



## NEW DEVELOPMENTS IN PEDIATRIC BACTERIAL VACCINES

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### I. INTRODUCTION

**T**hrough the expanded use of bacterial vaccines in many countries with the assistance of such organizations as the United States Agency for International Development, Pan American Health Organization, World Health Organization, and the United Nations Children's Fund (UNICEF), a drastic reduction in preventable childhood diseases has been achieved. The costs of vaccination programs have proven to be substantially lower than those associated with treatment of vaccine-preventable diseases.

Within the last five years a number of significant developments have occurred in relation to the availability of vaccines for prevention of pediatric bacterial diseases. New conjugate vaccines against *Haemophilus influenzae* type b (*Haemophilus* b) are now used widely in the United States and several European countries (1, 2). As a result, in the last two years the incidence of *Haemophilus* b disease in young children in the United States has been reduced from around 60 per 100,000 to about 1 per 100,000 population (3). Pneumococci are a major cause of invasive disease in children in developing countries and in some populations in the United States. To combat this problem, multivalent pneumococcal polysaccharide conjugate vaccines are now undergoing preliminary clinical studies (4). The pneumococcal conjugate vaccine contains several of the most common pediatric types, accounting for about 70% of pediatric invasive pneumococcal disease. New acellular pertussis vaccines have been in routine use for about 10 years in Japan and are now available elsewhere. In the United States, acellular pertussis vaccines are now combined with diphtheria and tetanus vaccines (DPT) for immu-

nization of toddlers (5). New vaccines are also available and under development for prevention of meningococcal disease. These include outer membrane protein vaccines against *Neisseria meningitidis* group B, and newly developed polysaccharide-protein conjugate vaccines for groups A and C disease (6, 7).

Almost all invasive bacterial pathogens of children have surface capsular polysaccharides. These polysaccharide capsules are virulence factors and are required for invasiveness. Antibodies to the capsule are protective, but their induction is age-dependent. The peak incidence of invasive disease occurs in children under 18 months of age, an age when polysaccharides are poorly immunogenic and often fail to induce protective levels of antibodies. Polysaccharides are T-cell-independent antigens, stimulating B cells directly, and do not prime for a booster response on re-exposure to the antigen. In contrast, proteins are T-cell-dependent antigens, eliciting help from T helper cells, and prime for an anamnestic antibody response in infants. When a polysaccharide or short oligosaccharide is covalently bound to a carrier protein, the resulting conjugate vaccine induces strong responses with immunologic memory in infants. The carrier protein provides the epitopes<sup>1</sup> required for the interaction of the conjugate with the T helper cells.

## II. *HAEMOPHILUS B* CONJUGATE VACCINES

In many countries *Haemophilus b* is the leading cause of invasive bacterial disease in children under 3 years of age. Meningitis accounts for approximately 50% of the invasive disease caused by *Haemophilus b*. Even with the best treatment, approximately 5 to 6% of children contracting *Haemophilus b* meningitis will die, and 25 to 35% of survivors will have neurological sequelae, most often hearing loss. The high costs of hospitalization and high incidence of sequelae make it very cost effective to prevent *Haemophilus b* disease through universal immunization along with other routine pediatric vaccines.

The first *Haemophilus b* conjugate vaccine licensed for immunization of young children was PRP-D, a vaccine produced by Connaught Laboratories and containing high molecular weight polysaccharide attached to diphtheria toxoid. This vaccine was approved in the United States in 1987 for use in children between 18 and 60 months of age and later approved for use in children as young as 15 months of age, although it was not licensed for use in infants, due to lower seroconversion rates with PRP-D compared with other *Haemophilus b* conjugate vaccines (2).

A *Haemophilus b* conjugate vaccine was approved for immunization of infants beginning at 2 months of age in 1990, and now three *Haemophilus b* conjugate vaccines have been approved in the United States and/or other countries. These are PRP-CRM, PRP-OMP, and PRP-T (see Table 1).

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<sup>1</sup> Also called "antigenic" determinants, they are recognition sites of the antigen that bind to the antibody in the antigen-antibody reaction.

