

Pneumococcal conjugate vaccines for childhood immunization

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Epidemiology, agent, and disease

Brent AJ, Ahmed I, Ndiritu M, Lewa P, Ngetsa C, Lowe B, Bauni E, English M, Berkley JA, Scott JA. Incidence of clinically significant bacteraemia in children who present to hospital in Kenya: community-based observational study. Lancet. 2006 Feb 11;367(9509):482-8.

BACKGROUND: Estimates of the burden of invasive bacterial disease in sub-Saharan Africa have previously relied on selected groups of patients, such as inpatients; they are, therefore, probably underestimated, potentially hampering vaccine implementation. Our aim was to assess the incidence of bacteraemia in all children presenting to a hospital in Kenya, irrespective of clinical presentation or decision to admit. **METHODS:** We did a community-based observational study for which we cultured blood from 1093 children who visited a Kenyan hospital outpatient department. We estimated bacteraemia incidence with a Demographic Surveillance System, and investigated the clinical significance of bacteraemia and the capacity of clinical signs to identify cases.

RESULTS: The yearly incidence of bacteraemia per 100,000 children aged younger than 2 years and younger than 5 years was 2440 (95% CI 1307-3573) and 1192 (692-1693), respectively. Incidence of pneumococcal bacteraemia was 597 (416-778) per 100,000 person-years of observation in children younger than age 5 years. Three-quarters of episodes had a clinical focus or required admission, or both; one in six was fatal. After exclusion of children with occult bacteraemia, the incidence of clinically significant bacteraemia per 100,000 children younger than age 2 years or 5 years fell to 1741 (790-2692) and 909 (475-1343), respectively, and the yearly incidence of clinically significant pneumococcal bacteraemia was 436 (132-739) per 100,000 children younger than 5 years old. Clinical signs identified bacteraemia poorly.

INTERPRETATION: Clinically significant bacteraemia in children in Kilifi is twice as common, and pneumococcal bacteraemia four times as common, as previously estimated. Our data support the introduction of pneumococcal vaccine in sub-Saharan Africa.

Bryce J, Boschi-Pinto C, Shibuya K, Black RE; WHO Child Health Epidemiology Reference Group. WHO estimates of the causes of death in children. Lancet. 2005 Mar 26-Apr 1;365(9465):1147-52.

BACKGROUND: Child survival efforts can be effective only if they are based on accurate information about causes of deaths. Here, we report on a 4-year effort by WHO to improve the accuracy of this information. **METHODS:** WHO established the external Child Health Epidemiology Reference Group (CHERG) in 2001 to develop estimates of the proportion of deaths in children younger than age 5 years attributable to pneumonia, diarrhoea, malaria, measles, and the major causes of death in the first 28 days of life. Various methods, including

single-cause and multi-cause proportionate mortality models, were used. The role of undernutrition as an underlying cause of death was estimated in collaboration with CHERG. FINDINGS: In 2000-03, six causes accounted for 73% of the 10.6 million yearly deaths in children younger than age 5 years: pneumonia (19%), diarrhoea (18%), malaria (8%), neonatal pneumonia or sepsis (10%), preterm delivery (10%), and asphyxia at birth (8%). The four communicable disease categories account for more than half (54%) of all child deaths. The greatest communicable disease killers are similar in all WHO regions with the exception of malaria; 94% of global deaths attributable to this disease occur in the Africa region. Undernutrition is an underlying cause of 53% of all deaths in children younger than age 5 years. INTERPRETATION: Achievement of the millennium development goal of reducing child mortality by two-thirds from the 1990 rate will depend on renewed efforts to prevent and control pneumonia, diarrhoea, and undernutrition in all WHO regions, and malaria in the Africa region. In all regions, deaths in the neonatal period, primarily due to preterm delivery, sepsis or pneumonia, and birth asphyxia should also be addressed. These estimates of the causes of child deaths should be used to guide public-health policies and programmes.

Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. Clin Infect Dis. 2000 Jan;30(1):100-21.

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.

Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II. Clinical Infectious Diseases 2000;30(1):122-40.

