Can Haemophilus influenzae type b disease be eliminated from the United States?

In this issue of The Journal, Singleton et al describe the epidemiology of Haemophilus influenzae type b disease and oropharyngeal carriage since the introduction of Hib conjugate vaccines in the Alaskan Native populations in 1990. Among the Alaskan Native populations, invasive Hib disease declined from 332 cases per 100,000 children <5 years of age to 17 cases per 100,000 from 1980 to 1991. However, when the vaccine type was switched from the meningococcal outer-membrane protein conjugate vaccine to Hib oligosaccharide-CRM197 vaccine for the first dose in 1995, the rates of Hib disease increased to 57.9 cases per 100,000 children <5 years of age. Oropharyngeal carriage studies in this population during 1997 and 1998 demonstrated rates of carriage that were as high as 9.3%. These rates of Hib carriage are...
to 3 times the rates of carriage that were observed in general U S populations before the introduction of H ib conjugate vaccines. T he continued cir-
culation of the organism in the commu-
nity, as evidenced by H ib carriage rates and the switch to a vaccine that did not induce protection after the first dose, are probably the major causes of re-emergence of disease in this popu-
lation. T hese findings have implications for the control of H ib disease both in the United States and developing countries around the world.

Before the widespread use of H ib conjugate vaccines in the United States, 20,000 cases of H ib disease occurred each year, and 50% to 60% of cases were meningitis. T he mortality rate from H ib disease ranged from 3% to 10%, and 20% to 30% of patients had neurologic sequelae. In the past 10 years, the incidence of H ib disease in the United States has declined by 99%. O ne of the Healthy People 2010 objectives is to eliminate H ib disease in the United States. Is this a realistic goal? H ib is a pathogen unique to humans, and there are no known reservoirs of infection outside of the human host. In addition, highly efficacious vaccines are currently available. T he H ib conjugate vaccines have also been demonstrated to markedly reduce oropharyngeal carriage, thus reducing the chances of exposure of susceptible individuals to the organism, which could result in reduction in disease among non-immunized children. T hrough these unique features, it should be possible to eliminate the disease with the widespread use of H ib vaccines. N evertheless, there are substantial constraints to achieving this goal.

T he age distribution of H ib disease varies widely. In many European countries such as Finland, the peak incidence of H ib disease occurs between 12 and 24 months of age, and <5% of cases occur before 6 months of age. In the general U S population, before the use of H ib conjugate vaccines, the peak incidence of disease occurred between 6 and 11 months of age, with <15% of cases occurring before 6 months of age. In contrast, over 80% of cases occur before 1 year of age and 30% to 40% of cases occur before 6 months of age among the Navajo and Apache populations. In developing countries, the age distribution of H ib disease is similar to that of the Native American populations in the United States.

F rom 1996 to 1997, there were only 144 cases of documented H ib disease in the United States. T he highest rates of H ib disease among children <5 years of age occurred among the Native American populations (12.4 vs 0.7 among the non-H ispanic white population). In the United States, 48% of cases occurred before 6 months of age in 1996 to 1997 compared with <15% of cases in that age group before 1990. T his shift in age distribution of the disease suggests that the current vaccine programs in the United States are more effective in preventing H ib cases in infants and children >6 months of age compared with younger infants.

Among the 3 H ib conjugate vaccines that are used in the United States (PRP-O M P, H ib oligosaccharide-CRM 197 vaccine, and PRP-T, tetanus toxoid vaccine), only the PRP-O M P induces a significant antibody response after the first dose. In the efficacy trial conducted among the Navajo population from 1988 to 1990, PRP-O M P was demonstrated to begin protection after the first dose. B etween the first dose of the PRP-O M P vaccine at 2 months of age and the second dose at 4 months of age, 8 cases occurred in the placebo group, but there were no cases in the vaccine group (vaccine efficacy, 100%; 95% CI, 41%-100%). T he other 2 vaccines have not been demonstrated to begin protection until the second dose. T hus if a susceptible infant comes in contact with the H ib organism before receiving at least 2 doses of H bO C or PRP-T, the infant may not be protected. O n the other hand, both PRP-T and H bO C have been shown to induce higher antibody levels after completion of the primary series compared with PRP-O M P. Previous studies have demonstrated that infants who receive the first dose of PRP-O M P vaccine at 2 months of age, followed by one of the other H ib conjugate vaccines, have better antibody responses after the primary series than infants who complete the series with PRP-O M P alone. T hus a vaccine schedule consisting of the PRP-O M P, followed by either PRP-T or H bO C, would provide higher antibody levels both after the first dose and after the primary series. U nfortunately, the “protective levels” of H ib antibodies are not known for H ib conjugate vaccines. T herefore it is not clear that the peak antibody levels after the primary series have any clinical relevance. Because H ib conjugate vaccines induce a T-cell–dependent response even if the infant has low levels of antibodies, there should be a brisk antibody re-
sponse when he or she comes in contact with the organism. Two children who were previously immunized with PRP-T were documented to become carriers of H ib during the study period. T hese individuals had dramatic rises in levels of anti-PRP antibody levels (1.2 to 550 µg/mL and 0.2 to 61.8 µg/mL).