**Table 1.** *Haemophilus b* conjugate vaccines

Trade name	Vaccine abbreviation	Manufacturer	Saccharide size	Protein carrier	Age at first immunization
Prohibit <sup>®</sup>	PRP-D	Connaught	Polysaccharide	Diphtheria toxoid	15 mo.
HibTITER <sup>®</sup>	PRP-CRM	Lederle-Praxis	Oligosaccharide Small	CRM <sub>197</sub> *	2 mo.
PedvaxHIB <sup>®</sup>	PRP-OMP	Merck Sharp & Dohme	polysaccharide	OMPC**	2 mo.
ActHIB <sup>®</sup>	PRP-T	Institute Mérieux	Polysaccharide	Tetanus toxoid	2 mo.

\* CRM<sub>197</sub> is a nontoxic mutant of diphtheria toxin.  
\*\* OMPC is vesicles of the outer membrane of *N. meningitidis* depleted of lipopolysaccharide.

PRP-CRM was approved for infant immunization on the basis of an efficacy trial in the Northern California Kaiser Permanente, a health maintenance organization, using a three dose primary immunization schedule at 2, 4, and 6 months of age (8). This trial was not randomized and placebo-controlled, but one in which the control group comprised two populations: those not offered the vaccine (excluded by day of birth) and those who were offered the vaccine, but refused. The trial, conducted in over 60,000 infants, showed the vaccine to be both safe and effective with an estimated efficacy of 100% after three doses. No *Haemophilus b* disease occurred after two doses, but little or no protection was seen after the first dose at 2 months of age.

The efficacy study with PRP-OMP was a double-blind-placebo controlled trial in over 4,000 Native American children, a high risk population with an incidence of *H. influenzae* type b disease approximately 10 times higher than the general United States population (9). Children were immunized with PRP-OMP at 2 and 4 months of age. Efficacy was analyzed after the primary two dose series. There was 1 case of disease in the vaccinated children compared to 14 in the placebo group, for an estimated efficacy of 93%. The single infection in the vaccine group occurred at 15 months of age before a booster dose could be offered. Between the first and second doses no cases of *Haemophilus b* disease occurred.

In the United States a decision was made to require a booster injection at 15 months of age for infants receiving PRP-CRM, and between 12 and 15 months of age for those receiving PRP-

OMP vaccine. This decision was based on several considerations. A number of the reported vaccine failures occurred a year or more after the primary immunization series in children who had not received a booster. A decline over time in vaccine-induced antibodies was observed, and the decline following PRP-OMP appeared to be greater than for PRP-CRM or PRP-T. By 12 to 15 months of age the geometric mean titer in PRP-OMP vaccinated children was only about 0.3 mg/ml, compared with over 1 mg/ml for PRP-CRM and PRP-T. A booster dose with any *Haemophilus* b conjugate vaccine at 12 to 15 months of age will induce a marked anamnestic response (10).

Immunologic surrogates for efficacy of *Haemophilus* b conjugate vaccine can be used to approve a future *Haemophilus* b vaccine. Studies of four different *Haemophilus* b conjugate vaccines have shown a number of common features that clearly differentiate the immune responses to conjugate vaccines compared to the unconjugated *Haemophilus* b polysaccharide. These include induction of antibodies in infants at an age when they do not respond to the native polysaccharide, induction of higher levels of IgG1 relative to IgG2, and priming of infants for a booster response to the native polysaccharide. Protection against *Haemophilus* b disease is associated with opsonic and bactericidal antibodies directed against the capsular polysaccharide (11). It is likely that opsonic activity alone is sufficient, because individuals with deficiencies in the late complement components appear not to be at increased risk of *Haemophilus* b disease, as they are for meningococcal disease. Bactericidal and opsonic antibody levels to *H. influenzae* type b are correlated (11). These immune surrogates were used in the United States as the basis for approval of PRP-T.

The *Haemophilus* b conjugate vaccine manufactured by Lederle-Praxis, PRP-CRM, is unique in that it does not contain the *Haemophilus* b polysaccharide, but oligosaccharides of about 25 repeat units attached directly to the diphtheria CRM<sub>197</sub> protein (Cross Reacting Mutant of *Corynebacterium diphtheriae*) (12). The CRM<sub>197</sub> protein is a naturally nontoxic variant of diphtheria toxin. PRP-CRM is a liquid formulation containing 10 mg of *Haemophilus* b oligosaccharide and 25 mg of CRM<sub>197</sub> protein per dose. The recommended immunization series is at 2, 4, 6, and 15 months of age.

