WHO Position Paper on *Haemophilus influenzae* Vaccines

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Selected references

EPIDEMIOLOGY

Gessner BD, Sutanto A, Linehan M, Djelantik IG, Fletcher T, Gerudug IK, Ingerani, Mercer D, Moniaga V, Moulton LH, Moulton LH, Mulholland K, Nelson C, Soemohardjo S, Steinhoff M, Widjaya A, Stoeckel P, Maynard J, Arjoso S. Incidences of vaccine-preventable *Haemophilus influenzae* type b pneumonia and meningitis in Indonesian children: hamlet-randomised vaccine-probe trial. Lancet. 2005 Jan 1-7;365(9453):43-52.

BACKGROUND: Most studies of *Haemophilus influenzae* type b (Hib) disease in Asia have found low rates, and few Asian countries use Hib vaccine in routine immunisation programmes. Whether Hib disease truly is rare or whether many cases remain undetected is unclear. METHODS: To estimate incidences of vaccine-preventable Hib pneumonia and meningitis among children younger than 2 years in Lombok, Indonesia, during 1998-2002, we undertook a hamlet-randomised, controlled, double-blind vaccine-probe study (818 hamlets). Children were immunised (WHO schedule) with diphtheria, tetanus, pertussis (DTP) or DTP-PRP-T (Hib conjugate) vaccine. Vaccine-preventable disease incidences were calculated as the difference in rates of clinical outcomes between DTP and DTP-PRP-T groups. Analyses included all children who received at least one vaccine dose. FINDINGS: We enrolled 55073 children: 28147 were assigned DTP-PRP-T and 26926 DTP. The proportion of pneumonia outcomes prevented by vaccine ranged from less than 0 to 4.8%. Calculated incidences of vaccine-preventable Hib disease (per 10(5) child-years of observation) for outcome categories were: substantial alveolar consolidation or effusion, less than zero (-43 [95% CI -185 to 98]); all severe pneumonia, 264 (95% CI less than zero to 629); all clinical pneumonia, 1561 (270 to 2853); confirmed Hib meningitis, 16 (1.4 to 31); meningitis with cerebrospinal-fluid findings consistent with a bacterial aetiology, 67 (22 to 112); and admission for suspected meningitis or presenting to a clinic with convulsions, 158 (42 to 273). INTERPRETATION: Hib vaccine did not prevent the great majority of pneumonia cases, including those with alveolar consolidation. These results do not support a major role for Hib vaccine in overall pneumonia-prevention programmes. Nevertheless, the study identified high incidences of Hib meningitis and pneumonia; inclusion of Hib vaccine in routine infant immunisation programmes in Asia deserves consideration.

Peltola H. Worldwide *Haemophilus influenzae* type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. Clin Microbiol Rev. 2000 Apr;13(2):302-17.

Vaccination against *Haemophilus influenzae* type b (Hib) diseases began a quarter of a century ago with a polysaccharide vaccine; this vaccine was followed by four different conjugates 10 years later. In this review, the burden of global Hib disease is quantified following this 25-year period of vaccine availability to determine the potential impact of conjugate vaccines. This task was accomplished by analysis of data available in 10 languages in 75 geographical regions of over 50 countries. All severe Hib diseases, not only meningitis, were characterized, and special attention was paid to the most vulnerable age group, i.e., children aged 0 to 4 years. Prior to vaccination, the weighted worldwide incidence of meningitis in patients younger than 5 years was 57/100,000, and for all Hib diseases except nonbacteremic pneumonia, it was 71/100,000, indicating 357,000 and 445,000 cases per year, respectively. At least 108,500 of these children died. For all age groups combined, there were 486,000 cases of Hib disease, excluding pneumonia, with 114,200 deaths and probably an equal number of sequelae per annum. If the figures for nonbacteremic pneumonia are included, a conservative estimate is that over 2.2 million cases of infection and 520,000 deaths from Hib disease occurred worldwide, but the true numbers might have been greater. Despite these large numbers and availability of safe and efficacious vaccines, only 38,000 cases annually are prevented-a meager 8% or less than a 2% reduction in cases, depending on whether nonbacteremic pneumonia is included in the calculations. Although vaccination has had great success in some affluent countries, the current level of activity has had a very small impact globally. The use of conjugates, preferably with a reduced number of doses and in combination with other vaccines or perhaps in fractional doses, should be extended to less privileged countries, where most Hib disease occurs.

Levine OS, Lagos R, Munoz A, Villaroel J, Alvarez AM, Abrego P, Levine MM. Defining the burden of pneumonia in children preventable by vaccination against *Haemophilus influenzae* type b. Pediatr Infect Dis J. 1999 Dec;18(12):1060-4.

