**Haemophilus influenzae type b (Hib) Vaccination Position Paper – July 2013**

Summaries of cited journal articles.


This study estimated the global Hib disease burden for the year 2000, and found that Hib caused about 8.13 million serious illnesses worldwide in 2000 (uncertainty range 7.33-13.2 million). It was estimated that Hib caused 371,000 deaths (247,000-527,000) in children aged 1-59 months, of which 8100 (5600-10,000) were in HIV-positive and 363,000 (242,000-517,000) in HIV-negative children in children younger than 5 years. A comprehensive literature search of studies of Hib disease incidence, case-fatality ratios, age distribution, syndrome distribution, and effect of Hib vaccine was performed. Vaccine trial data was used to estimate the proportion of pneumonia cases and pneumonia deaths caused by Hib and these proportions were applied to WHO country-specific estimates of pneumonia cases and deaths to estimate Hib pneumonia burden. Data from surveillance studies was used to develop estimates of incidence and mortality of Hib meningitis and serious non-pneumonia, non-meningitis disease. If available, high-quality data were used for national estimates of Hib meningitis and the non-pneumonia, non-meningitis disease burden. Otherwise, estimates were based on data from other countries matched as closely as possible for geographic region and child mortality. Estimates were adjusted for HIV prevalence and access to care.


To determine the effect of various demographic factors on the incidence of Hemophilus influenzae type b meningitis, Rhode Island residents with Hib in 1970-1974 were identified by review of data from the State Department of Health, a private health care research organization, death certificates, and hospital bacteriology laboratories. Of the 108 cases of Hib, 99 (92%) occurred in children under five years of age. The disease incidence among African American children under five (103.6/100,000/annum) was significantly (P less than 0.0005) higher than that among Caucasian children (23.9/100,000/annum). By eliminating the 29 of 185 census tracts in which the total population was greater than 5% African American, disease incidence was studied in a virtually monoracial population. In these census tracts the occurrence of H.influenzae was not related to family income, education, number of household members, population density, or rate of hospitalization. These findings confirm the increased incidence of H. influenzae in African American children and indicate that socioeconomic factors do not affect the incidence of the disease in Caucasian children.


This paper reviews the literature on the epidemiology of Hib disease and the effectiveness of Hib conjugate vaccine (HibCV) in HIV-infected children. The current three-dose primary Hib conjugate vaccine schedule in low-income settings has had a striking impact on the incidence of Hib disease. However, HIV-infected children have an almost 6-fold higher risk of Haemophilus influenzae type b (Hib) invasive disease than HIV-uninfected children and HibCV effectiveness is lower in this population. HIV-related HibCV failures are difficult to detect without well-functioning surveillance systems and HIV testing of cases. Breakthrough Hib cases have been noted in vaccinated HIV-infected children in South Africa. A HibCV booster dose in addition to the three-dose primary schedule is routine in many, but not all, high-income countries. In order to determine whether a booster dose should be given to HIV-infected children in developing countries, well-designed studies need to be conducted to better determine the persistence of protective antibody concentrations, response to booster doses.
of vaccine as well as timing of and risk factors for vaccine failure in HIV-infected children both treated and naive to antiretroviral drug therapy (ART). Meanwhile, physicians and public health personnel should be especially vigilant at ensuring that HIV-infected infants receive their primary doses of HibCV, ART and co-trimoxazole prophylaxis. Until more definitive evidence is available, physicians may also need to consider a booster dose for such children irrespective of ART status. In any updating of vaccine schedules, HIV-infected children need particular consideration.


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. This study prospectively evaluated use of the vaccine in South African children. The burden of invasive Hib disease in children aged < 1 year 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. 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. 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.


