses were generally within the same range in PHiD-CV and 7vCRM groups. Observed anti-PRP responses remained higher in PHiD-CV recipients after the booster dose.
CONCLUSIONS: Coadministration of PHiD-CV with commonly used childhood vaccines induced high levels of seroprotection-seropositivity against all targeted diseases. No evidence of negative interference on the immune response to any of the coadministered vaccine antigens was observed when compared with the current routine practice of 7vCRM coadministration.


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.


The safety and immunogenicity of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV, Synflorix™) were assessed in 240 healthy Chilean children randomized to receive 3 doses of PHiD-CV (PHiD-CV group) or hepatitis A vaccine (HAV control group) at 2-4-6 months of age. All were offered 1 HAV dose at 12 months (outside study). The PHiD-CV group received a second HAV dose at 18-21 months and PHiD-CV booster at 20-23 months. The HAV control group received 2 PHiD-CV catch-up doses at 18-21 and 20-23 months. Adverse events were recorded and pneumococcal antibody responses and opsonophagocytic activity (OPA) were measured. Both PHiD-CV vaccination schedules were well tolerated and immunogenic against the pneumococcal vaccine serotypes and protein D. The reactogenicity of PHiD-CV primary, booster and catch-up doses was in line with previous PHiD-CV studies, although generally higher than with HAV. For each vaccine serotype, the percentage of subjects with antibody concentrations \( \geq 0.2 \mu g/ml \) (GSK's 22F-inhibition ELISA) was at least 93.2% following 3 PHiD-CV primary
doses and at least 97.4% post-booster; percentages with OPA titers ≥8 were at least 91.7% post-booster. After 2-dose catch-up, at least 94.3% of children had antibody concentrations ≥0.2 µg/ml against each serotype except 6B (84.3%); at least 95.2% had OPA titers ≥8 except against serotypes 1, 5 and 6B. In conclusion, the safety profiles of 2 PHiD-CV vaccination schedules (3-dose primary plus booster and 2-dose catch-up) were in line with previous studies and PHiD-CV was immunogenic for all 10 vaccine serotypes and protein D.


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.

BACKGROUND: Administration of pneumococcal conjugate vaccine (PCV) to HIV-infected children during infancy confers limited long-term protection in the absence of antiretroviral therapy. The objective of the present study was to determine the immune responses to PCV at 5 years of age in HIV-infected and HIV-uninfected children who had been primed with vaccine during infancy (i.e., previous vaccinees) and in those receiving their first dose of vaccine (i.e., control subjects).

METHODS: Serotype-specific antibodies were quantified by enzyme immunoassay, and antibody functionality to serotypes 6B, 9V, and 19F were evaluated using an opsonophagocytic killing assay 1 month after vaccination.

RESULTS: Of the HIV-infected children, 19.7% were receiving antiretroviral therapy, and 40.5% had a CD4(+) cell percentage <15%. Geometric mean concentrations of antibody and the proportion with a concentration ≥0.35 μg/mL after vaccination were greater among HIV-uninfected children than among HIV-infected children for both previous vaccinees and control subjects. Antibody concentrations after vaccination were lower for 3 of 7 serotypes among HIV-infected previous vaccinees than among control subjects. Detectable opsonophagocytic activity to all studied serotypes was lower among HIV-infected than among HIV-uninfected previous vaccinees and control subjects. Postvaccination antibody-mediated killing activity as determined by the opsonophagocytic killing assay was enhanced in control subjects compared with previous vaccinees among HIV-uninfected children.

CONCLUSION: HIV-infected vaccinees experience a partial loss of anamnestic responses to PCV. The optimal timing and frequency of booster vaccination as well as the responses to them among HIV-infected children need to be determined.


The long-term immunogenicity and vaccine efficacy (VE) of a 9-valent conjugate pneumococcal vaccine was studied in HIV infected and HIV non-infected children. VE against vaccine-serotype invasive pneumococcal disease following 6.16 years of follow-up persisted in HIV non-infected children (77.8%; 95% CI 34.4–92.5 compared to 83% after 2.3 years of follow-up), and declined from 65% to 38.8% (95% CI −7.8 to 65.2) in HIV infected children. HIV non-infected vaccinees had equal (serotypes 4, 6B, 14, 19F) or greater (serotypes 9V, 18C, 23F) proportions of serotype-specific antibody concentrations of ≥0.2 μg/ml to vaccine-serotypes analyzed compared to HIV infected vaccines at 5.3 years of age.

A double-blind, randomized, placebo controlled trial to assess the safety, immunogenicity, and impact on carriage of a nonvalent pneumococcal vaccine given at ages 6, 10, and 14 weeks. Examined 500 infants in Soweto, South Africa. No serious local or systemic side effects were recorded. Significant antibody responses to all pneumococcal serotypes were observed 4 weeks after the third dose. Haemophilus influenzae type b polyriboylribitol phosphate (geometric mean titer, 11.62 mg/mL) and diphtheria (1.39 IU/mL) antibodies were significantly higher in children receiving pneumococccal conjugate, compared with placebo recipients (4.58 mg/mL and 0.98 IU/mL, respectively). Nasopharyngeal carriage of vaccine serotypes decreased in vaccinees at age 9 months (18% vs. 36%), whereas carriage of nonvaccine serotypes increased (36% vs. 25%). Carriage of penicillin-resistant pneumococci (21% vs. 41%) and cotrimoxazole-resistant pneumococci (23% vs. 35%) were significantly reduced 9 months after vaccination, compared with controls.


Efficacy of the new serotypes in the 13-valent pneumococcal conjugate vaccine (PCV13) against invasive pneumococcal disease (IPD) was based on a putative correlate of protection. In England and Wales, PCV13 replaced PCV7 in the 2, 4, and 13 month schedule in April 2010. Using non-vaccine type IPD cases as controls, we estimated vaccine effectiveness (VE) for the new serotypes. Among 166 IPD cases in PCV13 eligible children reported by July 2011 with known serotype and vaccination status, VE for 2 doses under a year was 78% (95% confidence interval –18% to 96%) and 77% (38–91%) for one dose over a year. VE for 7F and 19A was 76% (21–93%) and 70% (10–90%) respectively for ≥one dose. VE for serotypes 1 and 3 was 62% and 66% respectively although confidence intervals spanned zero. IPD due to PCV13-only serotypes halved in children under 2 years in the study period.