OBJECTIVES: To determine the burden of pneumonia requiring hospitalization in infants and young children preventable by vaccination against *Haemophilus influenzae* type b (Hib). DESIGN: Vaccination centers in Santiago, Chile, were randomly selected to administer PRP-T, an Hib conjugate vaccine, combined with diphtheria-tetanus toxoids-pertussis (DTP) vaccine or DTP alone. SUBJECTS: Infants who received > or =2 doses of DTP or DTP and Hib conjugate vaccine combined. MAIN OUTCOME MEASURES: Pneumonia episodes leading to hospitalization accompanied by indicators of likely bacterial infection including radiologic evidence of alveolar consolidation or pleural effusion, an elevated erythrocyte sedimentation rate (> or =40 mm/h) or bronchial breath sounds on auscultation. RESULTS: In participants age 4 to 23 months, PRP-T reduced the incidence of pneumonia associated with alveolar consolidation or pleural effusion by 22% (95% confidence interval, -7 to 43) from 5.0 to 3.9 episodes per 1000 children per year. When the pneumonia case definition included any of the following, alveolar consolidation, pleural effusion, erythrocyte sedimentation rate > or =40 mm/h or bronchial breath sounds, PRP-T provided 26% protection (95% confidence interval, 7 to 44) and prevented 2.5 episodes per 1000 children per year. CONCLUSIONS: Hib vaccine provides substantial protection against nonbacteremic pneumonia, particularly those cases with alveolar consolidation, pleural effusion or other signs of likely bacterial infection. Hib vaccination prevented approximately 5 times as many nonbacteremic pneumonia cases in infants as meningitis cases, thus

indicating that the largest part of the effect of Hib vaccination might be undetectable by routine culture methods.

Yang Y, Shen X, Jiang Z, Liu X, Leng Z, Lu D, Rao J, Liu J, Chang L. Study on *Haemophilus influenzae* type b diseases in China: the past, present and future. Pediatr Infect Dis J. 1998 Sep;17(9 Suppl):S159-65.

Meningitis caused by *Haemophilus influenzae* type b (Hib) is a common and serious disease for which there now are WHO-certified vaccines that are recommended for universal infant immunization in North America and European countries. If these vaccines are to be recommended in Asia, it is necessary to know the incidence, age distribution and clinical outcome of Hib meningitis and other systemic infections in this region. Data on Hib disease in China are scanty. Hib meningitis was common during the 1950s in China, accounting for up to 16% of all of pyogenic meningitis (up to 38% of cases were caused by unknown pathogens), despite severe epidemics of meningococcal meningitis during that period. Since 1989 we have conducted hospital- and community-based etiologic and epidemiologic studies of bacterial meningitis. Hib accounts for 30 to 50% of bacterial meningitis in China. The incidence of Hib meningitis in Hefei City was 10.4 per 100000 children <5 years, a result relatively lower than in the West but higher than the rate of 2.7 found in a retrospective study in Hong Kong. Pneumonia is the primary cause of death for Chinese children. From 1991 to 1993 the average mortality of children<5 years because of pneumonia was 1563.2 per 100000. To achieve the goal of reducing the death rate of children by one-third by the year 2000, greater efforts should be made to reduce the mortality of children with pneumonia. Our preliminary study showed that about one-fourth to one-third of cases of pneumonia in Chinese children might be caused by Hib. Therefore Hib vaccination for infants and children in China might be an effective and valuable procedure to achieve the goal.

John TJ, Cherian T, Raghupathy P. *Haemophilus influenzae* disease in children in India: a hospital perspective. Pediatr Infect Dis J. 1998 Sep;17(9 Suppl):S169-71.

We review and summarize published information on diseases caused by *Haemophilus influenzae* in India and unpublished data from our center covering more than three decades. Since the mid-1950s *H. influenzae* has been the most common cause of pyogenic meningitis in children admitted to our hospital, accounting for one-third to one-half of cases. Information from other centers in India has been scanty; the lower frequency of isolation of *Haemophilus* in studies in some centers may be caused by unsatisfactory media and culture methods. The annual numbers of admissions for pyogenic meningitis in our hospital have been quite similar to the numbers of cases of poliomyelitis. Assuming that the similar numbers of children hospitalized with these two diseases indicate similar incidence rates in the community and taking into account the frequency of *Haemophilus* isolations in pyogenic meningitis, we estimate that there may be as many as 75 to 100 cases of meningitis caused by this organism per year per 100000 children <5 years of age. Although pneumonia caused by *H. influenzae* has been recognized in a few studies, information is too scanty to attempt the estimation of incidence. Pus-producing infections caused by *Haemophilus* are rare. Epiglottitis caused

by *Haemophilus* does not seem to occur in India. In recent years we have found that most invasive *Haemophilus* infections are caused by *H. influenzae* type b (Hib); other types or untypable strains are infrequent. An increasing prevalence of resistance to chloramphenicol and ampicillin has been recognized in our center and elsewhere. Thus from a hospital perspective, primary prevention by using Hib vaccine seems to be a rational and beneficial intervention. Community-based studies to measure the disease burden of Hib are urgently needed for a more satisfactory assessment of the need for, and cost benefit of, Hib immunization of all infants.