Haemophilus influenzae type b (Hib) is an important cause of invasive bacterial disease in children, including meningitis and pneumonia. The introduction of Hib conjugate vaccines into routine vaccination schedules has contributed to a substantial reduction in the burden of Hib-related disease in many developed countries. However, introduction of Hib conjugate vaccines in developing countries has progressed more slowly. We review the worldwide use and effectiveness of Hib conjugate vaccines. At present, 119 countries have programmes for routine Hib immunisation. WHO estimates that in the developed world, 92% of the eligible population is vaccinated against Hib; however, average coverage is 42% in developing countries and only 8% in the poorest countries. Africa and southeast Asia have the lowest rates of Hib vaccine introduction. Vaccine costs and debate about the burden of disease are obstacles to the global use of Hib conjugate vaccine. Even with new funding support, there are many ongoing challenges and vaccine use remains suboptimal, particularly in developing countries.
Conjugate vaccines against Haemophilus influenzae type b (Hib) are widely used. The full implications of Hib vaccination schedule for vaccine effectiveness (VE) are unclear. We searched the literature for observational studies reporting the effectiveness of conjugate Hib vaccines administered according to different schedules. We summarised dose-specific VE estimates, where appropriate, using random effects meta-analysis. 31 eligible articles (reporting 30 studies conducted in 17 countries) were identified. A meta-analysis of case-control studies using community controls produced VE estimates against Hib meningitis of 55% (95% CI 2-80%, based on 3 studies), 96% (86-99%, 3 studies) and 96% (86-99%, 4 studies) after 1, 2 and 3 doses of vaccines other than PRP-OMP. Estimates were similar using hospital controls. VE against invasive Hib disease in case-control studies was estimated as 59% (30-76%, 3 studies) and 97% (87-99%, 3 studies) for 1 and 3 doses (insufficient data were identified to estimate two-dose VE). Point estimates from two studies suggested VE >90% after one dose of PRP-OMP, but meta-analysis was not possible. Using data from 4 cohort studies, three-dose VE was estimated as 94% (88-97%). There was some evidence that Hib vaccine was less effective when administered with acellular (rather than whole cell) pertussis vaccine. Weak evidence from two studies suggested that a booster confers some additional protection following full primary vaccination and may compensate for an incomplete primary series.


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


Bacterial meningitis (BM) is a severe infection responsible for high mortality and disabling sequelae. Early identification of patients at high risk of these outcomes is necessary to prevent their occurrence by adequate treatment as much as possible. For this reason, several prognostic models have been developed. The objective of this study is to summarize the evidence regarding prognostic factors predicting death or sequelae due to BM in children 0-18 years of
In the prevaccination era, meningitis represented 40 to 70% of all classical Hib diseases. Epiglottitis was the second most common presentation, except in southern Europe (data not available from former socialist countries). The overall incidence of meningitis and of all Hib disease combined for children ages 0 to 4 years was 23 and 41 per 100000, suggesting 9900 and 17800 cases per year, respectively. Including all age groups and entities, >20000 Hib cases occurred annually. Vaccination, accomplished with two or three primary doses and a late booster, has almost eliminated Hib disease in >10 countries, and >10000 cases per year are prevented. An age analysis of Hib meningitis suggests that strong early immunogenicity is not as imperative in Europe as in some other regions. The incidence of non-type b H. influenzae infections has not increased. Where Hib epidemiology is comparable with that in Europe, good protection is achieved by various conjugate vaccines with two primary doses only. However, active research on the whole Hib issue should be a priority, especially in southern and eastern European countries.


After the introduction of effective Haemophilus influenzae type b (Hib) conjugate vaccines, clinical practice has driven the development of combination vaccines comprising Hib conjugates with the infant diphtheria-tetanus-pertussis (DTP) vaccines. However, when such combinations contain an acellular pertussis component (Pa), the antibody response to Hib is lower than that with separate injections and doubts have been raised about their efficacy. We believe that such concerns are unwarranted, since the serological correlates of efficacy previously applied for Hib polysaccharide vaccines seem inappropriate for Hib conjugates. Furthermore, our own studies have shown that the lower antibody responses are not associated with impaired function of the antibodies induced, nor, and possibly more importantly, with the induction of immune memory against Hib. Therefore, with the proviso that careful clinical surveillance of Hib disease is maintained, we encourage the introduction of DTPa-Hib combinations to facilitate the inclusion of Hib into the already crowded childhood immunisation schedule.