BACKGROUND: Diseases caused by Streptococcus pneumoniae(S. pneumoniae) continue to cause substantial morbidity and mortality throughout the world. Whilst pneumococcal polysaccharide vaccines (PPV) have the potential to prevent disease and death, the degree of protection afforded against various clinical endpoints and within different populations is uncertain.

OBJECTIVES: To assess the effectiveness of PPV in preventing disease or death in adults. Adverse events were not assessed.

SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2007, Issue 2); MEDLINE (January 1966 to June 2007); and EMBASE (1974 to June 2007).

SELECTION CRITERIA: A) Randomised controlled trials (RCTs) comparing PPV with placebo, control vaccines, or no intervention,B) Non-RCTs assessing PPV effectiveness against invasive pneumococcal disease (IPD).

DATA COLLECTION AND ANALYSIS: A) RCTs: trial quality assessment was conducted by two review authors and data extracted by three authors; odds ratios (OR) and 95%
confidence intervals (CI) were estimated using a random-effects model. B) Non-RCTs: study quality, including measures to control for confounding, was assessed and data extracted by two review authors; OR and 95% CI were calculated using a random-effects model following the conversion of each study outcome to a log OR and standard error.

MAIN RESULTS: Twenty-two studies met our inclusion criteria (15 RCTs involving 48,656 participants and 7 non-RCTs involving 62,294 participants). Meta-analysis of the RCTs found strong evidence of PPV efficacy against IPD with no statistical heterogeneity (OR 0.26, 95% CI 0.15 to 0.46; random-effects model, I-squared (I(2)) = 0%). Efficacy against all cause pneumonia was inconclusive with substantial statistical heterogeneity (OR 0.71, 95% CI 0.52 to 0.97; random-effects model, I(2) = 87.3%). PPV was not associated with substantial reductions in all-cause mortality (OR 0.87, 95% CI 0.69 to 1.10; random-effects model, I(2) = 75.3%). Vaccine efficacy against primary outcomes appeared poorer in adults with chronic illness but the difference was not statistically significant. Non-RCTs provided evidence for protection against IPD in populations for whom the vaccine is currently utilised (OR 0.48, 95% CI 0.37 to 0.61; random-effects model, I(2) = 31.4%).

AUTHORS' CONCLUSIONS: This meta-analysis provides evidence supporting the recommendation for PPV to prevent IPD in adults. The evidence from RCTs is less clear with respect to adults with chronic illness. This might be because of lack of effect or lack of power in the studies. The meta-analysis does not provide compelling evidence to support the routine use of PPV to prevent all-cause pneumonia or mortality.


Pneumococcal polysaccharide-protein conjugate vaccines (PCVs) generally protect against vaccine-serotype-specific pneumococcal disease. Additional serotypes included in the new 13-valent PCV (PCV-13) formulation and not in the first-generation 7-valent PCV (PCV-7) formulations are 1, 3, 5, 6A, 7F and 19A. Importantly, serotype 1 is associated with a high proportion and burden of pneumococcal disease in low-income countries, whilst serotype 19A emerged as the dominant disease-causing serotype following widespread PCV-7 immunization in the USA. In this article we present the available data on the immunogenicity and safety of PCV-13 in infants and children. Noninferiority studies indicate a similar immunogenicity profile between PCV-13 and PCV-7 recipients against most of the common serotypes. A favorable immunogenicity profile was also observed for at least five of the additional serotypes in PCV-13. An attenuated anamnestic response to serotype 3 was reported in five out of 14 studies. PCV-13 was demonstrated to have a similar acceptable safety profile to PCV-7 and no interference in immunogenicity of other concomitantly administered childhood vaccines was observed among PCV-13 recipients.

RCT to evaluate the safety and immunogenicity of a nonavalent pneumococcal conjugate vaccine and the antigenic interaction when administered simultaneously with diphtheria, tetanus and pertussis vaccines.

Two hundred seven infants were randomized to receive three doses of either nonavalent protein conjugate pneumococcal vaccine (PnCV) or inactivated polio vaccine (IPV) at 2, 3 and 4 months of age with routine Expanded Program of Immunization vaccines as scheduled. No serious reactions were observed. Local induration and tenderness were observed more commonly at the site of administration of diphtheria, tetanus and pertussis vaccines than at the site of administration of IPV or PnCV. Between 79 and 91% achieved >1 mg/ml antibody against specific pneumococcal serotypes. Antibody responses to diphtheria and pertussis antigens were similar in both groups; however, antibody response to tetanus toxoid was significantly lower in infants who received PnCV (geometric mean concentration, 11.1 vs. 17.4; P < 0.001). Nasopharyngeal carriage in PnCV-vaccinated children was reduced but not significantly different from those vaccinated with IPV.


BACKGROUND: Streptococcus pneumoniae is a leading cause of bacterial pneumonia, meningitis, and sepsis in children worldwide. However, many countries lack national estimates of disease burden. Effective interventions are available, including pneumococcal conjugate vaccine and case management. To support local and global policy decisions on pneumococcal disease prevention and treatment, we estimated country-specific incidence of serious cases and deaths in children younger than 5 years.

METHODS: We measured the burden of pneumococcal pneumonia by applying the proportion of pneumonia cases caused by S pneumoniae derived from efficacy estimates from vaccine trials to WHO country-specific estimates of all-cause pneumonia cases and deaths. We also estimated burden of meningitis and non-pneumonia, non-meningitis invasive disease using disease incidence and case-fatality data from a systematic literature review. When high-quality data were available from a country, these were used for national estimates. Otherwise, estimates were based on data from neighbouring countries with similar child mortality. Estimates were adjusted for HIV prevalence and access to care and, when applicable, use of vaccine against Haemophilus influenzae type b.

FINDINGS: In 2000, about 14.5 million episodes of serious pneumococcal disease (uncertainty range 11.1-18.0 million) were estimated to occur. Pneumococcal disease caused about 826,000 deaths (582,000-926,000) in children aged 1-59 months, of which 91,000 (63,000-102,000) were in HIV-positive and 735,000 (519,000-825,000) in HIV-negative children. Of the deaths in HIV-negative children, over 61% (449,000 [316,000-501,000]) occurred in ten African and Asian countries.

