Haemophilus influenzae type b vaccine

Summary and conclusions

Wherever thorough studies have been performed, *Haemophilus influenzae* type b (Hib) has been shown to be an important cause of childhood meningitis and a major cause of bacterial pneumonia in children. Although little population-based incidence data are available from most of Asia and the newly independent States of the former Soviet Union, Hib is estimated to cause at least 3 million cases of serious disease and hundreds of thousands of deaths annually, worldwide. The most important manifestations of Hib disease, namely pneumonia and meningitis, are seen mainly in children under five years of age, particularly infants. Currently, several different Hib vaccines, all conjugate vaccines, are on the market. These vaccines have shown protective efficacy in early infancy. Hib vaccines are now used as part of routine childhood vaccination programmes in more than 20 countries including Australia, Canada, New Zealand, the United States, and many countries of western Europe, and have proved to be highly efficacious and virtually free from serious side-effects. Also, excellent results of trials or national introduction in Chile, Uruguay, and the Gambia show that Hib conjugate vaccines are effective in developing country settings. Because these vaccines significantly reduce nasopharyngeal carriage, a herd effect is achieved through Hib vaccination.

In view of the demonstrated safety and efficacy of the Hib conjugate vaccines, Hib vaccine should be included, as appropriate to national capacities and priorities, in routine infant immunization services. In geographical regions where the burden of Hib disease is unclear, efforts should be made to evaluate the magnitude of the problem.

Public health impact

H. influenzae type b (Hib) is estimated to cause at least 3 million cases of serious disease and 400 000–700 000 deaths each year in young children. Rarely occurring in infants under three months, and after the age of six years, the disease burden is highest at 4–18 months of age. In both developed and developing countries Hib is the dominant cause of non-epidemic bacterial meningitis in this age group, and is frequently associated with severe neurological sequelae despite prompt and adequate antibiotic treatment. In economically developed countries meningitis accounts for the majority of invasive Hib disease, whereas in developing countries acute respiratory infection, particularly the estimated 2–3 million cases of Hib pneumonia occurring each year, represents an even heavier disease burden. Other important, but less frequent, manifestations of Hib disease include epiglottitis, osteomyelitis, septic arthritis, and septicaemia.

Following introduction of Hib conjugate vaccines into routine childhood immunization services in the 1990s, Hib disease has largely disappeared in Australia, Canada, New Zealand, the United States and Western Europe.

The pathogen

H. influenzae is a Gram-negative bacterium. Serious infection is usually caused by strains carrying a polysaccharide capsule. Of the six capsular types, type b (Hib) causes almost all systemic infections. This polysaccharide is a polymer of D-ribose-ribitol-phosphate (PRP) and is an essential virulence factor. Up to 15% of children in non-immunized populations may harbour Hib in their nasopharynx. However, only a fraction of those acquiring the microorganism will subsequently develop clinical disease. Transmission of Hib is by droplets originating from colonized persons and hence, asymptomatic carriers are important disseminators of the organism. The non-encapsulated strains that are more frequently isolated from naso-pharyngeal secretions are mainly associated with mucosal infections such as bronchitis and otitis.

Facilities for reliable cultivation of Hib and identification of the capsular polysaccharide by immunological techniques are found in laboratories well-equipped for clinical microbiology, but are not easily available throughout the world.

Immune response

In older children and adults the Hib polysaccharide induces production of bactericidal antibodies. However, this polysaccharide does not reliably elicit protective levels of antibodies in children less than 18 months of age. Furthermore, it does not induce immunological memory and consequently no booster response with subsequent exposure to the polysaccharide. For these reasons, a new generation of vaccines was developed by conjugating a T-cell dependent protein antigen to the Hib polysaccharide. These Hib conjugate vaccines not only induce protective circulating antibodies and immunological memory in infants, but also result in decreased nasopharyngeal colonization of Hib. Thus, a herd effect is achieved through reduced transmission of the microorganism.

Justification for vaccine control of Hib disease

Hib disease, mainly meningitis and pneumonia in young children, is a significant public health concern in both developed and developing countries. In developed countries meningitis is the most important manifestation, whereas in developing countries pneumonia is more common. However, due to inherent problems regarding etiological diagnosis, especially of pneumonia, the true burden of Hib may be seen only by a reduction in the incidence of pneumonia and meningitis following vaccination. Antibiotics are essential for treatment, but have only a minor role in control, and development of bacterial resistance to some of the most efficient antibiotics underlines the need for prevention. Vaccines are the only public health tool available to prevent the vast majority of Hib disease.