Over 10 years of international experience with Hib conjugate vaccines has demonstrated that they are safe and effective. Routine use of Hib conjugate vaccine has consistently led to decreases in the incidence of invasive Hib disease of 90% or more across a wide range of epidemiologic situations in industrialized countries. In some countries, the vaccine has caused a near-disappearance of invasive Hib disease through a combination of direct protection and herd immunity. Developing countries that have implemented routine vaccination (eg, The Gambia, Chile) have also had
substantial disease reduction. In countries where Hib conjugate vaccine is being used, reducing Hib disease incidence to the lowest possible level will depend on maintaining high vaccine coverage levels, conducting surveillance for Hib disease, and investigating Hib disease cases. The optimal Hib vaccination strategy will depend on many factors, including local epidemiology and programmatic considerations. In countries that are not using Hib conjugate vaccine, information on the local burden of Hib disease will be essential for leaders considering vaccine introduction. Where disease burden is high, a multifaceted approach is urgently needed to evaluate and overcome barriers to vaccine introduction. In areas where Hib disease burden is not well characterized, additional work will be needed to understand the epidemiology of Hib disease and to communicate the value of Hib conjugate vaccine.


Advantages to combining childhood vaccines include reducing the number of visits, injections and patient discomfort, increasing compliance and optimising prevention. The World Health Organization (WHO) recommends that routine infant immunisation programmes include a vaccination against Haemophilus influenzae (H. influenzae) type B (HIB) in the combined diphtheria-tetanus-pertussis (DTP)-hepatitis B virus (HBV) vaccination. The effectiveness and safety of the combined vaccine should be carefully and systematically assessed to ensure its acceptability by the community. Randomised controlled trials (RCTs) or quasi-RCTs comparing vaccination with any combined DTP-HBV-HIB vaccine, with or without three types of inactivated polio virus (IPV) or concomitant oral polio vaccine (OPV) in any dose, preparation or time schedule were compared with separate vaccines or placebo, administered to infants up to two years old. We performed a meta-analysis to pool the results of 20 studies with 5874 participants in an immunogenicity analysis and 5232 participants in the reactogenicity analysis. There were no data on clinical outcomes for the primary outcome (prevention of disease) and all studies used immunogenicity and reactogenicity (adverse events). The number of vaccine doses differed significantly between the studies. Heterogeneous interventions, study location, healthcare environment and combining research across disparate geographical locations, may have led to bias. The risk of bias was unclear across most of the included studies. Comparisons found little heterogeneity. In two immunological responses the combined vaccine achieved lower responses than the separate vaccines for HIB and tetanus. No significant differences in immunogenicity were found for pertussis, diphtheria, polio and hepatitis B. Serious adverse events were comparable with mainly hospitalisation and acute bronchiolitis cases. Minor adverse events such as pain and redness were more common in children given the combined vaccine. Overall, the direction shown by the results is in favour of the DTPw (diptheria-tetanus-whole cell pertussis)-HBV-HIB vaccine rather than the DTPa (diptheria-tetanus-acellular pertussis)-HBV-HIB vaccine when compared to the separate vaccines (size of effect: risk ratio (RR) 1.43; 95% confidence interval (CI) 0.98 to 2.10, for 5269 participants).

Low et al. Comparing Haemophilus influenzae type b Conjugate Vaccine Schedules: A Systematic Review and Meta-Analysis of Vaccine Trials, Pediatric Infectious Disease Journal: 
Post acceptance, 18 June 2013, online PDF,
http://journals.lww.com/pjid/Abstract/publishahead/Comparing_Haemophilus_influenzae_type_b_Conjugate.98295.aspx