INTERPRETATION: S pneumoniae causes around 11% (8-12%) of all deaths in children aged 1-59 months (excluding pneumococcal deaths in HIV-positive children). Achievement of the UN Millennium Development Goal 4 for child mortality reduction can be accelerated by prevention and treatment of pneumococcal disease, especially in regions of the world with the greatest burden.

In a group-randomised study, the vaccine to children younger than 2 years from the Navajo and White Mountain Apache Indian reservations; meningococcal type C conjugate vaccine (MnCC) served as the control vaccine. Vaccine schedules were determined by age at enrolment. Episodes of invasive pneumococcal disease and serotyped isolates were recorded. Analyses were by intention to treat and per protocol. 8292 children enrolled in the trial. In the per protocol analysis of the primary efficacy group (children enrolled by 7 months of age) there were eight cases of vaccine serotype disease in the controls and two in the PnCRM7 group; in the intention-to-treat analysis 11 cases of vaccine serotype disease in the MnCC control group and two in the PnCRM7 group. After group randomisation had been controlled for, the per protocol primary efficacy of PnCRM7 was 76.8% (95% CI –9.4% to 95.1%) and the intention-to-treat total primary efficacy was 82.6% (21.4% to 96.1%).


OBJECTIVES: To determine the immunogenicity and safety of heptavalent pneumococcal polysaccharide vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) conjugated to CRM(197) (7-valent conjugate pneumococcal vaccine [7VPnC]) among infants with sickle cell disease (SCD) and a comparison group of infants without SCD (non-SCD).

DESIGN: Two cohorts of infants were enrolled and received open-label doses of 7VPnC vaccine; infants enrolled before 2 months of age received 7VPnC vaccine at 2, 4, and 6 months of age followed by 23-valent pneumococcal polysaccharide vaccine (PS-23) at 24 months of age for those infants with SCD (schedule A), and infants enrolled between 2 and 12 months of age received 7VPnC at 12 months of age followed by PS-23 at 24 months of age for infants with SCD (schedule B). Safety data were collected for 3 days after each dose of vaccine. Antibody concentrations were measured to each of the 7VPnC serotypes by enzyme-linked immunosorbent assay before each vaccine dose and 1 month after the last 7VPnC dose and the PS-23 vaccine dose.

RESULTS: Forty-five infants (34 SCD and 11 non-SCD) were vaccinated according to schedule A and 16 infants (13 SCD and 3 non-SCD) according to schedule B. The 7VPnC vaccine was highly immunogenic for all serotypes among infants with and without SCD who received 3 doses of vaccine according to schedule A: depending on serotype, 89% to 100% achieved antibody concentrations above 1.5 microg/mL and 56% to 100% achieved antibody concentrations above 1.0 microg/mL. Among infants immunized according to schedule B, a single dose of 7VPnC vaccine resulted in antibody concentrations above 1.5 microg/mL in 53% to 92% by serotype and above 1.0 microg/mL in 31% to 71% by serotype. A single dose of PS-23 resulted in dramatic increases in the antibody concentrations to all serotypes regardless of 1- or 3-dose priming. There was no difference in the reactogenicity of the 7VPnC vaccine between those with and without SCD. There were no serious reactions to the 7VPnC or PS-23 vaccines, even among those with high antibody concentrations before immunization.
CONCLUSIONS: Infants with SCD respond to 7VPnC vaccine with antibody concentrations that are at least as high as infants without SCD. Infants immunized with 7VPnC vaccine at 2, 4, and 6 months of age developed antibody concentrations in the same range as those achieved among infants without SCD enrolled in a large trial that demonstrated vaccine efficacy against invasive disease. Significant rises were seen in antibody concentrations to all 7VPnC serotypes after the PS-23 booster in children receiving schedule A or B.


RCT to assess the immunogenicity and impact on carriage of fewer doses of pneumococcal conjugate vaccine (PCV7) followed by booster with pneumococcal polysaccharide vaccine (PPV) were investigated. 684 infants were assigned randomly to one of the three groups that received one (A), two (B) or three (C) doses of PCV7 between 2 and 4 months of age, plus PPV at 10 months. Following primary vaccination protective antibody titer of >0.35g/ml against the PCV7 serotypes combined increased significantly with the number of PCV7 doses, 44% vs. 77% vs. 94% (p < 0.001), and correlated positively with the opsonophagocytic indices, but negatively with nasopharyngeal carriage of pneumococcus. The differences in antibody responses and pneumococcal carriage between the groups diminished following booster with PPV, implying that administration of one or two doses of PCV7, with a booster dose of PPV might lower the cost of protection against IPD in young children in resource poor countries.


Pneumococcal conjugate vaccines (PCV) may reduce nasopharyngeal carriage (NPC) of Streptococcus pneumoniae vaccine strains (VT), but serotype replacement with non-vaccine strains (NVT) has been reported. Bacterial NPC after PHiD-CV vaccination was assessed in the second year of life. Open descriptive study of NPC reported for 414 subjects vaccinated at 3-5 and 12-15 months of age with PHiD-CV with or without prophylactic paracetamol (PP) compared to 336 age-matched PCV-naïve controls. Carriage was assessed prior to and 1, 3, 7 and 12 months after PHiD-CV booster or MenACWY-TT control vaccination at 12-15 months of age. At each visit, carriage of VT was reduced by 22-35% in PHiD-CV recipients. Vaccine efficacy across all visits was 21.7% [95% CI 2.6; 37.0] (26.8% carriage in the PHiD-CV group versus 34.2% in controls). Carriage rates of NVT tended to be higher in PHiD-CV recipients. Pre-booster, these findings were more pronounced when PP had not been administered. No substantial effect of PHiD-CV vaccination was observed on NPC of other bacterial pathogens including non-typeable Haemophilus influenzae. Primary and booster vaccination with PHiD-CV reduced NPC of VT in the second year of life and tended to slightly increase that of NVT in line with previous experience with the 7-valent PCV.
The global burden of disease due to Streptococcus pneumoniae remains high. The licensed 7-valent pneumococcal conjugate vaccine (7vCRM, Prevenar/Prevnar) has successfully reduced invasive disease in the USA, but serotype coverage is incomplete and some evidence suggests that serotype replacement has occurred. Recently, a new 10-valent pneumococcal nontypeable Haemophilus influenzae (NTHi) protein D (PD) conjugate vaccine (PHiD-CV, Synflorix) has been licensed in more than 40 countries, including Europe, for the prevention of invasive disease and acute otitis media (AOM) due to pneumococcus in infants and children. PHiD-CV is immunogenic in infants when administered as a three-dose primary vaccination in a range of schedules and has a safety profile comparable to that of 7vCRM. Additional serotypes in PHiD-CV (1, 5 and 7F) increase overall serotype coverage and improve coverage in specific age groups and against specific disease syndromes. The use of the PD carrier, which provided protection against AOM caused by NTHi in a large efficacy trial testing a prototype of the final vaccine formulation, suggests that PHiD-CV will also provide some protection against AOM due to NTHi.