Abstract: To assess whether certain serogroups of *Streptococcus pneumoniae* are preferentially associated with specific disease manifestations, we analyzed all recent pneumococcal disease studies and assessed the relative frequency of isolation of each serogroup by clinical site (as a proxy for different disease states). In all age groups, serogroups 1 and 14 were more often isolated from blood, and serogroups 6, 10, and 23 were more often isolated from cerebrospinal fluid (CSF); in young children, serogroups 3, 19, and 23 were more often isolated from middle ear fluid (MEF). Serogroups represented in conjugate vaccines were isolated slightly less frequently from CSF than

from blood or MEF. Nonetheless, serogroups in the 9-valent conjugate vaccine formulation still comprised approximately 75% of pneumococcal isolates from the CSF of young children in Europe and in the United States and Canada. These analyses indicate that pneumococcal conjugate vaccines could potentially prevent a substantial proportion of episodes of bacteremic disease, pneumonia, meningitis, and otitis media, especially in young children

Goetghebuer T, West TE, Wermenbol V, Cadbury AL, Milligan P, Lloyd-Evans N, Adegbola RA, Mulholland EK, Greenwood BM, Weber MW. Outcome of meningitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in children in The Gambia. *Trop Med Int Health*. 2000 Mar;5(3):207-13.

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.

Torzillo PJ, Hanna JN, Morey F, Gratten M, Dixon J, Erlich J. Invasive pneumococcal disease in central Australia. *Med J Aust*. 1995 Feb 20; 162(4):182-6.

OBJECTIVES: To document the incidence, case fatality, clinical and demographic features of invasive pneumococcal disease in central Australia. **DESIGN:** Invasive isolates from the regional central laboratory were prospectively recorded over five years and case notes retrospectively reviewed. Population denominators were calculated from national Census data from 1986 and 1991. **RESULTS:** The population estimates for the region were 14,568 for Aboriginals and 28,680 for non-Aboriginals. There were 185 episodes of invasive pneumococcal disease over the five years, 162 (87.5%) in Aboriginals and 23 (12.5%), in non-Aboriginals. The incidence in Aboriginal children under two years of age was 2052.7 per 100,000 and for those 20-59 years was 178.2 per 100,000. The relative risk in Aboriginals compared with non-Aboriginals was 10.8 (95% CI, 5.6-20.7; P < 0.0001) for those aged 0-4 years and 20.4 (95% CI, 9.7-42.5; P <

0.0001) for those 15-59 years. Forty-one Aboriginal adults aged over 14 (62%) had at least one conventional risk factor for pneumococcal disease; alcohol abuse was present in 27 (41%). There were 13 Aboriginal deaths and the case fatality rose from 2% in those under four years to 40% for those over 59 years. **CONCLUSIONS:** Central Australian Aboriginals have the highest incidence of invasive pneumococcal disease reported. The rate for children under two years is 59 to 80 times the rates for children in the United States and Sweden. These data have implications for improving vaccine use, health service delivery and environmental health in Aboriginal communities.

Pneumococcal vaccines

Efficacy in Clinical Trials

Hansen J, Black S, Shinefield H, Cherian T, Benson J, Fireman B, Lewis E, Ray P, Lee J. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia: updated analysis using World Health Organization standardized interpretation of chest radiographs. *Pediatr Infect Dis J.* 2006 Sep;25(9):779-81.

BACKGROUND: A World Health Organization (WHO) working group in 2001 developed a method for standardizing interpretation of chest radiographs in children for epidemiologic purposes. We reevaluated radiographs from the Kaiser Permanente Pneumococcal Efficacy trial using this method. **METHODS:** Seven-valent pneumococcal conjugate vaccine was evaluated in a randomized, controlled study including 37,868 infants. Effectiveness against pneumonia was previously evaluated using the original treating radiologist reading. There were 2841 sets of radiographs from this trial and all available radiographs were scanned and read blindly by 2 WHO crosstrained readers (A and B); discordance between the 2 primary readers was resolved through a consensus reading by an adjudicating panel of 2 radiologists. **RESULTS:** Of the 2841 radiographs, 2446 were available for scanning and were reviewed using WHO-defined descriptive categories. Two hundred fifty of the 2446 radiographs were read as positive by both readers. An additional 129 were read as positive by reader A only and 142 by reader B only for a total of 521 radiographs that were read as positive by one or both of the reviewers. The concordance rate between the 2 reviewers was 250 of 521 (48%). Of the 271 discordant radiographs, 45 of 129 (34.9%) of reader A and 66 of 142 (46.5%) for reader B were finalized as positive by the adjudicating panel. Overall, 361 radiographs were finalized as positive (12.7%). With these 361 images as the standard, the sensitivity and specificity of reader A were 82% and 97%, respectively, and for reader B, 88% and 97%, respectively. Kappa between the 2 readers was 0.58. Of 25 control radiographs read as positive by both A and B, 80% were also read as positive by the panel and all 25 control negative radiographs were read as negative by the panel. Using original readings by point-of-care radiologists, efficacy against first episode of radiograph confirmed pneumonia was 17.7% (95% confidence interval [CI] = 4.8-28.9%) in intent-to-treat and 20.5% (95% CI = 4.4-34%) in per protocol. Using the WHO method, the efficacy against first episode of radiograph confirmed pneumonia adjusting for age, gender and year of vaccination of 25.5% (95% CI = 6.5-40.7%, P = 0.011) for intent-to-treat and 30.3% (95% CI = 10.7-45.7%, P = 0.0043) for per