MICROBIOLOGY

Cerquetti M, Cardines R, Ciofi Degli Atti ML, Giufre M, Bella A, Mastrantonio P, Slack M. Presence of multiple copies of the capsulation b locus in invasive *Haemophilus influenzae* type b (Hib) strains isolated from children with Hib conjugate vaccine failure. J Infect Dis. 2005 Sep 1;192(5):819-23.

Most invasive *Haemophilus influenzae* type b strains possess a duplication of the capsulation locus. Further amplification resulting in as many as 5 copies has been described. To verify whether amplification is involved in vaccine failure, the number of copies of the locus was determined by Southern blotting in 90 strains from children with true vaccine failure (TVF) between 1993 and 1999 and in 139 strains from unvaccinated children (50 collected between 1993 and 1999 and 89 collected between 1991 and 1992, before routine immunization was introduced). A significantly greater proportion of strains from TVFs contained multiple copies, compared with strains from control children (24% vs. 10%; P = .0379), which suggests that amplification of the capb locus may be a contributory factor in vaccine failure. The presence of multiple-copy strains was associated with disease other than meningitis.

de Almeida AE, de Filippis I, Abreu AO, Ferreira DG, Gemal AL, Marzochi KB. Occurrence of *Haemophilus influenzae* strains in three Brazilian states since the introduction of a conjugate *Haemophilus influenzae* type b vaccine. Braz J Med Biol Res. 2005 May;38(5):777-81.

Few vaccines in history have induced such a dramatic decline in incidence over such a short period of time as the *Haemophilus influenzae* type b (Hib) conjugate. This vaccine was introduced in 1988 in the United States, but only in 1999 was Hib immunization introduced by the Brazilian Ministry of Health as part of the routine infant National Immunization Program. The authors analyzed 229 *H. influenzae* (Hi) isolates from Public Health Laboratories in three Brazilian states: Pernambuco (Northeast, N = 54), Santa Catarina (South, N = 19), and Rio de Janeiro (Southeast, N = 156). The isolates were collected from Brazilian children 0-10 years of age with meningitis and other infections from 1990 to 2003 and were part of the research collection of the National Institute of Quality Control in Health, FIOCRUZ. Bacterial strains were characterized by serotyping and biotyping. During the pre-vaccination period the prevalence infection due to Hib was of 165 isolates and only 2 non-b Hi among all the notified meningitis infections caused by Hi. Our results showed a significant decrease in the prevalence of

Hib meningitis from 165 to 33 isolates after 1999. However, during the post-vaccination period of 2001-2003 we observed an increase in the number of non-b Hi isolates: only 2 non-b strains isolated from 1990 to 1999 and 29 from 1999 to 2003. Based on the present data, the authors emphasize the need for more sensitive epidemiological and bacteriological studies aiming the improvement of the available Hib vaccine, in order to protect the susceptible population to infections due to other serological types of Hi and the reevaluation of immunization schedules used by the National Immunization Program.

IMMUNOLOGY

Huebner RE, Nicol M, Mothupi R, Kayhty H, Khomo E, Klugman KP. Dose response of CRM197 and tetanus toxoid-conjugated *Haemophilus influenzae* type b vaccines. Vaccine. 2004 Dec 21;23(6):802-6.

High vaccine cost has limited use of conjugate vaccines in the developing world where the disease burden is greatest. Fixed fractional doses of *Haemophilus influenzae* type b (Hib) vaccines have been shown to be immunogenic, but dose responses of these vaccines in humans are needed to determine the lowest immunogenic dose as an option for lowering vaccine cost. We randomized children to receive one of five doses (0.625, 1.25, 2.5, 5.0 and 10 microg) of either a diphtheria CRM197 or tetanus toxoid-conjugated Hib vaccine. The children received a primary three-dose series at 6, 10, and 14 weeks of age and a booster dose at 9 months. Anti-PRP IgG antibodies were measured at each vaccination, at 18 weeks, and at one week following the booster dose. Concentrations of > or =1.25 microg of HibCRM197 vaccine produced mean anti-PRP responses at 18 weeks of > or =5.72 microg/ml and > or =0.15 microg/ml was achieved in >98% of the children with at least 79% reaching anti-PRP concentrations of > or =1.0 microg/ml. Concentrations of > or =1.25 microg of Hib-tetanus vaccine produced mean anti-PRP responses at 18 weeks of > or =8.63 microg/ml and > or =0.15 microg/ml was achieved in 100% of the children with at least 88.9% reaching anti-PRP concentrations of > or =1.0 microg/ml. While mean antibody concentrations after either vaccine decreased over time, the proportion of children with antibody levels of > or =0.15 microg/ml had not changed significantly at the 9 month measurement. Immunologic memory was demonstrated by significant increases in mean antibody concentrations one week after the booster dose for doses > or =1.25 microg of HibCRM197 and Hib-tetanus to mean concentrations > or =37.71 and 16.07 microg/ml, respectively. There were no differences in antibody responses for vaccine doses > or =1.25 microg of the same vaccine or between the same concentrations of the two different vaccines. Our data suggest that doses of these vaccines of > or =1.25 microg may be sufficient to stimulate an immune response that offers both short and longer term protection from invasive Hib disease.