BACKGROUND: Acute otitis media is one of the most commonly-diagnosed childhood infections. This study assessed the efficacy of a novel vaccine that contained polysaccharides from 11 different Streptococcus pneumoniae serotypes each conjugated to Haemophilus influenzae-derived protein D in prevention of acute otitis media.

METHODS: 4968 infants were randomly assigned to receive either pneumococcal protein D conjugate or hepatitis A vaccine at the ages of 3, 4, 5, and 12-15 months and were followed-up until the end of the second year of life. Middle-ear fluid was obtained for bacteriological culture and serotyping in children who presented with abnormal tympanic membrane or presence of middle-ear effusion, plus two predefined clinical symptoms. The primary endpoint was protective efficacy against the first episode of acute otitis media caused by vaccine pneumococcal serotypes. Analysis was per protocol.

FINDINGS: From 2 weeks after the third dose to 24-27 months of age, 333 clinical episodes of acute otitis media were recorded in the protein D conjugate group (n=2455) and 499 in the control group (n=2452), giving a significant (33.6% [95% CI 20.8-44.3]) reduction in the overall incidence of acute otitis media. Vaccine efficacy was shown for episodes of acute otitis media caused by pneumococcal vaccine serotypes (52.6% [35.0-65.5] for the first episode and 57.6% [41.4-69.3] for any episode). Efficacy was also shown against episodes of acute otitis media caused by non-typable H influenzae (35.3% [1.8-57.4]). The vaccine reduced frequency of infection from vaccine-related cross-reactive pneumococcal serotypes by 65.5%, but did not significantly change the number of episodes caused by other non-vaccine serotypes.

INTERPRETATION: These results confirm that using the H influenzae-derived protein D as a carrier protein for pneumococcal polysaccharides not only allowed protection against pneumococcal otitis, but also against acute otitis media due to non-typable H influenzae.
Whether this approach would also allow improved protection against lower respiratory tract infections warrants further investigation.


OBJECTIVES: To estimate the incidence and epidemiological characteristics of invasive pneumococcal disease (IPD) in children<5 years of age living in a rural area of southern Mozambique.

METHODS: As part of the clinical management of children admitted to Manhiça District Hospital, prospective surveillance for invasive bacterial disease was conducted from June 2001 to May 2003. The level of antibiotic resistance of the isolates was also analysed.

RESULTS: Pneumococcus was the most commonly isolated bacterium, accounting for 212 episodes. The estimated crude incidence rate of IPD in the study area among children<5 years of age was 416/100,000 per child-year at risk. The youngest age group (<3 months) had the highest incidence (779/100,000). Cases were detected during both rainy and dry seasons. The most common clinical diagnosis was pneumonia, made in 146/212 (69%) of the episodes of IPD. The overall case fatality rate was 10%, being highest among children with pneumococcal meningitis (5/9=56%). Pneumococcal isolates were highly susceptible to penicillin (86% susceptible and 14% with intermediate resistance) and chloramphenicol (98% susceptible). In contrast, up to 37% of the isolates tested were non-susceptible to cotrimoxazole.

CONCLUSIONS: Incidence rates of IPD and associated mortality shown in this study highlight the need for pneumococcal vaccines in rural Africa, which must be effective in infants and young children.


The immunogenicity and safety of the 10-valent pneumococcal conjugate vaccine, PHiD-CV, have been documented in European and Asian studies. In this open study conducted in Mexico (NCT00489554), 230 healthy infants received three doses of PHiD-CV and DTPa-HBV-IPV/Hib vaccines at 2, 4 and 6 months of age and two doses of oral human rotavirus vaccine at 2 and 4 months. Serotype-specific pneumococcal responses and opsonophagocytic activity (OPA) were measured one month post-dose 3. PHiD-CV's primary vaccination course was highly immunogenic against each of the 10 pneumococcal vaccine serotypes and carrier protein D. Antibody responses against pneumococcal serotypes and protein D were generally higher in Mexican infants compared with European antibody responses, and functional OPA responses were also higher or in the same range. The most frequent solicited local symptom was pain, with high but similar incidences of grade 3 pain reported at both injection sites (up to 15% of all doses). PHiD-CV was well tolerated, with no serious adverse events considered as causally related to vaccination. Most solicited symptoms were mild and there was no increase in incidence of solicited symptoms with successive vaccine doses.

Russell, F.M., et al., Immunogenicity following one, two, or three doses of the 7-valent pneumococcal conjugate vaccine. Vaccine, 2009. 27(41): p. 5685-91

A RCT to identify an appropriate infant pneumococcal vaccination strategy for resource poor countries. Fijian infants received zero, one, two, or three doses of 7-valent pneumococcal conjugate vaccine (PCV) in early infancy. Following three PCV doses, geometric mean concentration (GMC) to all seven serotypes were ≥1.0g/mL, and >85% of children achieved antibody levels ≥0.35g/mL at 18 weeks.

Following two doses, GMC were lower for 6B, 14, and 23F, but higher for 19F compared with three doses. Following a single dose, significant responses were seen for all serotypes post-primary series compared with the unvaccinated. By 12 months, differences between two and three doses persisted for serotype 14 only. Although GMC following three doses are higher than after two doses, the differences were small. A single dose may offer some protection for most serotypes.