protocol. CONCLUSION: Using WHO criteria for reading of radiographs increased point estimates of vaccine efficacy presumably as a result of improved specificity.

Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, Oluwalana C, Vaughan A, Obaro SK, Leach A, McAdam KP, Biney E, Saaka M, Onwuchekwa U, Yallop F, Pierce NF, Greenwood BM, Adegbola RA; Gambian Pneumococcal Vaccine Trial Group. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet*. 2005 Mar 26-Apr 1;365 (9465):1139-46. (Erratum in: *Lancet*. 2005 Jul 2-8;366(9479):28)

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.

O'Brien KL, Moulton LH, Reid R, Weatherholtz R, Oski J, Brown L, Kumar G, Parkinson A, Hu D, Hackell J, Chang I, Kohberger R, Siber G, Santosham M. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. *Lancet*. 2003 Aug 2;362(9381):355-61.

BACKGROUND: *Streptococcus pneumoniae* is the main cause of invasive bacterial disease in children aged younger than 2 years. Navajo and White Mountain Apache children have some of the highest rates of invasive pneumococcal disease documented in the world. We aimed to assess the safety and efficacy of a seven-valent polysaccharide protein conjugate pneumococcal vaccine (PnCRM7) against such disease. **METHODS:** In a group-randomised study, we gave this 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 enrollment. We recorded episodes of invasive pneumococcal disease and serotyped isolates. Analyses were by intention to treat and per protocol. FINDINGS: 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 we noted 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%). INTERPRETATION: PnCRM7 vaccine prevents vaccine serotype invasive pneumococcal disease even in a high risk population. Other regions with similar disease burden should consider including this vaccine in the routine childhood vaccine schedule.

Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N; Vaccine Trialists Group. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003 Oct 2;349(14):1341-8.

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.

Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, Elvin L, Ensor KM, Hackell J, Siber G, Malinoski F, Madore D, Chang I, Kohberger R, Watson W, Austrian R, Edwards K. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J.* 2000, Mar;19(3):187-95.

OBJECTIVE: 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. **METHODS:** 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. **RESULTS:** 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%. **CONCLUSION:** This heptavalent pneumococcal conjugate appears to be highly effective in preventing invasive disease in young children and to have a significant impact on otitis media.

Observed effectiveness/ Vaccine impact

Millar EV, O'Brien KL, Watt JP, Bronsdon MA, Dallas J, Whitney CG, Reid R, Santosham M. Effect of community-wide conjugate pneumococcal vaccine use in infancy on nasopharyngeal carriage through 3 years of age: a cross-sectional study in a high-risk population. *Clin Infect Dis.* 2006 Jul 1;43(1):8-15.

BACKGROUND: A 7-valent pneumococcal conjugate vaccine (PnCRM7) has been shown to be highly effective in preventing invasive pneumococcal disease. Pneumococcal conjugate vaccines also protect against nasopharyngeal carriage of vaccine serotypes, but the duration of protection against nasopharyngeal carriage is not known. **METHODS:** A group-randomized efficacy trial of PnCRM7 (vaccine serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) was conducted on the Navajo and White Mountain