The optimal schedule and the need for a booster dose are unclear for Haemophilus influenzae type b (Hib) conjugate vaccines. We systematically reviewed relative effects of Hib vaccine schedules by searching 21 databases to May 2010 or June 2012 and selected randomized controlled trials (RCTs) or quasi-RCTs that compared different Hib schedules (three primary doses with no booster dose [3p+0], 3p+1 and 2p+1) or different intervals in primary schedules and between primary and booster schedules.
Outcomes were clinical efficacy, nasopharyngeal carriage and immunological response. Twenty trials from 15 countries were included; 16 used vaccines conjugated to tetanus toxoid (PRP-T). No trials assessed clinical or carriage outcomes. Twenty trials examined immunological outcomes and found few relevant differences. Comparing PRP-T 3p+0 with 2p+0 there was no difference in seropositivity at the 1.0[μg/ml threshold by six months after the last primary dose (combined risk difference -0.02, 95%CI -0.10, 0.06). Only small differences were seen between schedules starting at different ages, with different intervals between primary doses, or with different intervals between primary and booster doses. Individuals receiving a booster were more likely to be seropositive than those at the same age who did not. There is no clear evidence from trials that any 2p+1, 3p+0 or 3p+1 schedule of Hib conjugate vaccine is likely to provide better protection against Hib disease than other schedules. Until more data become available, scheduling is likely to be determined by epidemiological and programmatic considerations in individual settings.

Southern J et al. Immunogenicity of a fourth dose of Haemophilus influenzae type b Hib conjugate vaccine and antibody persistence in young children from the United Kingdom who were primed with acellular or whole cell pertussis component-containing Hib combinations. Clinical Vaccine Immunology, 2007, 14 (10): 1328-1333.

In response to the rising incidence of Haemophilus influenzae type b (Hib) disease in the United Kingdom, a national campaign to give a booster dose of single-antigen Hib conjugate vaccine to children aged 6 months to 4 years was undertaken in 2003. Children (n = 386) eligible for Hib vaccine in the campaign were recruited. Hib antibody concentrations were measured before boost and at 1 month, 6 months, 1 year, and 2 years after boost and were analyzed according to children's ages at booster dose, and whether a Hib combination vaccine containing acellular pertussis (aP) or whole-cell pertussis (wP) components was given in infancy. The geometric mean antibody concentrations (GMCs) before the booster declined as the time since primary immunization increased (P < 0.001), and GMCs were threefold higher in recipients of wP-Hib than aP-Hib combination vaccines (P < 0.001). GMCs 1 month after the booster increased with age (P < 0.001) as follows: 6 to 11 months; 30 microg/ml (95% confidence interval [CI], 22 to 40); 12 to 17 months, 68 microg/ml (95% CI, 38 to 124); and 2 to 4 years, 182 microg/ml (151 to 220), with no difference according to the type of priming vaccine received. Antibody levels declined after the booster, but 2 years later, GMCs were more than 1.0 microg/ml for all age groups. By extrapolating data for the decline in antibody levels, we found the GMCs 4 years after boosting were predicted to be 0.6, 1.4, and 2.6 microg/ml for those boosted at 6 to 11 months, 12 to 17 months, and 2 to 4 years, respectively, with levels of at least 0.15 microg/ml in about 90% of individuals. A booster dose of Hib vaccine given after the first year of life should provide long-lasting protection.


Before vaccination, Alaska Natives experienced very high rates of invasive Haemophilus influenzae type b (Hib) disease and carriage. Vaccination with Hib conjugate vaccine PRP-OMP (polyribosylribitol phosphate Neisseria meningitidis outer membrane protein) began in 1991 and resulted in a sharp decline in cases. In 1996, after switching to a different Hib conjugate vaccine, DTP-HbOC (which combines diphtheria-tetanus-whole cell pertussis vaccines with HbOC [Hib oligosaccharide CRM197]), cases of invasive Hib disease increased, suggesting ongoing Hib transmission despite widespread vaccination. To determine the prevalence of, and risk factors for, carriage, a cross-sectional study of oropharyngeal Hib carriage was conducted among Alaska Native children aged 1-5 years in remote south-western Alaska. Of 496 children with swabs taken, 46 (9.3%) were colonized with Hib. Carriage rates varied by village from 2.2% to 13.2%, and by age from 6.1% in 1-year-olds to 14.7% in 5-year-olds. Crowding was associated with Hib carriage. Widespread vaccination with PRP-OMP Hib conjugate vaccine did not eliminate carriage in this population of Alaska Natives, and ongoing carriage contributed to disease resurgence.