Safety and tolerability of 3 lots of 13-valent pneumococcal conjugate vaccine in healthy infants given with routine pediatric vaccinations in the USA. 2nd global vaccine congress; 2008 Dec 7; Boston, MA, USA. 2008.


Acute otitis media (AOM), one of the most common childhood diseases, is associated with a substantial medical, social and economic burden. Non-typeable Haemophilus influenzae (NTHi) and Streptococcus pneumoniae are the two main causes of bacterial OM. The 7-valent pneumococcal CRM(197)-conjugate vaccine (7vCRM, Prevnar/Prevenar, Wyeth) demonstrated efficacy against AOM caused by vaccine pneumococcal serotypes. Protection against overall AOM was also observed with an 11-valent pneumococcal protein D-conjugate vaccine (11Pn-PD) in the Pneumococcal Otitis Efficacy Trial (POET). Following POET, an optimized 10-valent pneumococcal non-typeable H. influenzae protein D-conjugate vaccine (PHiD-CV; Synflorix, GlaxoSmithKline Biologicals) was developed. This vaccine includes serotypes 1, 5, and 7F, in addition to those already included in 7vCRM, and was recently licensed in Europe for active immunization against invasive disease and AOM caused by S. pneumoniae in infants and children from 6 weeks up to 2 years of age. The use of protein D as carrier protein permits avoidance of possible interferences known to occur with some conjugate vaccines, and has the added potential benefit of providing protection against NTHi. This review seeks to highlight the recent advances in the field of OM vaccination, with a focus on data regarding the recently licensed PHiD-CV.


This randomized, double-blind study evaluated concomitant administration of 13-valent pneumococcal conjugate vaccine (PCV13) and trivalent inactivated influenza vaccine (TIV) in adults aged ≥65 years who were naïve to 23-valent pneumococcal polysaccharide vaccine. Patients (N=1160) were randomized 1:1 to receive PCV13+TIV followed by placebo, or Placebo+TIV followed by PCV13 at 0 and 1 months, with blood draws at 0, 1, and 2 months. Slightly lower pneumococcal serotype-specific anticapsular polysaccharide immunoglobulin G geometric mean concentrations were observed with PCV13+TIV relative to PCV13. Concomitant PCV13+TIV demonstrates acceptable immunogenicity and safety compared with either agent given alone.


This randomized trial compares safety and immunogenicity when vaccinating infants with a pneumococcal-meningococcal conjugate vaccine in two doses vs. three doses. Infants (N=223) received 9vPnC-MnCC (CRM197-conjugated pneumococcal serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F and meningococcal C polysaccharides) either at 3 and 5 or 3, 4 and 5 months and a booster with either 9vPnC-MnCC or 23-valent pneumococcal-polysaccharide vaccine (23vPPS) and CRM197-MnCC, at 12 months. Safety was monitored and IgG measured at 3, 6, 12 and 13 months in all subjects and serum bactericidal activity (SBA) in half. The 9vPnC-MnCC vaccine was safe and induced significant IgG to all components. Three doses induced higher antibody GMCs (geometric mean concentrations) at 6 months to seven of nine pneumococcal serotypes. This was most significant for 6B and 23F (p<0.001), that also showed lower rate of responders>0.35 (6B, 23F) and >0.5 microg/mL (6B). Antibody GMCs remained lower following 9vPnC-MnCC booster in subjects primed with two doses although only significant for serotype 18C. Significant memory responses were observed 1 week after the 23vPPS toddler dose. MnCC-IgG GMC was lower after two doses, however with comparable SBA. This study shows that the 9vPnC-MnCC vaccine is safe and induces successful immunological memory, whether given in two or three primary doses.


BACKGROUND: Immunogenicity of 10-valent pneumococcal nontypeable Haemophilus influenzae protein d conjugate vaccine (PHiD-CV), administered as 2-dose or 3-dose priming followed by a booster dose, has been described previously. The present study evaluated
immunologic memory following PHiD-CV vaccination according to these vaccination schedules.

METHODS: A dose of PHiD-CV (to test anamnestic responses) was administered to 172 children at 36 to 46 months of age; 110 of them had previously been vaccinated with PHiD-CV according to 2 + 1 or 3 + 1 schedules (PHiD-CV [2 + 1] and PHiD-CV [3 + 1] groups) and 62 were unprimed age-matched controls. To measure immune responses before and 7 to 10 days after the PHiD-CV dose, 22F-inhibition enzyme-linked immunosorbent assay and opsonophagocytic activity (OPA) assay were used.

RESULTS: Serotype-specific IgG geometric mean concentrations (GMCs) and OPA geometric mean titers increased substantially (from before to 7 to 10 days after the additional PHiD-CV dose) for all 10 vaccines and 2 cross-reactive serotypes (6A and 19A) in the children previously vaccinated with PHiD-CV, regardless of the vaccination schedule used. Antibody GMCs and OPA geometric mean titers after the administration of the PHiD-CV dose were markedly higher in both previously PHiD-CV-vaccinated groups than in the unprimed control group, clearly demonstrating prior induction of immunologic memory. Antiprotein D antibody GMCs had also increased substantially from before to 7 to 10 days after vaccination in all 3 groups, with higher antibody GMCs in the previously vaccinated groups than in the control group.

CONCLUSION: PHiD-CV vaccination according to 2 + 1 or 3 + 1 schedules resulted in comparable anamnestic immune responses. These findings suggest that similar protective efficacy may be achieved with both the schedules.


BACKGROUND: The immunogenicity of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D-conjugate vaccine (PHiD-CV) was determined following a simplified 2-dose priming and the more commonly employed 3-dose priming both followed by a booster dose.

METHODS: A total of 351 healthy subjects were primed with PHiD-CV at either 3 and 5 or 3, 4 and 5 months of age followed in all subjects by a booster dose at 11 to 12 months of age. Serotype-specific pneumococcal responses were measured by 22F-inhibition ELISA and opsonophagocytic assays 1 month following primary and booster vaccinations.