A ll of the H ib conjugate vaccines have been shown to not only protect against disease but also to reduce oropharyngeal carriage. T he rates of H ib disease among infants <2 months of age in the United States began to de-

Table: Hib Vaccines

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<tr>
<th>Vaccine</th>
<th>Components</th>
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<tr>
<td>HbOC</td>
<td>Haemophilus influenzae type b oligosaccharide-CRM197 vaccine</td>
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<tr>
<td>Hib</td>
<td>Haemophilus influenzae type b conjugate vaccine</td>
</tr>
<tr>
<td>PRP-OMP</td>
<td>Polyribosylribitol phosphate-outer-membrane protein conjugate vaccine</td>
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<tr>
<td>PRP-T</td>
<td>Polyribosylribitol phosphate-tetanus toxoid vaccine</td>
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cline before the routine immunization with HIB conjugate vaccines in this age group. This phenomenon probably occurred because reduction in oropharyngeal carriage among vaccinated infants resulted in reduction in transmission of the organism. In Alaska, the rates of carriage remained high despite widespread use of HIB vaccine in the population. In contrast, in studies among the Navajo and Apache populations, the rates of oropharyngeal carriage of HIB were found to be substantially lower in recent years compared with the period when HIB conjugate vaccines were not routinely used on the reservation (unpublished data). In the Navajo and Apache populations, PRP-O-M-P has been the predominant vaccine used in the last 10 years. It is unclear why the rates of oropharyngeal carriage have remained high in Alaskan Natives compared with the Navajo and Apache populations. Neither study was designed to evaluate the relative efficacy of HIB vaccines in reducing HIB carriage. Data in rat models suggest that higher antibody levels correlate with ability to reduce nasopharyngeal carriage. However, it is unlikely that the ability of a vaccine to reduce carriage is based solely on the antibody levels.

Several factors may influence the rates of carriage in a population, including age of the subject, environment (smoking, use of wood burning stoves), and intensity of exposure (crowding, day-care attendance, number of siblings in the household). Unfortunately, none of the studies to date have evaluated the dynamics of HIB carriage in the household. It is possible that in Alaska, adults act as a reservoir and transmit the HIB organism to the infants. In the United States in 1994 to 1995, 159 of 340 cases (44%) HIB cases occurred in individuals >5 years of age—an age group for which HIB vaccination is not currently recommended. As long as the HIB organism continues to circulate in the population, un-immunized susceptible individuals will continue to be at risk for disease. If we are to achieve the goal of eliminating HIB disease in the United States, the dynamics of transmission must be understood so that appropriate interventions can be implemented to reduce or eliminate carriage.

Given this situation, is it possible to eliminate HIB disease by the year 2010? Eradication is defined as permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed. Elimination of disease is defined as reduction to zero of the incidence of a specific disease in a defined geographic area as a result of deliberate efforts; continued intervention measures are required. It is my view that eradication is not a realistic goal. However, elimination of HIB disease in the United States is a realistic goal, provided that appropriate resources and interventions are put in place in the next few years.

Every new case of HIB disease should be considered a sentinel event, and the circumstances surrounding the event should be investigated, including immunization coverage in the community, HIB carriage among the household members, and immunization status of the susceptible individuals in the household. Additional studies should be conducted to understand the dynamics of HIB transmission within the community and the household, especially in high-risk populations such as American Indians and Alaskan Natives. The ability of HIB vaccines to induce a booster response should be evaluated in children 5 to 10 years after receipt of the HIB vaccine at the recommended schedule before 2 years of age. High-risk adult populations such as individuals with human immunodeficiency virus and those who are immunocompromised should be vaccinated with HIB vaccines. Most importantly, the immunization coverage rates in all communities should be maintained at rates as high as possible. In communities in which relatively high rates of disease continue to occur despite high rates of vaccine coverage, the dynamics of transmission of HIB carriage should be evaluated, and appropriate interventions should be implemented. In communities in which a substantial proportion of cases occur before 6 months of age, PRP-O-M-P should be used for the first dose.

Worldwide, 500,000 deaths are estimated to occur as a result of HIB disease each year. The obstacles to elimination of HIB disease in developing countries are formidable. Physicians in many countries do not believe that HIB is an important cause of morbidity and mortality in their respective populations, primarily because of lack of data on disease burden. In addition, the cost of the vaccine is prohibitive relative to the economic means of most developing countries. There are also major barriers to the production and distribution of HIB vaccines in developing countries. Nevertheless, if there is political will, it should be possible to provide HIB vaccine to every child in the world. If that goal can be achieved, elimination of disease worldwide may be a realistic possibility in the future. A journey of a thousand miles begins with the first step. I believe that we have already taken the first step. Let us continue our journey until we reach our destination—elimination of HIB disease.

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REFERENCES