South Africa started routine infant immunization against Haemophilus influenzae serotype b (Hib) disease in 1999 with an accelerated three-dose schedule of Hib conjugate vaccine (HibCV) without a booster dose. Following initial declines in Hib disease, national surveillance has identified increasing numbers of Hib disease episodes in fully vaccinated children. We reviewed national laboratory-based surveillance data from 2003 through 2009 for invasive Hib disease episodes among children <5 years, including HIV status and vaccination histories. We defined HibCV failures as invasive Hib disease in children at least four months of age who had received all recommended doses of HibCV. Despite high HibCV vaccination coverage, detection rates of Hib disease in children <5 years increased from 0.7 per 100,000 population in 2003 to 1.3/100,000 in 2009 (p<0.001). Among 263 episodes of invasive Hib disease among children with known vaccination status, 135 (51%) were classified as vaccine failures. Of vaccine failures, 55% occurred among case patients ≥18 months old. HIV status was documented for 90 children with vaccine failure; 53% were not HIV infected. Vaccine failures, which occurred in both HIV-infected and -uninfected children, comprised half of the rise in invasive Hib disease detected in South African children 10 years after national introduction of Hib vaccine. These findings suggest that HibCV recommendations may require revision. In November 2010, children in South Africa began receiving a booster dose of HibCV as part of a pentavalent vaccine.


It is not known how long children with Haemophilus influenzae serotype b (Hib) vaccine failure retain protective Hib antibody concentrations after infection. The objective of this study was to determine Hib antibody concentrations in children several years after infection and to identify risk factors for low antibody concentrations. The families of children from the United Kingdom who developed invasive Hib disease after prior immunization with Hib conjugate vaccine (i.e., Hib vaccine failure) from October 1992 through December 2005 were asked to complete a questionnaire. A blood sample was also obtained from each child. Of 323 families approached, 260 (80.5%) returned a completed questionnaire, and 175 (54.2%) children provided a blood sample. The median age at follow-up was 8.4 years (interquartile range [IQR], 6.2-15.4 years), and the median duration of follow-up was 4.1 years (IQR, 3.5-9.7 years). Twenty-seven children (16.1%) had been born prematurely and/or had an underlying medical condition, and 18 (10.8%) had immunoglobulin deficiency. The median Hib antibody concentration was 0.70 microg/mL (IQR, 0.22-5.8 microg/mL). Overall, 95 children (56.9%) had antibody concentrations <1.0 microg/mL, and 27 (16.2%) had antibody concentrations <0.15 microg/mL. All 3 children with Down syndrome and 10 (42%) of 24 children aged <5 years at follow-up had Hib antibody concentrations <0.15 microg/mL. An antibody concentration <0.15 microg/mL was independently associated with underlying conditions, young age at onset of Hib disease, and shorter time from Hib disease to follow-up. More than one-half of the children with Hib vaccine failure had antibody concentrations below those considered to confer long-term protection, which suggests that these children might be at further risk of invasive Hib disease and would benefit from another dose of Hib vaccine.


Prevalence of non-typeable Haemophilus influenzae (NTHi) in the etiology of invasive infections in immunocompromised individuals is increasing. Serum IgG antibody levels to H. influenzae protein D (PD) are significantly lower in adults suffering from chronic conditions causing secondaryimmunodeficiency (COPD, cancer, chronic renal failure, and diabetes) compared to age-matched healthy controls. A lack of naturally acquired antibody against this highly conserved antigen may contribute to an increased susceptibility to invasive NTHi disease. As
COPD patients frequently infected with NTHi during disease exacerbations were unable to develop antibody responses to PD, such a defect could potentially contribute to the pathogenesis. Considering that paediatric PD-containing vaccines shows protective effect against NTHi-caused otitis media, our data suggest the possibility of improving the defence against NTHi in COPD patients using immunization against PD. Although more research on the role of anti-PD antibody in protection against invasive NTHi disease is warranted, development of adult formulations of PD-based vaccines may be advantageous for prevention of severe infections in immunocompromised individuals.