RESULTS: Depending on the serotype, the percentages of subjects reaching the ELISA antibody threshold of 0.2 microg/mL were 92.8% to 98.0% following 2 primary doses and 96.1% to 100% following 3 primary doses except for serotype 6B (55.7% and 63.1%, respectively) and serotype 23F (69.3% and 77.6%, respectively). Opsonophagocytic activity (OPA) could be measured in 74.4% to 100% and 88.9% to 100% of the subjects after the 2-dose or 3-dose priming, respectively, except for serotype 1 (60.8% and 62.9%, respectively). In both groups, robust increases in ELISA antibodies and OPA titers were observed for all serotypes after the booster dose. Higher postprimary and postbooster ELISA antibody levels and OPA titers were observed for most serotypes following the 3+1 schedule.
CONCLUSION: PHiD-CV was immunogenic in both schedules, but further effectiveness data are needed to fully understand the public health benefit to be expected from these schedules in terms of prevention against invasive and mucosal infections.


BACKGROUND: A 2-, 4-, and 12-month schedule of a novel 13-valent-pneumococcal conjugate vaccine (PCV13), containing serotype 1, 3, 4, 5, 6A, 6B 7F, 9V, 14, 18C, 19A, 19F, and 23F polysaccharides individually conjugated to CRM197 was evaluated in a randomized, double-blind, controlled infant study.

METHODS: Two hundred eighty-six healthy infants received PCV13 or the 7-valent-pneumococcal conjugate vaccine (PCV7) at 2, 4, and 12 months of age, alongside a serogroup C meningococcal (MenC) vaccine (2 and 4 months of age), DTaP-IPV-Hib (2, 3, and 4 months), and a Hib-MenC vaccine (12 months). Specific antibody responses were assessed at age 5, 12, and 13 months.

RESULTS: At 13 months of age, >97% of PCV13 recipients had pneumococcal serotype-specific serum IgG concentrations ≥0.35 µg/mL for each vaccine serotype except serotype 3 (88.2%), and at least 93% of PCV13 recipients had OPA titers ≥1:8 for each serotype. At 5 months, 110/114 (96.5%) of PCV13 recipients and 100/102 (98.0%) of PCV7 recipients had serum anti-PRP (Hib) IgG concentration ≥0.15 µg/mL (difference, 1.5%; CI, -7.1%–3.7%), while 119/120 (99.2%) and 117/118 (99.2%), respectively, had MenC serum bactericidal assay titers of ≥1:8. All PCV13 recipients and 110/113 (97.3%) of PCV7 recipients had IgG concentrations against fimbrial agglutinogens of ≥2.2 EU/mL; IgG concentrations for the remaining pertussis antigens were ≥5 EU/mL for all participants. Local reactions and systemic events were similar in the PCV13 and PCV7 groups.

CONCLUSIONS: A 2-, 4-, and 12-month course of PCV13 was immunogenic for all 13 vaccine serotypes and was well tolerated.


An observational study to examine Streptococcus pneumoniae carriage in Norwegian children was initiated after two cases of pneumococcal meningitis, caused by the England(14)-9 clone, occurred in one day-care centre in Oslo. All children recruited from the day-care centre where the cases occurred were vaccinated with a seven-valent pneumococcal conjugate vaccine; the other participants who attended three other day-care centres nearby were not. The children were followed for 9 months, and three samplings took place. At the first visit, 45.7% of the children were colonised by pneumococci in the nasopharynx. The children harboured a variety of serotypes, with serotypes 6A, 23F, 6B and 19F being the most frequent. The numbers of children carrying vaccine serotypes decreased in both the vaccinated and the non-vaccinated groups. Thus, no significant effect of vaccine on carriage was detected in this relatively small study.

BACKGROUND: Seasonal fluctuation in the incidence of invasive pneumococcal disease has been attributed to winter virus exposure (e.g., influenza and respiratory syncytial virus [RSV]). Evidence of a direct correlation of invasive pneumococcal disease with laboratory-confirmed virus seasons, however, is limited. Using two prospective surveillance networks, the temporal relation between invasive pneumococcal disease and isolation of circulating winter viruses was explored.


RCT to examine the effects of a 2-dose and 21-dose PCV-7 schedule on nasopharyngeal pneumococcal carriage in young children compared with controls. Enrolling 1003 healthy newborns and 1 of their parents in a general community in the Netherlands, with follow-up to age 24 months and conducted between July 7, 2005, and February 14, 2008. Intervention Infants were randomly assigned to receive 2 doses of PCV-7 at 2 and 4 months; 21 doses of PCV-7 at 2, 4, and 11 months; or no dosage (control group). At 12 months, vaccine serotype pneumococcal carriage was significantly decreased after both PCV-7 schedules, with vaccine serotype pneumococcal carriage rates of 25% (95% confidence interval [CI], 20%-30%) and 20% (95% CI, 16%-25%) in the 2-dose and 21-dose schedule groups, respectively, vs 38% (95% CI, 33%-44%) in the control group (both P.001). At 18 months, in the 21-dose schedule group, vaccine serotype pneumococcal carriage had further decreased to 16% (95% CI, 12%-20%) and, at 24 months, to 14% (95% CI, 11%-18%; both P.001); whereas in the 2-dose schedule group, vaccine serotype pneumococcal carriage had remained stable at 18 months (24%; 95% CI, 20%-29%), but at 24 months had further decreased to 15% (95% CI, 11%-19%; both P.001). In the control group, vaccine serotype pneumococcal carriage remained around 36% to 38% until 24 months.


A randomized, controlled trial was performed with 161 children, 2 to 8 years of age, with documented persistent bilateral OME. All subjects were treated with tympanostomy tubes (TTs). One half of the subjects were assigned randomly to additional vaccination with a 7-valent pneumococcal conjugate vaccine 3 to 4 weeks before and a 23-valent pneumococcal polysaccharide vaccine 3 months after tube insertion. The overall recurrence rate of bilateral OME was 50%. Pneumococcal vaccinations induced significant 4.6- to 24.4-fold increases in the geometric means of all conjugate vaccine serotype antibody titers but did not affect recurrence of OME.