Compared to the other conjugate vaccines, the Merck Sharp & Dohme vaccine has a number of unique properties. The protein carrier is not a component of the DPT vaccine, but is a lipopolysaccharide-depleted meningococcal outer membrane vesicle (13). Unlike the other vaccines, PRP-OMP induces a strong immune response in infants after the first dose. Recent studies suggest that the unique immunological properties of this vaccine are probably related to the nature of the protein carrier (14, 15). The vaccine is a freeze-dried product to be reconstituted with the aluminum hydroxide diluent provided by the manufacturer. Each dose of the reconstituted vaccine contains 15 mg of *Haemophilus* b polysaccharide covalently bound to 250 mg of meningococcal protein. The recommended immunization series is at 2, 4, and 12-15 months of age.

The full name of the *Haemophilus* vaccine produced by Pasteur Mérieux, in Lyon, France, is *Haemophilus* b conjugate vaccine (tetanus toxoid conjugate), but it is referred to as PRP-T.

Pasteur Mérieux used a conjugation procedure developed in the laboratory of John Robbins (16), whereby adipic acid dihydrazide is used to add a 6-carbon spacer molecule to the polysaccharide, which is then conjugated in the presence of EDAC [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide] to purified tetanus toxoid. The vaccine is lyophilized, and when reconstituted with saline contains 10 mg of polysaccharide and 24 mg of tetanus toxoid. The recommended immunization series is at 2, 4, 6, and 15 months of age.

Immunogenicity of these three *Haemophilus* b conjugate vaccines has been evaluated in comparative trials. The antibody levels after the primary immunization series are comparable (1, 17). Since PRP-OMP is the only vaccine that induces a strong antibody response after the first dose at 2 months of age, it may be the preferred vaccine for use in high-risk populations. There are as yet no data on whether one vaccine can be substituted for another during the primary immunization series.

During the first 20 months following approval of PRP-CRM and PRP-OMP for routine infant immunization in the United States, over 30,000,000 doses were administered, most frequently along with the DPT and oral polio vaccines. Attempts to assess the presence of possible rare adverse events in children receiving the *Haemophilus* vaccine are confounded because it is being administered with the much more reactogenic DPT vaccine and during the age period of the children coinciding with the peak incidence of sudden infant death syndrome (SIDS) and the appearance of neurologic problems. SIDS has a peak incidence between 3 and 5 months of age and occurs with a frequency of about 1 per 500 live births (18). Thus, the probability is high that SIDS will occasionally occur shortly after immunization and will therefore be reported to vaccine control authorities as vaccine associated. More studies are required to evaluate these associations.

### III. PNEUMOCOCCAL VACCINES

*Streptococcus pneumoniae* persists in many countries as an important cause of pneumonia, meningitis, and otitis media. These diseases remain some of the most prevalent infections in the United States and other areas of the world, particularly in young children, the elderly, and individuals with immunodeficiencies. In the United States, pneumococcal pneumonia accounts for 10 to 25% of all pneumonias, with an estimated 40,000 deaths each year. Pneumococcal bacteremia occurs in children under 2 years at a rate of 160 per 100,000, while the incidence of pneumococcal meningitis is 1-2 per 100,000 (19). Pneumococcal infections occur at all ages and are very common in infants. The incidence of pneumococcal disease decreases rapidly to a low level between 10 and 15 years of age, and then increases steadily with advancing age. Some pneumococcal types, including types 6, 14, 19, and 23, are more frequently associated with infections in pediatric patients than in older individuals.

The interest and emphasis on prevention of pneumococcal diseases through vaccination is growing. The immunologic defense mechanisms that resist pneumococcal infection involve interactions of host leukocytes and humoral components with the bacteria. Anti-polysaccharide

IgM and IgG antibodies confer specific protective immunity against pneumococcal infection. A major problem, however, is that the antibody response in young children to most of the capsular types is poor.

The immune system of infants differs from that of adults in both its relative lack of previous antigenic exposure and its functional immaturity. The immune system of the human infant becomes fully mature with regard to its response to polysaccharide antigens between 4 and 8 years of age (20). The lack of responsiveness to these antigens makes the age period between 6 and 24 months a time of especially high attack rates for pneumococcal infections, especially otitis media.