The safety, efficacy and effectiveness of the Hib conjugate vaccines are clearly demonstrated in developed countries, where rapid declines in disease incidence have been documented in every country in which the vaccine has been used routinely in childhood immunization services. Furthermore, several studies demonstrate high efficacy of the vaccines against invasive disease in high-incidence and developing country settings, including studies in Chile, in the Gambia and in a Native American population in the United States. In the Gambian trial, vaccinated infants were protected against laboratory-confirmed Hib pneumonia, and the incidence of all X-ray documented pneumonia was reduced by approximately 20%.

A series of cost-benefit analyses in industrialized countries underscores the value of routine immunization against Hib disease. Substantially more disease could be prevented in the developing world, where the burden of disease and death is many times higher. An assessment of the situation in representative countries of most geographical regions was recently made by the Children's Vaccine Initiative. This study showed that inclusion of Hib vaccine into the respective childhood immunization schedules may be cost-effective, even in the lowest income strata.

Haemophilus influenzae type b conjugate vaccines (Hib-vaccines)

The vaccines currently licensed for use against Hib disease are based on Hib-polysaccharide conjugated to a protein carrier, such as diphtheria toxoid (PRP-D), a diphtheria toxoid-like protein (PRP-HbOC), tetanus toxoid (PRP-T), or meningococcal outer membrane protein (PRP-OMP). The conjugation of PRP to the protein induces a T-cell dependent immune response to the Hib-polysaccharide. The conjugate vaccines differ in their carrier protein, method of chemical conjugation and by polysaccharide size, giving them somewhat different immunological properties.

The vaccine is usually given in infancy as repeated doses together with diphtheria/tetanus/pertussis (DTP) and other vaccines of the national childhood immunization services. A booster dose is recommended in most countries at 12–18 months of age, but may not be necessary, especially in developing countries where most of the Hib disease occurs before this age. In adults and children over 18 months of age a single dose is sufficient to induce immunity.

All conjugate Hib vaccines are given by the intramuscular route. No serious side-effects are recorded, and no contraindications known, except for hypersensitivity to the vaccine components. The Hib vaccine may safely be administered concurrently with any vaccine of the EPI or corresponding national childhood vaccination programmes, as well as with pneumococcal and meningococcal vaccines.

WHO position on Hib vaccines

The commercially available Hib conjugate vaccines are all of known good quality. The indication for the use of these vaccines is protection of children below five years of age, particularly infants. WHO encourages the introduction of Hib vaccines worldwide. However, because of differences in epidemiology, health priorities and economic capacity, Hib vaccines will in practice be introduced at different speeds into national immunization services. The emphasis is on introduction in countries with the highest disease burden.

The efficacy and effectiveness of the Hib conjugate vaccines have been clearly demonstrated in developed countries, where rapid declines in disease incidence have been documented in every country in which the vaccine has been used routinely. Several studies also demonstrate the efficacy in high-incidence and developing-country settings.

Three out of the four currently-licensed Hib conjugate vaccines (PRP-HbOC, PRP-OMP, PRP-T) have proven to be comparably efficacious in infancy, provided a complete primary series is given. Furthermore, these vaccines are easily adapted to the routine schedule of the national immunization services. One of the vaccines (PRP-D) performs less well in children below 18 months of age, and is therefore not licensed for use in infants in many countries. All conjugate vaccines have an excellent safety record, and, where tested, do not interfere substantially with the immunogenicity of simultaneously given vaccines.

Unfortunately, in large areas of Asia as well as in the Newly Independent States, population-based data on the burden of Hib disease are largely missing, and so far, few Asian countries have adopted Hib vaccine as part of their routine immunization service. Data from additional surveillance studies are needed to assist public health planners in these areas. A WHO-sponsored protocol to evaluate Hib disease burden is available on request. However, the lack of simple, rapid and reliable techniques for etiological diagnosis of pneumonia is a challenge to future research.

Other issues which must be faced as the vaccine is introduced into developing countries include combination with other antigens such as locally produced DTP, and conceivably with pneumococcal and/or meningococcal vaccines. Also, questions of appropriate formulation including multidose vials, and liquid versus lyophilized vaccine preparations, will have to be addressed.

This chapter was last published as a WHO position paper: The WHO position paper on *Haemophilus influenzae* type b conjugate vaccines. *Weekly Epidemiological Record,* 1998, 73:64–68. It is also available on the Internet http://www.who.int/wer/pdf/1998/wer7310.pdf.

Administration summary

Type of vaccine	Conjugate
Number of doses	Two or three doses in the primary series (depending on manufacturer)
Schedule	6, 10, 14 weeks of age for three doses of primary series (depending on manufacturer)
Booster	None
Contraindications	Hypersensitivity to previous dose
Adverse reactions	Mild local reaction
Special precautions	None

Key references

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