Apache reservations from April 1997 to October 2000. A group C meningococcal conjugate vaccine was used as the control vaccine. Infants enrolled between 6 weeks and 7 months of age received 3 doses of vaccine 2 months apart and a fourth dose at 12-15 months of age. Vaccinees were enrolled in a nasopharyngeal carriage study from February 2001 to January 2002 to assess the duration of protection against pneumococcal carriage induced by PnCRM7. **RESULTS:** We included 749 children in the analysis, including 468 children vaccinated with PnCRM7 and 281 children vaccinated with group C meningococcal conjugate vaccine. The median age was 3.3 years (range, 1-7 years), and the median time since last dose of study vaccine was 27 months (range, 12-48 months). Frequencies of overall pneumococcal carriage were similar among PnCRM7 and group C meningococcal conjugate vaccine recipients (63.9% vs. 60.5%, respectively). The absolute frequency of vaccine-type pneumococcal carriage was lower among PnCRM7 recipients (10.3%) than among controls (17.1%; $P = .01$). This reduction was offset by an increase of nonvaccine-type pneumococcal carriage among PnCRM7 recipients (39.2% vs. 29.8%; $P = .01$). **CONCLUSION:** Community-wide PnCRM7 vaccination in infancy reduces the prevalence of vaccine-type carriage and increases the prevalence of nonvaccine-type carriage through at least 3 years of age.

Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold A, Thomas AR, Harrison LH, Bennett NM, Farley MM, Facklam RR, Jorgensen JH, Besser J, Zell ER, Schuchat A, Whitney CG; Active Bacterial Core Surveillance of the Emerging Infections Program Network. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N Engl J Med*. 2006 Apr 6;354(14):1455-63. Erratum in: *N Engl J Med*. 2006 Aug 10;355(6):638.

BACKGROUND: Five of seven serotypes in the pneumococcal conjugate vaccine, introduced for infants in the United States in 2000, are responsible for most penicillin-resistant infections. We examined the effect of this vaccine on invasive disease caused by resistant strains. **METHODS:** We used laboratory-based data from Active Bacterial Core surveillance to measure disease caused by antibiotic-nonsusceptible pneumococci from 1996 through 2004. Cases of invasive disease, defined as disease caused by pneumococci isolated from a normally sterile site, were identified in eight surveillance areas. Isolates underwent serotyping and susceptibility testing. **RESULTS:** Rates of invasive disease caused by penicillin-nonsusceptible strains and strains not susceptible to multiple antibiotics peaked in 1999 and decreased by 2004, from 6.3 to 2.7 cases per 100,000 (a decline of 57 percent; 95 percent confidence interval, 55 to 58 percent) and from 4.1 to 1.7 cases per 100,000 (a decline of 59 percent; 95 percent confidence interval, 58 to 60 percent), respectively. Among children under two years of age, disease caused by penicillin-nonsusceptible strains decreased from 70.3 to 13.1 cases per 100,000 (a decline of 81 percent; 95 percent confidence interval, 80 to 82 percent). Among persons 65 years of age or older, disease caused by penicillin-nonsusceptible strains decreased from 16.4 to 8.4 cases per 100,000 (a decline of 49 percent). Rates of resistant disease caused by vaccine serotypes fell 87 percent. An increase was seen in disease caused by serotype 19A, a serotype not included in the vaccine (from 2.0 to 8.3 per 100,000 among children under two years of age). **CONCLUSIONS:** The rate of antibiotic-resistant invasive pneumococcal infections decreased in young children and

older persons after the introduction of the conjugate vaccine. There was an increase in infections caused by serotypes not included in the vaccine.

Whitney CG, Pilishvili T, Farley MM, Schaffner W, Craig AS, Lynfield R, Nyquist AC, Gershman KA, Vazquez M, Bennett NM, Reingold A, Thomas A, Glode MP, Zell ER, Jorgensen JH, Beall B, Schuchat A. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet. 2006 Oct 28;368(9546):1495-502

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.

Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease--United States, 1998-2003. MMWR Morb Mortal Wkly Rep. 2005 Sep 16;54(36):893-7.