The current pneumococcal vaccine contains polysaccharides from 23 types, including types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. The 23-valent vaccine was licensed in the United States in 1983, replacing a 14-valent vaccine licensed in 1977. The types included in this vaccine account for approximately 88% of pneumococcal disease isolates found in the United States and Europe (21). The immunogenicity of pediatric pneumococcal types, e.g. types 6 and 14, is decreased in children under 5 (19, 22, 23).

The pneumococcal polysaccharide vaccine is effective in reducing morbidity and mortality in children due to acute lower respiratory tract infections (24). However, immunization of infants with this vaccine does not induce sufficiently high antibody levels to provide lasting protection against pneumococcal diseases (25). In pediatric patients, antibody titers against some types can fall to pre-immune levels 3-5 years after vaccination (26, 27). In contrast, in healthy adults the serum antibody titers to most vaccine types remain elevated for more than 5 to 10 years after vaccination (28).

Many studies support the use of the pneumococcal vaccine for certain high-risk groups of children, including those over 2 with chronic diseases, such as sickle cell disease, asplenia, nephrotic syndrome, cerebrospinal fluid leaks, conditions associated with immunosuppression, and HIV infection. The current polysaccharide vaccine is not indicated for patients whose only risk factors are recurrent upper respiratory tract disease, such as otitis media and sinusitis. Revaccination after 3 to 5 years should be considered for children with nephrotic syndrome, asplenia, or sickle cell anemia, who would be less than 10 years old at revaccination (28).

As with other polysaccharide vaccines, the pneumococcal vaccine is poorly immunogenic in children under 2. Alternative approaches are therefore being developed. One approach is to make pneumococcal polysaccharide-protein conjugate vaccines (5, 29). Such vaccines may successfully induce protective levels of antibodies in infants. Another approach to improve the pneumococcal vaccine is to add additional pneumococcal antigens. The pneumococcus has a number of virulence factors in addition to the capsular polysaccharide, such as pneumolysin and other cell-surface antigens (30, 31), which are being studied for their ability to induce increased antibodies and long-term memory. The ideal candidate would be a protein molecule produced by all types of pneumococci and suitable for use as a carrier for the polysaccharide in a conjugate vaccine. For example, enhanced immunogenicity of the type 6A and 19F polysac-

charides has been achieved by covalent attachment to carrier proteins, including inactivated pneumolysin (16, 32).

#### IV. PERTUSSIS VACCINES

Pertussis (whooping cough) remains a deadly disease, especially in young children. The disease can, however, be effectively controlled by vaccination. The effectiveness of vaccination is illustrated by the experience in the United States. In the prevaccine era, the mean attack rate was 157 per 100,000 population; by 1981 the rate had decreased to less than 1 per 100,000 population (33). Deaths from the disease followed a similar decline.

Currently, two types of pertussis vaccines are in use, whole cell vaccines and acellular vaccines. Both types are usually combined with diphtheria and tetanus toxoids and are administered as tricomponent (DPT) vaccines. The whole cell pertussis vaccine, as its name indicates, is composed of killed whole cells of *Bordetella pertussis*. Although production methods often differ between manufacturers, in general, *B. pertussis* cultures are grown, harvested, concentrated, and then killed by heat or chemicals such as thimerosal or by a combination of both. This component is then combined with the diphtheria and tetanus toxoids.

Efficacy of most whole cell pertussis vaccines is generally considered to be 80% or greater, as demonstrated by the original efficacy trials conducted by the British Medical Research Council (34). More recent studies have confirmed that the efficacy of whole cell pertussis vaccines is 80% or greater (35), although lower estimates for vaccine efficacy have been reported (36).

Although millions of doses of whole cell pertussis vaccines are administered each year and effectively control the disease, they do have certain side-effects. While most of the side-effects are relatively minor in nature, more serious reactions can and do occur. The vaccine has been associated with both local and systemic reactions (37). Local reactions include redness, swelling, and pain at the injection site. Systemic reactions include fever (greater than or equal to 38° C), drowsiness, fretfulness, vomiting, anorexia, and persistent crying. Certain serious reactions such as seizures, hypotonic-hyporesponsive state, encephalopathy, and even death have been temporally associated with vaccination; however, the evidence for a causal effect is weak (33).