A polyribosylribitol phosphate (polysaccharide)-tetanus protein conjugate vaccine (PRP-T) against *Haemophilus influenzae* type b (Hib) was evaluated for safety and efficacy after vaccination of more than 100,000 infants. No major side effects were attributed to the vaccine. Immunogenicity studies showed an antibody response in 70% to 100% of infants after two doses, and in 98% to 100% of infants after three doses, within the first 6 months of life. Antibodies persisted in 90% of recipients, in whom significant anamnestic responses developed after a booster dose at 18 months of age. In comparison with other available Hib vaccines, PRP-T induces equal or higher mean titres after three doses. Although licensure of other vaccines interrupted efficacy trials, up to that point five cases of Hib disease in those trials had occurred in placebo recipients, and no Hib disease has been reported in the more than 100,000 vaccinated infants who have received more than one dose of PRP-T. Thus PRP-T combined immunogenicity early in life with induction of immunologic memory.


We evaluated the safety of the PRP-D conjugate Hib vaccine (ProHIBit, Connaught) in 29,309 children vaccinated at 18-60 months of age in the Southern California Kaiser Permanente medical clinics during the period April 1, 1988, to July 31, 1989. Surveillance for potential reactions involved postcard questionnaires, telephone surveys, reports of Kaiser staff and review of hospitalizations and covered two periods following immunization: (1) the first 48 hours and (2) days 2 through 30. Surveillance for invasive Hib disease involved the above methods in addition to systematic reviews of laboratory and hospital records through January 31, 1990. Rates of local and systemic reactions within 48 hours of vaccination with PRP-D alone were low (less than or equal to 2% for fever greater than 102 degrees F, local redness or swelling) and similar to those previously reported after vaccination with PRP. Hospitalization and seizures (0.15% and 0.09% of vaccinated children, respectively) occurring within 1 month of immunization appeared to be unrelated to vaccination. One 29-month-old child had onset of a fatal episode of Hib sepsis/meningitis within 48 hours of vaccination. Also, a 30-month-old child developed Hib meningitis 10 months after PRP-D vaccination. We conclude that PRP-D is safe when given alone or in combination with other childhood vaccines between 18 and 60 months of age.


With the arrival of new, more expensive vaccines, economic evaluation has become an important tool for assessing the feasibility of introducing a new vaccine into a country's routine immunization schedule. *Haemophilus influenzae* type b (Hib) vaccine has been available since the early 1990s, but uptake of the vaccine was slow in low-income countries until the GAVI Alliance started offering financial support for it. However, at some point, GAVI Alliance-supported countries will have to identify other sources of financing for Hib vaccine, meaning cost-effectiveness evidence will be important to support resource allocation decisions. Several middle-income countries have not yet introduced the vaccine. Thus, the aim of this literature review was to identify and evaluate the published evidence on the cost-effectiveness of the Hib...
vaccine, with particular emphasis on low- and middle-income countries. Few studies are available from resource-poor countries and some of these are of low quality.

Griffiths UK et al. Costs of meningitis sequelae in children in Dakar, Senegal. *Pediatric Infectious Disease Journal, 2012, 31(11):e189-195.* Survivors of bacterial meningitis risk lifelong sequelae. In economic evaluations of vaccines protecting against meningitis, treatment and productivity costs due to meningitis sequelae are rarely included in studies from low-income countries, mainly due to lack of data. The aim of this study was to estimate the costs of meningitis sequelae in children in Senegal from the perspective of households. Children who had suffered from bacterial meningitis were identified from a database at Albert Royer Hospital in Dakar. Sixty-eight children were located at their home and caregivers interviewed about costs during the acute meningitis episode and due to meningitis sequelae, including productivity loss from caring for a disabled child. Lifetime costs were predicted by assuming a life expectancy of 30 years for disabled children. Seventy-one percent of the children had either minor or major sequelae. Mean discounted lifetime sequelae costs amounted to US$ 34,895 (95% confidence interval: US$ 67-96,755) per child. Discounted childcare costs amounted to US$ 3158 (9%), treatment costs US$ 460 (1%) and productivity costs US$ 31,276 (90%). No children were receiving rehabilitation services by the time the study was conducted. Caring for a disabled child is a considerable financial as well as emotional burden for the individual family. None of the families could afford the treatment they desired for their child.