Streptococcus pneumoniae (pneumococcus) is a leading cause of pneumonia and meningitis in the United States and disproportionately affects young children and the elderly. In 2000, a 7-valent pneumococcal conjugate vaccine (PCV7) was licensed in the United States for routine use in children aged <5 years. Surveillance data from 2001 and 2002 indicated substantial declines in invasive pneumococcal disease (IPD) in children and adults compared with prevaccine years. This report updates assessment of the impact of PCV7 on IPD through 2003 by using population-based data from the Active Bacterial Core surveillance (ABCs) of the Emerging Infections Program Network, a cooperative surveillance program conducted by several state health departments and CDC. The results of this analysis indicated that 1) routine vaccination

of young children with PCV7 continued to result in statistically significant declines in incidence of IPD through 2003 in the age group targeted for vaccination and among older children and adults, 2) the vaccine prevented more than twice as many IPD cases in 2003 through indirect effects on pneumococcal transmission (i.e., herd immunity) than through its direct effect of protecting vaccinated children, and 3) increases in disease caused by pneumococcal serotypes not included in the vaccine (i.e., replacement disease) occurred in certain populations but were small compared with overall declines in vaccine-serotype disease. Ongoing surveillance is needed to assess whether reductions in vaccine-serotype IPD are sustained and whether replacement disease will erode the substantial benefits of routine vaccination.

Kellner JD, Church DL, MacDonald J, Tyrrell GJ, Scheifele D. Progress in the prevention of pneumococcal infection. *Canadian Med Assoc J* 2005;173:1149-51.

No abstract available.

O'Brien KL, Dagan R. The potential indirect effect of conjugate pneumococcal vaccines. *Vaccine*. 2003 May 16;21(17-18):1815-25

Pneumococcal conjugate vaccines are highly effective in preventing invasive disease in infants and young children, with favorable safety and immunogenicity profiles. These pediatric vaccines have also shown efficacy in reducing cases of non-invasive disease (i.e. otitis media, pneumonia). Recently, pneumococcal conjugate vaccines have demonstrated additional protective qualities that may enhance their use worldwide. For example, they can reduce nasopharyngeal acquisition of vaccine-specific serotypes of *Streptococcus pneumoniae*, which may in turn reduce the incidence of pneumococcal disease among non-vaccinated individuals; this is termed indirect or herd immunity. Although the emergence of antibiotic-resistant strains has complicated disease management, pneumococcal conjugate vaccines have been shown to protect against pneumococcal disease caused by such strains because most antibiotic-resistant strains are of the serotypes included in these vaccines. Thus, widespread use of these conjugate vaccines may prevent disease by providing both direct and indirect immunity, and may reduce the use of antibiotics and the development of antibiotic resistance worldwide.

Dagan R, Givon-Lavi N, Zamir O, Sikuler-Cohen M, Guy L, Janco J, Yagupsky P, Fraser D. Reduction of nasopharyngeal carriage of *Streptococcus pneumoniae* after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers. *J Infect Dis* 2002 Apr 1;185(7):927-36.

A double-blind, randomized study involving 264 toddlers attending day care centers was conducted to document the effect of a 9-valent pneumococcal conjugate vaccine on the carriage rate of pneumococci. Of 3750 cultures done on nasopharyngeal samples obtained from subjects during a 2-year follow-up period after vaccination, 65% were positive for *Streptococcus pneumoniae*. In all age windows, the rate of carriage of vaccine-type pneumococci was lower among subjects who received the pneumococcal vaccine than among control subjects, because the acquisition rate was lower in the

former group. The effect was most pronounced among subjects aged < or =36 months. The sample size enabled us to study protection against carriage of *S. pneumoniae* serotypes 6B, 9V, 14, 19F, and 23F; significant protection against all serotypes except 19F was seen in the pneumococcal-vaccine group. The rate of carriage of serotype 6A (not included in the vaccine) was also reduced significantly, but the rate of carriage of serotype 19A (not included in the vaccine) was not. The rate of carriage of non-vaccine-type pneumococci (excluding serotype 6A) was higher in the pneumococcal-vaccine group than in the control group.

Safety

WHO's Global Advisory Committee on Vaccine Safety (GACVS). Meeting in Geneva Nov 29-30, 2006. Safety of pneumococcal conjugate vaccine (p.24). Weekly Epidemiological Record (WER) 2007,82,17-24.

No abstract

Wise RP, Iskander J, Pratt RD, Campbell S, Ball R, Pless RP, Braun MM. Postlicensure safety surveillance for 7-valent pneumococcal conjugate vaccine. JAMA. 2004 Oct 13;292(14):1702-10.

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.

Special populations

Madhi SA, Kuwanda L, Cutland C, Klugman KP. The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and -uninfected children. Clin Infect Dis. 2005 May 15;40(10):1511-18.