Because whole cell pertussis vaccines are associated with certain side-effects, attempts were begun in the late 1970s to develop a new type of pertussis vaccine that would contain protective immunogens from the bacteria but none of the toxic materials produced by the organism. These new types of vaccines are called acellular pertussis vaccines, because they do not contain whole cells of *B. pertussis* but only a few bacterial proteins.

To determine which proteins from *B. pertussis* should be included as antigens in the new vaccines, researchers studied the pathogenesis of *B. pertussis* infection to obtain clues as to which antigens might be protective. Virulent forms of *B. pertussis* first attach to ciliated epithelial cells of the respiratory tract. The organism produces toxins which likely allow the organism to evade host defenses, cause local tissue damage, and impair the host's immune system (38-40). Therefore, adhesins and inactivated toxins as well as exposed outer membrane proteins were potential candidates for protective antigens. Four types of proteins that fit these criteria and

could also be purified in quantities sufficient for vaccine production were identified. They were inactivated pertussis toxin, filamentous hemagglutinin (FHA), pertactin, and fimbriae.

Inactivated pertussis toxin is included in all acellular pertussis vaccines in use as well as experimental acellular pertussis vaccines that are currently undergoing evaluation for efficacy. Pertussis toxin is released by the organism and is believed to act, at least in part, by impairing the immune system of the host (40). Since this protein is toxic, it must be inactivated before inclusion in vaccines. Current methods for inactivation include chemical methods such as treatment with formaldehyde (41) or hydrogen peroxide (42) or inactivation using recombinant DNA techniques (43). A monovalent vaccine composed of formaldehyde-inactivated pertussis toxin was shown to protect humans against the disease (44).

Most acellular pertussis vaccines also contain FHA in addition to pertussis toxin. FHA is a filamentous protein. It has a molecular weight of approximately 200,000 and mediates the attachment of the organism to cells (45). Clinical trials in humans demonstrated that a vaccine composed of FHA and inactivated pertussis toxin protected humans against infection better than a vaccine composed of inactivated pertussis toxin alone (46).

Certain acellular pertussis vaccines also contain pertactin and/or fimbriae. Pertactin is an outer membrane protein that appears to play a role in attachment of the organism to the cell (47). The biological role of *B. pertussis* fimbriae remains unclear. Both types of proteins have been shown to be protective in animal models (48, 49). The ability of these antigens to contribute to protection against disease in humans is currently under study.

Clinical trials have demonstrated that acellular pertussis vaccines are generally associated with fewer local reactions and less fever than whole cell vaccines (50), although reaction rates vary among the vaccines. Evidence for efficacy of acellular pertussis vaccines comes from three sources: epidemiologic data from Japan, household contact studies in Japan, and a randomized, placebo-controlled double-blind trial of two acellular pertussis vaccines conducted in Sweden in 1985-1986. Epidemiologic data from Japan indicate that the incidence of pertussis there since 1981, the year that acellular pertussis vaccines were introduced, has remained low, suggesting that Japanese acellular pertussis vaccines as a group are effective (51).

Several household contact studies that have been conducted provide some product-specific efficacy information (52, 53). Data from the large-scale phase III trial conducted in Sweden gave an estimate of efficacy 54% (95% confidence interval 26-72%) for a monovalent (pertussis toxoid) vaccine and 69% (95% confidence interval 47-82%) for a bivalent (pertussis toxoid plus FHA) vaccine when a case was defined as cough of greater than seven days with culture confirmation (44). Vaccine efficacy estimates increased to 80% for the monovalent vaccine and 79% for the bivalent vaccine when protection against a more serious form of the disease, culture-confirmed pertussis with more than 30 days cough, was considered.

In both Japan and the United States, acellular pertussis vaccines are generally recommended only for immunization of children 15 months of age or older, although immunization of infants as young as 3 months has recently begun in Japan. Since little product-specific efficacy

data are available for infants less than six months old, clinical studies are continuing to gather the data that would be necessary to allow expanded use of these vaccines in younger children.

## V. OTHER VACCINES USED IN PEDIATRIC POPULATIONS

Significant developments have been reported for improved protection against two additional bacterial pathogens: *Salmonella typhi* and *N. meningitidis*.

Typhoid fever is a systemic disease of humans caused by encapsulated *S. typhi*. Typhoid fever is still a common disease with a significant morbidity and mortality in countries that do not have adequate drinking water and sewage disposal. Immunization can provide protection for individuals traveling to or living in such countries.