Kelly DF, Moxon ER, Pollard AJ. *Haemophilus influenzae type* b conjugate vaccines. Immunology. 2004 Oct;113(2):163-74.

Haemophilus influenzae type b (Hib) is one of the leading causes of invasive bacterial infection in young children worldwide. During childhood, acquisition of antibody

directed against the polysaccharide capsule of the organism, presumably as a result of asymptomatic carriage, confers protection and disease is much less common after the age of 4 years. Like other polysaccharides, the polyribosyl ribitol phosphate (PRP) of the Hib capsule is a T-independent antigen and not immunogenic when administered as a vaccine in infancy. Because the highest rates of disease occur in the first 2 years of life, efficacious Hib vaccines have been designed by covalently linking the PRP capsule to a carrier protein that recruits T-cell help for the polysaccharide immune response and induces anti-PRP antibody production even in the first 6 months of life. Introduction of Hib protein-polysaccharide conjugate vaccines into many industrialized countries over the past 15 years has resulted in the virtual elimination of invasive Hib disease. However, despite the success of the vaccine programme several factors may interfere with the effectiveness of the vaccine in the routine programme, as observed in the UK recently. Such factors may include interference with other concomitant vaccines, waning immunity in the absence of booster doses of vaccine, and reduced natural boosting as a result of decreased transmission of the organism. However, the burden of disease remains highest in resource-poor countries and urgent efforts are needed to provide the benefits of this vaccine for children living in regions where it cannot be used for economic and logistical reasons.

Slack MH, Schapira D, Thwaites RJ, Burrage M, Southern J, Goldblatt D, Miller E. Responses to a fourth dose of *Haemophilus influenzae* type B conjugate vaccine in early life. Arch Dis Child Fetal Neonatal Ed. 2004 May;89(3):F269-71.

OBJECTIVE: To describe the immune response of preterm infants, with a reduced response to primary *Haemophilus influenzae* type B (Hib) immunisation, to a fourth dose of Hib conjugate vaccine given in early life. DESIGN: Prospective observational study. SETTING: Five Wessex Neonatal Units. PATIENTS: Infants born at < 32 weeks and immunised with three doses of combined acellular pertussis-Hib vaccine, with a Hib IgG geometric mean concentration (GMC) < 1.0 microg/ml after these primary immunisations. INTERVENTIONS: An additional fourth dose of Hib conjugate vaccine given before 1 year of age. Blood taken to assess Hib IgG concentration and avidity after immunisation. MAIN OUTCOME MEASURES: Hib IgG GMC and avidity index. RESULTS: Ninety six infants (mean gestational age at birth 29.1 weeks) received a fourth dose of Hib at a mean age of 7.8 months. Hib IgG GMC after the primary immunisations was 0.17 microg/ml (95% confidence interval (CI) 0.14 to 0.20) rising to 4.68 microg/ml (95% CI 3.36 to 6.57) after the fourth dose ($p < 0.0001$). The IgG response to the fourth dose correlated positively with the response after the primary immunisations ($p < 0.001$). Hib IgG geometric mean avidity index (GMAI) after the primary immunisations was 30.87 (95% CI 20.40 to 46.73). This increased to 124.73 (95% CI 109.93 to 141.51) after the fourth dose ($p < 0.0001$). CONCLUSION: Preterm infants with very low IgG responses to Hib after primary immunisations with a combined acellular pertussis-Hib vaccine mount a good response to a fourth dose of Hib. This study suggests that all infants will benefit from a fourth dose of Hib, regardless of the age at which it is given.

Makela PH, Kayhty H, Leino T, Auranen K, Peltola H, Ekstrom N, Eskola J. Long-term persistence of immunity after immunisation with *Haemophilus influenzae* type b conjugate vaccine. Vaccine. 2003 Dec 12;22(2):287-92.

Although *Haemophilus influenzae* type b (Hib) conjugate vaccines, after licensure in 1987, are now recommended for world-wide use, the duration of protective immunity afforded by them is not known. We therefore assessed the immunogenity at 9-10 years of age in 37 children who had received the first Hib conjugate, PRP-D, in infancy (the Hib-conjugate group) and were now given a dose of Hib polysaccharide (PS) as a test vaccine. The anti-Hib PS antibodies (Hib-ab) were measured before and after this test vaccination, and the values compared to those in 37 control children who had not previously received any Hib vaccine and in 13 children who had received Hib PS vaccine in infancy (the Hib-PS group). Prior to the test vaccination, the Hib-ab concentrations in the Hib-conjugate group were 3.6-fold higher than in the control group. After the test vaccination, the Hib-conjugate group had higher total Hib-ab concentrations, higher proportion of IgG and higher avidity of Hib-ab than the control or the Hib-PS group, suggesting persisting immunological memory in a Hib-c group. A mathematical model, including memory, predicted accurately the Hib-ab concentrations, which are maintained through anamnestic responses to intervening stimuli (Hib or cross-reacting bacteria).