INTRODUCTION: Pneumococcal conjugate vaccine (PnCV) may be used as a probe to define the burden of pneumococcal disease and better characterize the clinical presentation of pneumococcal pneumonia. **METHODS:** This study used a 9-valent PnCV to define different end points of vaccine efficacy and the preventable burden of pneumococcal pneumonia in 39,836 children who were randomized in a double-blind, placebo-controlled trial in South Africa. **RESULTS:** Whereas the point-estimate of vaccine efficacy was greatest when measured against the outcome of vaccine-serotype specific pneumococcal bacteremic pneumonia (61%; $P = .01$), the sensitivity of blood culture to measure the burden of pneumococcal pneumonia prevented by vaccination was only 2.6% in human immunodeficiency virus (HIV)-uninfected children and 18.8% in HIV-infected children. Only 37.8% of cases of pneumococcal pneumonia prevented by PnCV were detected by means of chest radiographs showing alveolar consolidation. A clinical diagnosis of pneumonia provided the best estimate of the burden of pneumococcal pneumonia prevented through vaccination in HIV-uninfected children (267 cases prevented per 100,000 child-years) and HIV-infected children (2573 cases prevented per 100,000 child-years). **CONCLUSION:** Although outcome measures with high specificity, such as bacteremic pneumococcal pneumonia, provide a better estimate as to vaccine efficacy, the burden of disease prevented by vaccination is best evaluated using outcome measures with high sensitivity, such as a clinical diagnosis of pneumonia.

O'Brien KL, Swift AJ, Winkelstein JA, Santosham M, Stover B, Luddy R, Gootenberg JE, Nold JT, Eskenazi A, Snader SJ, Lederman HM. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM(197) among infants with sickle cell disease. Pneumococcal Conjugate Vaccine Study Group. Pediatrics. 2000 Nov;106(5):965-72

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.15 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.15 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.

Vaccine Schedule

Goldblatt D, Southern J, Ashton L, Richmond P, Burbidge P, Tasevska J, Crowley-Luke A, Andrews N, Morris R, Borrow R, Cartwright K, Miller E. Immunogenicity and boosting after a reduced number of doses of a pneumococcal conjugate vaccine in infants and toddlers. *Pediatr Infect Dis J.* 2006 Apr;25(4): 312-9

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.

Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis. 1999 Oct;180(4):1171-6.

The safety, immunogenicity, and impact on carriage of a nonvalent pneumococcal vaccine given at ages 6, 10, and 14 weeks were examined in a double-blind, randomized, placebo-controlled trial in 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 polyribosylribitol phosphate (geometric mean titer, 11.62 microg/mL) and diphtheria (1.39 IU/mL) antibodies were significantly higher in children receiving pneumococcal conjugate, compared with placebo recipients (4.58 microgram/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.

Cost-effectiveness analyses

Sinha A, Levine O, Knoll MD, Muhib F, Lieu TA. Cost-effectiveness of pneumococcal conjugate vaccination in the prevention of child mortality: an international economic analysis. Lancet. 2007 Feb 3;369 (9559):389-96.

BACKGROUND: Routine vaccination of infants against Streptococcus pneumoniae (pneumococcus) needs substantial investment by governments and charitable organisations. Policymakers need information about the projected health benefits, costs, and cost-effectiveness of vaccination when considering these investments. Our aim was to incorporate these data into an economic analysis of pneumococcal vaccination of infants in countries eligible for financial support from the Global Alliance for Vaccines & Immunization (GAVI). **METHODS:** We constructed a decision analysis model to compare pneumococcal vaccination of infants aged 6, 10, and 14 weeks with no vaccination in the 72 countries that were eligible as of 2005. We used published and unpublished data to estimate child mortality, effectiveness of pneumococcal conjugate vaccine, and immunisation rates. **FINDINGS:** Pneumococcal vaccination at the rate of diphtheria-tetanus-pertussis vaccine coverage was projected to prevent 262,000 deaths per year (7%) in children aged 3-29 months in the 72 developing countries studied, thus averting 8.34 million disability-adjusted life years (DALYs) yearly. If every child could be reached, up to 407,000 deaths per year would be prevented. At a vaccine cost of International 5 dollars per dose, vaccination would have a net cost of 838 million dollars, a cost of 100 dollars per DALY averted. Vaccination at this price was projected to be highly cost-effective in 68 of 72 countries when each country's per head gross domestic product per DALY averted was used as a benchmark. **INTERPRETATION:** At a vaccine cost of between 1 dollar and 5 dollars per dose, purchase and accelerated

uptake of pneumococcal vaccine in the world's poorest countries is projected to substantially reduce childhood mortality and to be highly cost-effective.