A double-blind, randomized RCT to study the efficacy of a 7-valent pneumococcal conjugate vaccine on acute otitis media recurrences, its immunogenicity and impact on nasopharyngeal Streptococcus pneumoniae carriage in children with a history of frequent acute otitis media.
74 Belgian children, aged 1—7 years, with at least 2 clinically diagnosed episodes of acute otitis media in the previous year were enrolled. Children were immunized with either a 7-valent pneumococcal conjugate vaccine followed by a 23-valent pneumococcal polysaccharide booster or a control hepatitis A vaccine. Total follow-up was 26 months. Despite adequate serum IgG responses to all conjugate vaccine pneumococcal serotypes, no reduction of acute otitis media episodes was observed in the pneumococcal vaccine group as compared to the control group (rate ratio: 1.16; 95% CI: 0.69—1.96). Overall nasopharyngeal pneumococcal carriage remained stable.

METHODS: Episodes of invasive pneumococcal disease in five Tennessee counties were collected prospectively from January 1995 through June 2002. Virus seasons were defined using prospective laboratory-based surveillance. Correlation between weekly identification of invasive pneumococcal disease and laboratory isolation of RSV and influenza, as well as comparisons of the frequencies of invasive pneumococcal disease episodes during viral and nonviral seasons were determined.

RESULTS: A total of 4147 invasive pneumococcal disease episodes were identified. Weekly frequency of invasive pneumococcal disease correlated directly with the weekly frequency of isolation of RSV ($r = 0.56$, $P <0.001$) and influenza ($r = 0.40$, $P <0.001$). The average weekly frequency of invasive pneumococcal disease during RSV and influenza seasons was higher than during the nonviral seasons ($P <0.001$ for each year).

CONCLUSION: Weekly episodes of invasive pneumococcal disease correlated temporally with laboratory-confirmed weekly isolation of RSV and influenza, and the incidence of invasive pneumococcal disease was increased when these viruses were circulating in the community.


A double-blind, RCT enrolled 383 patients aged 1–7 years who had had two or more episodes of AOM in the year before entry. Randomisation was stratified in four groups according to age (12–24 months vs 25–84 months) and the number of previous AOM episodes (two or three episodes vs four or more episodes). Children received either 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine, or hepatitis A or B vaccines. No reduction of AOM episodes in the pneumococcal vaccine group compared with controls (intention-to-treat analysis: rate ratio 1·25, 95% CI 0·99–1·57). Although nasopharyngeal carriage of pneumococci of serotypes included in the conjugate-vaccine was greatly reduced after pneumococcal vaccinations, immediate and complete replacement by non-vaccine pneumococcal serotypes took place.


BACKGROUND: The immunogenicity of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D-conjugate vaccine (PHiD-CV) was assessed and compared with the 7-valent pneumococcal conjugate vaccine (7vCRM).
METHODS: Healthy subjects (1650) were randomized to be vaccinated with 3 doses of PHiD-CV or 7vCRM (Prevenar/Prevnar) at 2-3-4 months of age and a fourth booster dose at 12-18 months. Serotype-specific pneumococcal responses (GlaxoSmithKline's ELISA with 22F-inhibition) and opsonophagocytic activity (OPA) were measured 1 month after primary and booster vaccinations.

RESULTS: The primary objective to demonstrate noninferiority of PHiD-CV versus 7vCRM (in terms of percentage of subjects with antibody concentration >or=0.2 microg/mL) for at least 7 of the 10 vaccine serotypes was reached as noninferiority was demonstrated for 8 serotypes. Although, noninferiority could not be demonstrated for ELISA responses against serotypes 6B and 23F, a post-hoc analysis of the percentage of subjects with OPA titers >or=8 suggested noninferiority for the 7 serotypes common to both vaccines including 6B and 23F. Priming of the immune system against all vaccine serotypes was confirmed by robust increases in ELISA antibody levels (approximately 6.0-17 fold) and OPA titers (approximately 8-93 fold) after a fourth consecutive dose of PHiD-CV.

CONCLUSIONS: PHiD-CV induces ELISA and functional OPA antibodies for all vaccine serotypes after primary vaccination and is noninferior to 7vCRM in terms of ELISA and/or OPA threshold responses. Effective priming is further indicated by robust booster responses.


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 (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.


The aim was to assess the effectiveness of the vaccine against various pneumococcal serotypes, and to measure the effectiveness of the recommended dose schedule and of catch-up and incomplete schedules. : Invasive disease, defined as isolation of pneumococcus from a sterile site, was identified in children aged 3-59 months through the US Centers for Disease Control and Prevention's Active Bacterial Core surveillance. We tested isolates for serotype and antimicrobial susceptibility. Three controls, matched for age and zip code were selected for each case. We calculated the matched odds ratio for vaccination using conditional logistic regression, controlling for underlying conditions. Vaccine effectiveness was calculated as one minus the adjusted matched odds ratio times 100%. 782 cases and 2512 controls were enrolled. Effectiveness of one or more doses against vaccine serotypes was 96% (95% CI 93-
98) in healthy children and 81% (57-92) in those with coexisting disorders. It was 76% (63-85) against infections that were not susceptible to penicillin. Vaccination prevented disease caused by all seven vaccine serotypes, and by vaccine-related serotype 6A. Several schedules were more protective than no vaccination; three infant doses with a booster were more protective against vaccine-type disease than were three infant doses alone (p=0.0323).


CONTEXT: Clinical trials evaluate a vaccine's safety before approval, but some risks may escape detection or adequate characterization until larger population exposures occur after licensure.

OBJECTIVE: To summarize reports of events occurring after vaccination with 7-valent pneumococcal conjugate vaccine (PCV), including those that may warrant further investigation to assess possible causation by PCV.

DESIGN: Descriptive epidemiology of reports submitted to the Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance database.

SETTING AND PATIENTS: United States during first 2 years after licensure of PCV (February 2000 through February 2002). Reports studied were for children younger than 18 years and vaccinated with PCV.

MAIN OUTCOME MEASURES: Numbers and proportional distributions of reports.

RESULTS: A total of 4154 reports of events following PCV were submitted to VAERS, for a rate of 13.2 reports per 100,000 doses distributed. Multiple vaccines were given in 74.3% of reports. The most frequently reported symptoms and signs included fever, injection site reactions, fussiness, rashes, and urticaria. Serious events were described in 14.6% of reports. There were 117 deaths, 23 reports of positive rechallenges, and 34 cases of invasive pneumococcal infections possibly representing vaccine failure. Immune-mediated events occurred in 31.3% of reports. All 14 patients with anaphylactic or anaphylactoid reactions survived. Thrombocytopenia developed in 14 patients and serum sickness in 6 others. Neurologic symptoms occurred in 38% of reports. Seizures described in 393 reports included 94 febrile seizures.