Madhi SA, Petersen K, Khoosal M, Huebner RE, Mbelle N, Mothupi R, Saloojee H, Crewe-Brown H, Klugman KP. Reduced effectiveness of *Haemophilus influenzae* type b conjugate vaccine in children with a high prevalence of human immunodeficiency virus type 1 infection. Pediatr Infect Dis J. 2002 Apr;21(4): 315-21.

BACKGROUND: *Haemophilus influenzae* type b (Hib) conjugate vaccines have successfully reduced the burden of invasive Hib disease in developed countries; however, their effectiveness in countries with a high incidence of pediatric HIV-1 is unknown. METHODS: The effectiveness of Hib conjugate vaccine was prospectively evaluated in South African children. The burden of invasive Hib disease in children < 1 year old was compared in 2 cohorts. The first cohort included 22,000 African children born in 1997 [969 (4.45%) of whom were estimated to be HIV-1-infected] who were not vaccinated with Hib conjugate vaccine. This group was compared with 19,267 children [1162 (6.03%) of whom were estimated to be HIV-1 infected] vaccinated at 6, 10 and 14 weeks of age with an Hib conjugate vaccine [TETRAMUNE (polyribosylribitol phosphate-CRM(197)-diphtheria-tetanus toxoids-whole cell pertussis)] between March, 1998, and June, 1999. RESULTS: The estimated burden of invasive Hib disease in nonimmunized HIV-1-infected children < 1 year of age was 5.9-fold [95% confidence interval (95% CI), 2.7 to 12.6] higher than in HIV-1-uninfected children. The overall estimated effectiveness of Hib conjugate vaccine in fully vaccinated children <1 year of age was 83.2% (95% CI 60.3 to 92.9). Vaccine effectiveness was significantly reduced in HIV-1-infected [43.9% (95% CI -76.1 to 82.1)] compared with uninfected children [96.5% (95% CI 74.4 to 99.5); P < 10(-5)]. Among three of the fully vaccinated HIV-1-infected children who developed invasive Hib disease, the anti-Hib polyribosylribitol phosphate serum antibody concentrations were 0.23, 0.25 and 0.68 microg/ml.

CONCLUSION: Although the Hib conjugate vaccine was less effective among HIV-1-infected than among uninfected children, it was 83% effective in preventing overall invasive Hib disease and therefore should be considered for inclusion in the routine vaccination schedule by other African countries.

Fernandez J, Levine OS, Sanchez J, Balter S, LaClaire L, Feris J, Romero-Steiner S. Prevention of *Haemophilus influenzae* type b colonization by vaccination: correlation with serum anti-capsular IgG concentration. J Infect Dis. 2000 Nov;182(5):1553-6.

Concentrations of serum anti-*Haemophilus influenzae* type b (anti-Hib) capsular polysaccharide (CPS) >/=0.15 and >/=1.0 microgram/mL are widely used as surrogates for protection against invasive Hib disease. However, the relationship between serum anti-Hib CPS following immunization and protection against colonization is not known, making it difficult to evaluate new Hib vaccines or combination vaccines. In the Dominican Republic, nasopharyngeal swabs were collected from 546 9-month-old infants who had received Hib conjugate vaccine at ages 2, 4, and 6 months and from 600 unvaccinated infants of the same age. The prevalence of Hib colonization was lower among vaccinated infants than among unvaccinated infants (0.9% vs. 2.3%). Among vaccinated infants, protection against colonization was significantly correlated with anti-Hib CPS concentrations >/=5 microgram/mL 1 month following for protection against colonization is greater than that needed for protection for invasive disease.the third dose of vaccine. These results suggest that the concentration of serum anti-Hib CPS needed

Adegbola RA, Mulholland EK, Secka O, Jaffar S, Greenwood BM. Vaccination with a *Haemophilus influenzae* type b conjugate vaccine reduces oropharyngeal carriage of H. influenzae type b among Gambian children. J Infect Dis. 1998 Jun;177(6):1758-61.