High rates of adverse reactions are associated with the use of the parenteral whole cell *S. typhi* vaccines. Two additional vaccines are now available, the live oral attenuated Ty21a vaccine and the typhoid Vi capsular polysaccharide (54, 55). Both have been shown to be effective in preventing typhoid fever in children, and both are markedly less reactogenic compared with the killed whole cell vaccines. The live oral Ty21a vaccine, produced by the Swiss Serum Institute, requires three or four doses given over a period of several days. The purified Vi polysaccharide vaccine produced by Pasteur Mérieux is administered as a single parenteral injection. A large randomized controlled efficacy trial of the Vi polysaccharide vaccine in Nepal showed 74% (49-87%) efficacy in children 5 years and older (56). The duration of protection in children is not fully known, but several countries recommend reimmunization with the Vi polysaccharide after 3 years (57).

Meningococcal disease remains a significant health problem in many countries, and prevention has proven to be a cost-effective public health measure (58). There are 12 different serogroups of *N. meningitidis*, but over 90% of meningococcal disease is caused by groups A, B, and C. Protection is due to induction of bactericidal and opsonic antibodies.

The United States Immunization Practices Advisory Committee (ACIP) has formulated recommendations for the use of currently available polysaccharide vaccines (59). The most effective use of meningococcal vaccines is for the control of outbreaks and epidemics and for vaccination of individuals entering high risk areas. The A/C polysaccharide vaccine is not recommended for routine immunization, but has been shown to be effective in stopping epidemics (60). The vaccine is effective above 2 years of age, but the duration of protection in young children may be less than 2 years (61). Meningococcal polysaccharide vaccines have been used on several occasions in the last few years to control group C outbreaks in the United States and Canada, especially outbreaks associated with educational institutions. A group B meningococcal outer membrane protein vaccine is used routinely in young children in Cuba with good results (62).

Although there is an effective polysaccharide vaccine for prevention of disease due to serogroups A and C in older children and adults, in children under 2 years of age the vaccine induces only short-term protection against group A and little or no protection against group C. In addition, the group B polysaccharide is poorly immunogenic and antibodies to the B polysaccharide do not appear to be protective.

Two significant developments that will help reduce the public health impact of meningococcal disease are the use of polysaccharide-protein conjugates for serogroups A and C and the use of outer-membrane protein vaccines for serogroup B (6, 7). Vaccines similar to the *Haemophilus b* conjugate vaccine were produced by conjugation of oligosaccharides derived from the group A and group C polysaccharides to the CRM<sub>197</sub> protein. The bivalent conjugate vaccine has been studied in adults and children for safety and immunogenicity (7).

A number of alternative cell surface antigens have been investigated as potential group B vaccine candidates, but only lipopolysaccharide-depleted outer membranes have been clinically evaluated. A number of efficacy trials with group B outer-membrane protein vesicle vaccines have been conducted, the first of which was in South Africa in the early 1980s (63). More recently trials have been conducted in Chile, Cuba, and Norway (64, 62, 65). These studies demonstrated efficacy rates between 50 and 80%. An important result of these efficacy trials is the demonstration that antibodies induced to non-capsular surface antigens can protect against meningococcal disease.

## VI. CONCLUSIONS

Significant advances have been made in the development of safer and more effective bacterial vaccines specifically indicated for the pediatric population. These newer vaccines are much less reactogenic than the whole cell vaccines, because they contain only purified bacterial components such as the capsular polysaccharide or toxoids, such as inactivated pertussis toxin. The infant is especially susceptible to a number of diseases because of an immature immune system. Infants respond well to protein antigens, such as the new acellular pertussis vaccine, because these antigens activate T-helper cells that stimulate an antibody response and immunologic memory. In contrast, since polysaccharides do not normally stimulate T-helper cells, effective vaccines against encapsulated bacteria have required modification of the polysaccharide by covalent attachment to protein carriers. Conjugate technology may be applied to a variety of encapsulated bacteria, thereby enhancing vaccine immunogenicity. *Haemophilus b* conjugate vaccines are now routinely administered to infants in many countries, where they have caused a marked reduction in *H. influenzae* type b disease. A reduction in whooping cough is anticipated as a result of higher vaccine coverage with the introduction of more widely accepted safe and effective acellular pertussis vaccines.

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