Ray GT, Whitney CG, Fireman BH, Ciuryla V, Black SB.

Cost-effectiveness of pneumococcal conjugate vaccine: evidence from the first 5 years of use in the United States incorporating herd effects. *Pediatr Infect Dis J.* 2006 Jun;25(6):494-501.

BACKGROUND: Pneumococcal conjugate vaccine (PCV) has been in routine use in the United States for 5 years. Prior U.S. cost-effectiveness analyses have not taken into account the effect of the vaccine on nonvaccinated persons. **METHODS:** We revised a previously published model to simulate the effects of PCV on children vaccinated between 2000 and 2004, and to incorporate the effect of the vaccine in reducing invasive pneumococcal disease (IPD) in nonvaccinated persons during those years. Data from the Active Bacterial Core Surveillance of the Centers for Disease Control and Prevention (2000-2004) were used to estimate changes in the burden of IPD in nonvaccinated adults since the introduction of PCV (compared with the baseline years 1997-1999). Results combined the simulated effects of the vaccine on the vaccinated and nonvaccinated populations. **RESULTS:** Before incorporating herd effects in the model, the PCV was estimated to have averted 38,000 cases of IPD during its first 5 years of use at a cost of dollar 112,000 per life-year saved. After incorporating the reductions in IPD for nonvaccinated individuals, the vaccine averted 109,000 cases of IPD at a cost of dollar 7500 per life-year saved. When the herd effect was assumed to be half that of the base case, the cost per life-year saved was dollar 18,000. **CONCLUSIONS:** IPD herd effects in the nonvaccinated population substantially reduce the cost, and substantially improve the cost-effectiveness, of PCV. The cost-effectiveness of PCV in actual use has been more favorable than predicted by estimates created before the vaccine was licensed.

Melegaro A, Edmunds WJ. Cost- effectiveness analysis of pneumococcal conjugate vaccination in England and Wales. *Vaccine.* 2004 Oct 22;22(31-32):4203-14.

AIM: To establish whether universal vaccination of infants with the pneumococcal conjugate vaccine is likely to be cost-effective from the perspective of the health care provider (NHS). **METHOD:** Two hypothetical cohorts--one vaccinated and one unvaccinated--were followed over their lifetime, and the expected net costs and benefits (measured in terms of life-years and quality adjusted life years (QALY) gained) were compared in the two cohorts. The impact of indirect effects of the vaccine, such as herd immunity and serotype replacement, were investigated and their relative importance was assessed by performing univariate sensitivity analysis and multivariate Monte Carlo simulations. **RESULTS:** Under base-case assumptions (no herd immunity and no serotype replacement) the programme is not expected to be cost-effective from the NHS perspective at the current price of the vaccine (assumed 30 pounds per dose, three-dose programme). A reduction of the cost of the vaccine to half of its current level could bring the cost per QALY gained within normally acceptable ranges. If the burden of disease is significantly underestimated by current surveillance systems, then the cost per QALY gained approaches acceptable levels at the current vaccine price. Herd immunity

may substantially reduce the burden of pneumococcal disease, particularly of pneumonia among the elderly, leading to a significant improvement in the cost per life year and QALY gained. Serotype replacement would partly offset these benefits, although only with a complete substitution of vaccine types with non-vaccine types and a low level of herd immunity, would pneumococcal vaccination programme would not be cost-effective. **CONCLUSIONS:** Conclusions on the cost-effectiveness of pneumococcal conjugate vaccine are sensitive to assumptions regarding the current burden of pneumococcal disease and the future impact that vaccination will have in the unvaccinated and on the future serotype distribution. This study quantifies, for the first time, how these indirect effects may change the cost-effectiveness of pneumococcal vaccination.

Relevant WHO document:

Meeting of the immunization Strategic Advisory Group of Experts Nov 2006. Conclusions and recommendations. Pneumococcal conjugate vaccines (pp 8-10). Weekly Epidemiological Record (WER) No. 1/2, 2007, 82, 1-16.