The effect of a *Haemophilus influenzae* type b (Hib) polyribosylribitol phosphate-tetanus toxoid conjugate vaccine (Hib/PRP-T) on oropharyngeal carriage of Hib was studied during an efficacy trial in Gambian infants. Children were vaccinated with Hib/PRP-T and diphtheria-tetanus toxoids-pertussis (DTP) or DTP alone at ages 2, 3, and 4 months. Groups of 1000 children aged 1-2 years were studied each year for 4 years. Hib was detected by production of a halo on antiserum agar plates. Carriage was significantly lower among children fully vaccinated with Hib/PRP-T given with DTP (4.4%; 95% confidence interval [CI], 3.8%-5.7%) than among children fully vaccinated with DTP alone (11.0%; 95% CI, 8.9%-13.0%) (protective effect adjusted by year = 60%; 95% CI, 44%-72%; P < .001). Hib carriage varied by year among nonvaccinated children. Hib conjugate vaccines are likely to produce a herd protective effect in underdeveloped communities, as recorded in Europe and the United States.

Daza P, Banda R, Misoya K, Katsulukuta A, Gessner BD, Katsande R, Mhlanga BR, Mueller JE, Nelson CB, Phiri A, Molyneux EM, Molyneux ME. The impact of routine infant immunization with *Haemophilus influenzae* type b conjugate vaccine in Malawi, a country with high human immunodeficiency virus prevalence. Vaccine. 2006 Sep 11;24(37-39):6232-9.

Malawi has extreme poverty and a high-human immunodeficiency virus (HIV) prevalence. Following *Haemophilus influenzae* type b (Hib) conjugate vaccine introduction during 2002, we evaluated vaccine impact by reviewing hospital surveillance data for acute bacterial meningitis in Blantyre district among children age 1-59 months admitted during 1997-2005. Documented annual Hib meningitis incidence rates decreased from 20-40/100,000 to near zero among both rural and urban residents despite no change in pneumococcal meningitis incidence rates. Before vaccine introduction, an average of 10 children/year had Hib meningitis and HIV infection compared to 2/year during 2003-2004 and none during 2005. Vaccine effectiveness was high following two or more doses of vaccine. The most urgent future need is for a sustainable routine infant immunization program, including a less expensive vaccine that preferably is delivered in a multivalent form.

Punjabi NH, Richie EL, Simanjuntak CH, Harjanto SJ, Wangsasaputra F, Arjoso S, Rofiq A, Prijanto M, Julitasari, Yela U, Herzog C, Cryz SJ. Immunogenicity and safety of four different doses of *Haemophilus influenzae* type b-tetanus toxoid conjugated vaccine, combined with diphtheria-tetanus-pertussis vaccine (DTP-Hib), in Indonesian infants. Vaccine. 2006 Mar 10;24(11):1776-85.

Widespread use of *Haemophilus influenzae* type b (Hib) conjugated vaccine in industrialized countries has resulted in a dramatic decline in the incidence of invasive Hib diseases, but the vaccine's cost has prevented its inclusion in basic immunization programs in developing countries. To overcome this problem, combination with diphtheria-tetanus-pertussis (DTP) vaccine or reduction in the dose of Hib vaccine has been proposed. To evaluate the immunogenicity and adverse reactions from lower doses of Hib-polyribosylphosphate (PRP) conjugated with tetanus toxoid (PRP-T), a double-blind study was conducted in Jakarta, Indonesia, and its suburbs. A total of 1048 infants 6 weeks to 6 months of age received three doses of DTP vaccine combined with the usual 10 microg dose or with a reduced dose of 5, 2.5 or 1.25 microg of PRP-T at two-monthly intervals. Antibodies were measured prior to the first dose and 4-6 weeks following the third dose. Adverse reactions were similar among all four groups. The only significant difference was a higher rate of irritability ($p<0.02$) and of temperature elevation >38 degrees C ($p<0.009$) after doses 1 and 2 in the lowest dose group (1.25 microg PRP-T) compared to the other groups. All participants tested had a 4-fold increase in antibodies against all DTP antigens. In addition, after a fourth booster dose of Hib, 99.6% of infants produced >or=0.15 microg/ml of antibody to Hib-PRP, and 96.4% showed levels >or=1.0 microg/ml after primary immunization, level that correlate with short- and long-term immunity, respectively. Antibody titers to the PRP antigen showed no significant differences among dosage groups with the exception of

the 5.0 microg group, which had a significantly higher GMC than the 1.25 microg group ($p<0.012$). This study demonstrates that primary vaccination with half, one-fourth, or one-eighth of the usual dose of PRP-T, combined with DTP vaccine, produces protective immune responses, and has side effects that are comparable to DTP vaccination alone. In these lower dosages, PRP-T conjugate vaccine can lower vaccine costs to a level that is affordable for infant immunization programs in developing countries.

Lottenbach KR, Granoff DM, Barenkamp SJ, Powers DC, Kennedy D, Irby-Moore S, Homan SM, Mink CM. Safety and immunogenicity of *Haemophilus influenzae* type B polysaccharide or conjugate vaccines in an elderly adult population. J Am Geriatr Soc. 2004 Nov;52(11):1883-7.