Griffiths UK, (2013). Cost-Effectiveness of *Haemophilus influenzae* Type b Conjugate Vaccine in Low- and Middle-Income Countries: Regional Analysis and Assessment of Major Determinants. *Journal of Pediatrics, 2013, 163(1 Suppl):S50-S59.e9.* This study estimated the cost-effectiveness of Haemophilus influenzae type b (Hib) conjugate vaccine in low- and middle-income countries and identified the model variables, which are most important for the result. A static decision tree model was developed to predict incremental costs and health impacts. Estimates were generated for 4 country groups: countries eligible for funding by the GAVI Alliance in Africa and Asia, lower middle-income countries, and upper middle-income countries. Values, including disease incidence, case fatality rates, and treatment costs, were based on international country estimates and the scientific literature. From the societal perspective, it is estimated that the probability of Hib conjugate vaccine cost saving is 34%-53% in Global Alliance for Vaccines and Immunization (GAVI)-eligible African and Asian countries, respectively. In middle-income countries, costs per discounted disability adjusted life year averted are between US$37 and US$733. Variation in vaccine prices and risks of meningitis sequelae and mortality explain most of the difference in results.

Samuelson et al. Characterization of *Haemophilus influenzae* isolates from the respiratory tract of patients with primary antibody deficiencies: evidence for persistent colonizations. *Scandinavian Journal of Infectious Disease, 1995, 27(4):303–313.* A total of 117 consecutive patients with primary antibody deficiencies were followed for up to 5 years with regard to acute respiratory tract infections. Nontypeable Haemophilus influenzae (NTHI) was the sole pathogen in 61% (202/330) of the samples from which a potential pathogen was recovered. Common variable immunodeficiency (CVI) was the most prevalent condition (27/39 patients) in the group where *H. influenzae* was isolated. In patients where *H. influenzae* was not found only 9/78 patients had CVI. 49 of these 78 patients had isolated IgG3 or IgA deficiency. Both of these entities seemed to be associated with a lower prevalence of NTHI infections. 13 of 18 patients with at least 2 isolates of NTHI were colonized with the same strain from 3 to 43 months as shown by total genomic DNA-fingerprinting. Recurrent symptomatic infections occurred in these patients despite substitution therapy with gammaglobulins and repeated antibiotic treatments. All but 2 of the 224 *H. influenzae* isolates were beta-lactamase negative and sensitive to ampicillin. The use of 10 lipopolysaccharide-specific monoclonal antibodies in a whole cell ELISA showed that the LPS-epitopes on the 224 *H. influenzae* isolates from the hypogammaglobulinemic group were very similar to 499 NTHI isolates from immunocompetent patients.
with respiratory infections. One may therefore conclude that i) patients with CVI, were prone to be permanently colonized with NTHI, and ii) the colonizing bacteria were ordinary strains showing the same LPS-phenotypes as those strains that cause acute respiratory tract infections in immunocompetent individuals.


Haemophilus influenzae type b (Hib) was the major cause of invasive bacterial disease in the United States and Canada before the introduction of Hib conjugate vaccines. Between 10000 and 20000 cases of Hib meningitis and other serious diseases occurred each year, leading to death in at least 3% of all patients and long term neurologic problems in up to 25% of survivors of meningitis. Introduction of Hib conjugate vaccines in Canada and the United States, first in children 18 months and older and later as a routine infant immunization, dramatically decreased the incidence of disease. By 1995 Hib disease levels had declined by more than 95% below preimmunization levels. The remarkably rapid reduction in disease incidence was partly because of the ability of the vaccine to reduce nasopharyngeal carriage of the organism, leading, when given widely, to reduced rates of exposure and infection even in those not immunized. Complete elimination of Hib disease in North America, however, will require achievement of relatively high coverage rates, especially in hard to reach populations where much of the remaining disease is occurring.