CONCLUSIONS: The majority of reports to VAERS in the first 2 years after licensure of PCV described generally minor adverse events previously identified in clinical trials. The proportion of reports portraying serious events was similar to that for other vaccines. Although there are important limitations in passive surveillance data, and caution in their interpretation is necessary, symptoms experienced by a few children more than once after successive PCV doses, including allergic reactions, prolonged or abnormal crying, fussiness, dyspnea, and gastrointestinal distress, warrant continued surveillance, as do reports of rare but potentially serious events, such as seizures, anaphylactic or anaphylactoid reactions, serum sickness, and thrombocytopenia.

BACKGROUND: When seven-valent pneumococcal conjugate vaccine was introduced in the USA, many children were vaccinated on schedules that differed from those tested in clinical trials. Our aim was to assess the effectiveness of the vaccine against various pneumococcal serotypes, and to measure the effectiveness of the recommended dose schedule and of catch-up and incomplete schedules.

METHODS: Invasive disease, defined as isolation of pneumococcus from a sterile site, was identified in children aged 3-59 months through the US Centers for Disease Control and Prevention's Active Bacterial Core surveillance. We tested isolates for serotype and antimicrobial susceptibility. Three controls, matched for age and zip code were selected for each case. We calculated the matched odds ratio for vaccination using conditional logistic regression, controlling for underlying conditions. Vaccine effectiveness was calculated as one minus the adjusted matched odds ratio times 100%.

FINDINGS: We enrolled 782 cases and 2512 controls. Effectiveness of one or more doses against vaccine serotypes was 96% (95% CI 93-98) in healthy children and 81% (57-92) in those with coexisting disorders. It was 76% (63-85) against infections that were not susceptible to penicillin. Vaccination prevented disease caused by all seven vaccine serotypes, and by vaccine-related serotype 6A. Several schedules were more protective than no vaccination; three infant doses with a booster were more protective against vaccine-type disease than were three infant doses alone (p=0.0323).

INTERPRETATION: The seven-valent pneumococcal conjugate vaccine prevents invasive disease in both healthy and chronically ill children. The vaccine is effective when used with various non-standard schedules.


BACKGROUND: Immunogenicity of the candidate 10-valent pneumococcal non-typeable Haemophilus influenzae protein D-conjugate vaccine (PHiD-CV) was assessed when coadministered with other routine pediatric vaccines including different Neisseria meningitidis C conjugate vaccines.

METHODS: One thousand five hundred forty-eight healthy infants received, according to a balanced (1:1:1:1) randomization, either PHiD-CV coadministered with (1) DTPa-HBV-IPV/Hib (Infanrix hexa) and MenC-CRM (Meningitec), (2) DTPa-HBV-IPV/Hib and MenC-TT (NeisVac-C), or (3) DTPa-HBV-IPV (Infanrix penta/Pediarix) and Hib-MenC-TT (Menitorix); or 7vCRM (Prevenar/Prevnar) coadministered with DTPa-HBV-IPV and Hib-MenC-TT at 2-4-6 months of age with a booster dose at 11-18 months. Serotype-specific pneumococcal responses were measured by 22F-inhibition ELISA and opsonophagocytic (OPA) assay.

RESULTS: In all 3 coadministration groups, PHiD-CV was immunogenic for each of the 10 pneumococcal vaccine serotypes as assessed by post-primary and post-booster antibody ELISA and OPA responses. When coadministered with DTPa-HBV-IPV, Hib, and MenC antigens, PHiD-CV responses after the third primary dose were within the same range as 7vCRM responses in terms of the percentage of subjects achieving an ELISA antibody
concentration >or=0.2 microg/mL for all common vaccine serotypes (over 92% of subjects) except for serotype 6B (at least 87% of subjects). ELISA and OPA immune responses were also evident after the second primary doses of PHiD-CV or 7vCRM vaccine, although antibody levels were below that achieved after 3 primary doses, particularly for serotypes 6B and 23F. The kinetics of the immune responses from after the second dose to after the booster dose were similar for most of the serotypes in both PHiD-CV and 7vCRM groups.

CONCLUSIONS: PHiD-CV was immunogenic when coadministered with other routine pediatric vaccines including MenC conjugate vaccines.


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.


BACKGROUND: 7-Valent pneumococcal conjugate vaccine (PCV7 [Prevnar, Wyeth Pharmaceuticals Inc, Philadelphia, PA], serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) is effective in preventing vaccine-serotype pneumococcal disease. 13-Valent pneumococcal conjugate vaccine (PCV13) (PCV7 serotypes plus 1, 3, 5, 6A, 7F, and 19A) was designed to provide broader pneumococcal disease coverage. We evaluated the immunogenicity and safety of PCV13 compared with PCV7.
METHODS: Infants received PCV13 or PCV7 at ages 2, 4, 6, and 12 to 15 months with routine pediatric vaccinations. Pneumococcal anticapsular polysaccharide-binding immunoglobulin G responses and functional antipneumococcal opsonophagocytic activity were assessed 1 month after dose 3, before the toddler dose, and 1 month after the toddler dose. Safety and tolerability were also assessed.

RESULTS: For the 7 common serotypes, PCV13 elicited immunoglobulin G titers were noninferior to those elicited by PCV7, although PCV13 responses were generally somewhat lower. PCV13 also elicited functional opsonophagocytic activity comparable with that elicited by PCV7. For the 6 additional serotypes in PCV13, PCV13 elicited binding and functional antibody levels notably greater than those in PCV7 recipients. After PCV13 immunization, concordance between antipolysaccharide and opsonophagocytic responses was noted for all 13 serotypes. The PCV13 toddler dose resulted in higher immune responses compared with infant-series doses. Safety and tolerability were comparable; reactogenicity was generally mild.

CONCLUSIONS: PCV13 will be as effective as PCV7 in the prevention of pneumococcal disease caused by the 7 common serotypes and could provide expanded protection against the 6 additional serotypes. The PCV13 safety profile was comparable to that of PCV7.