OBJECTIVES: To evaluate the safety and immunogenicity of unconjugated *Haemophilus influenzae* type b (Hib) polysaccharide (PRP) vaccine and two PRP-protein-conjugated vaccines as a model for the comparison of protein-conjugated versus plain polysaccharide vaccines in the elderly. DESIGN: Randomized, double-blind, prospective study. SETTING: University-based center for vaccine research and development. PARTICIPANTS: A total of 125 adults, aged 64 to 92, who were judged to be in general good health and lacking any significant underlying medical conditions. INTERVENTION: Subjects were randomized to receive one of three vaccines: Group 1 (n=39), PRP; Group 2 (n=44), PRP conjugated to an outer-membrane protein complex of *Neisseria meningitidis* (PRP-OMP); and Group 3 (n=42), PRP conjugated to diphtheria toxoid (PRP-D). Sera were obtained before immunization and 1 and 12 months later. MEASUREMENTS: Subjects maintained a diary of injection site and systemic reactions for 3 days after immunization. A radioantigen-binding assay was used to measure total concentrations of serum anticapsular antibody, and an enzyme-linked immunosorbent assay was used to measure immunoglobulin (Ig) G1 and IgG2 anticapsular antibody responses. Antibody functional activity was assessed using a complement-mediated bactericidal assay. RESULTS: Before vaccination, the geometric mean serum anticapsular antibody concentration was 0.8 microg/mL, but fewer than 10% of subjects had detectable bactericidal activity (titer>1:4). The magnitude, subclass distribution, and bactericidal activity of antibody responses to unconjugated PRP vaccine were similar to those observed in previous studies of younger adults immunized with PRP. The OMP conjugate, which is highly immunogenic after one dose in 2-month old infants, did not elicit anticapsular antibody responses in the elderly greater than those elicited by PRP vaccine (P=.43). In contrast, the D conjugate, which is poorly immunogenic in 2-month old infants, elicited higher anticapsular antibody responses than PRP vaccine in the elderly (P=.01) and higher levels than the OMP-conjugate 1 year after vaccination (P<.006). CONCLUSION: Elderly adults develop protective anticapsular antibody responses to unconjugated and conjugated PRP vaccine. The higher anticapsular antibody responses to the D conjugate but not to the OMP conjugate in the elderly, which is the reverse of that observed in immunized infants, implies fundamental differences in the immunological mechanisms by which the two age groups respond to PRP and by which the OMP and D conjugates elicit anticapsular antibody responses.
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Kalies H, Verstraeten T, Grote V, Meyer N, Siedler A, Breuer T, Moulton LH, von Kries R; Four and one-half-year follow-up of the effectiveness of diphtheria-tetanus toxoids-acellular pertussis/*Haemophilus influenzae* type b and diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus/*H. influenzae* type b combination vaccines in Germany. Pediatr Infect Dis J. 2004 Oct;23(10):944-50.

BACKGROUND: Recently an increase in the number of invasive *Haemophilus influenzae* type b (Hib) cases was observed in the United Kingdom, which coincided with a temporary change from diphtheria-tetanus toxoids-wild-type pertussis to diphtheria-tetanus toxoids-acellular pertussis (DTaP) Hib vaccines. A study in Germany based on approximately 2 years of follow-up, estimated vaccine effectiveness (VE) of DTaP/Hib and DTaP-inactivated poliovirus/Hib combination vaccines against invasive Hib disease to be high. OBJECTIVES: To assess VE of DTaP-containing Hib vaccines against Hib in Germany with the use of extended follow-up of case surveillance and vaccine uptake. SUBJECTS AND METHODS: Cases with confirmed systemic Hib infections in children born between June 1, 1996 and December 31, 1998 were ascertained by a nationwide active surveillance system from January 1998 through June 2002. A representative sub-cohort of 667 children born in the same time frame was randomly sampled in a nationwide vaccine coverage survey. VE was determined with a case-cohort approach of Cox regression with time-dependent covariates. RESULTS: Thirty-six cases of Hib disease were reported. Of these, 10 were vaccinated with DTaP-containing Hib vaccines only and 20 were not vaccinated. Of the 10 vaccinated cases, 4 had received an incomplete primary series (1-2 doses), and 6 had received the full primary series (3 doses), 3 of whom also received the booster dose. VE of combination vaccines against invasive Hib infection was 89.6% [95% confidence interval (CI), 67.0-96.7] for an incomplete primary series, 96.7% (95% CI 87.7-99.1) for a full primary series and 98.5% (95% CI 94.5-99.6) for a booster dose (irrespective of priming). CONCLUSION: Hib combination vaccines containing acellular pertussis antigens continue to be highly effective in Germany.

Verez-Bencomo V, Fernandez-Santana V, Hardy E, Toledo ME, Rodriguez MC, Heynngnezz L, Rodriguez A, Baly A, Izquierdo M, Villar A, Valdes Y, Cosme K, Deler ML, Montane M, Garcia E, Ramos A, Aguilar A,Medina E,Torano G, Sosa I, Hernandez I, Martinez R, Muzachio A, Carmenates A, Costa L, Cardoso F, Campa C, Diaz M, Roy R. A synthetic conjugate polysaccharide vaccine against *Haemophilus influenzae* type b. Science. 2004 Jul 23;305(5683): 522-5.

Glycoconjugate vaccines provide effective prophylaxis against bacterial infections. To date, however, no commercial vaccine has been available in which the key carbohydrate antigens are produced synthetically. We describe the large-scale synthesis, pharmaceutical development, and clinical evaluation of a conjugate vaccine composed of a synthetic capsular polysaccharide antigen of *Haemophilus influenzae* type b (Hib). The vaccine was evaluated in clinical trials in Cuba and showed long-term protective antibody titers that compared favorably to licensed products prepared with the Hib polysaccharide extracted from bacteria. This demonstrates that access to synthetic

complex carbohydrate-based vaccines is feasible and provides a basis for further development of similar approaches for other human pathogens.

Schmitt HJ, von Kries R, Hassenpflug B, Hermann M, Siedler A, Niessing W, Clemens R, Weil J. *Haemophilus influenzae* type b disease: impact and effectiveness of diphtheria-tetanus toxoids-acellular pertussis (-inactivated poliovirus)/*H. influenzae* type b combination vaccines. Pediatr Infect Dis J. 2001 Aug;20(8):767-74.

BACKGROUND: Since 1996 in Germany primary infant immunization against *Haemophilus influenzae* has been most commonly given in the form of diphtheria-tetanus toxoids-acellular pertussis/H. influenzae type b (DTaP/Hib) or diphtheria-tetanus toxoids-acellular pertussis (-inactivated poliovirus)/*H. influenzae* type b (DTaP-IPV/Hib) combination vaccines. These combination vaccines elicit lower anti-Hib antibody concentrations than the equivalent Hib conjugate administered as a separate injection, but the clinical relevance of this phenomenon is unknown. METHODS AND FINDINGS: To assess the impact of DTaP/Hib combination vaccines on the incidence of invasive Hib disease in Germany, two independent surveillance systems, one hospital- and one laboratory-based, were used during 1998 and 1999 for detection of cases. Vaccination histories of all cases detected were obtained by telephone contact with parents or health care providers. During the 2-year study period invasive *H. influenzae* disease in the <5-year age group continued to fall, with a mean annual incidence of 1.01/100 000 children. National vaccination coverage rates revealed that only 70% of children given DTaP/Hib or DTaP-IPV/Hib received the recommended three doses in their first year of life, but the overall effectiveness of these vaccines was high at 97.5% (95% confidence interval, 96.3 to 98.4) for those who had received at least one dose. In subjects who received the full 3-dose schedule, effectiveness was 98.8% (95% confidence interval, 98.2 to 99.3). CONCLUSION: Although it is well-documented that DTaP/Hib vaccines elicit lower anti-Hib titers than separate vaccines, such combinations are effective in reducing the incidence of invasive *H. influenzae* type b disease.

Lagos R, Levine OS, Avendano A, Horwitz I, Levine MM. The introduction of routine *Haemophilus influenzae* type b conjugate vaccine in Chile: a framework for evaluating new vaccines in newly industrializing countries. Pediatr Infect Dis J. 1998 Sep;17(9 Suppl):S139-48.

OBJECTIVE: To determine the burden of *Haemophilus influenzae* type b (Hib) disease, the safety and immunogenicity of Hib conjugate vaccine, the practicality of combining Hib conjugate and diphtheria-tetanus-pertussis vaccines and the effectiveness of routine vaccination. STUDY DESIGNS: A series of studies were carried out involving infants and children in Santiago, Chile. The study designs included retrospective surveillance, cost-benefit analysis, randomized placebo-controlled trials of safety and immunogenicity and a Phase IV post-licensure evaluation of vaccine effectiveness. RESULTS: The studies included in this stepwise process showed that Hib invasive

disease was a significant public health problem with a substantial economic burden; that combining Hib conjugate and diphtheria-tetanus-pertussis vaccines was practical, safe and elicited a strong immunologic response; and that the combined formulation afforded a high level of protection against invasive Hib disease (90% effectiveness). CONCLUSIONS: In July, 1996, Chile became only the third newly industrializing country to introduce routine Hib conjugate vaccination. New vaccines, such as Hib conjugates, will be more expensive than existing ones. The stepwise process used in Chile may serve as an example for the evaluation of new vaccines in non-industrialized countries.

WHO policy documents

***Haemophilus influenza* type b. Conclusions and recommendations from the Nov 2005 meeting of the WHO Immunization Strategic Advisory Group (SAGE). Weekly Epidemiological Record 2006, 81,7-8.** Http://www.who.int/WER.

WHO, Department of Vaccines and Biologicals, 2000: Introduction of Haemophilus influenza types b vaccine into immunization programmes. Management guidelines, including information for health workers and parents. www.who.int/vaccines-access/vacman/mdvp/who00.09doc.pdf