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

In this issue of The Journal, Singleton et al[1] 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 pop-

ulations, 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-CRM_{197} 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 2

to 3 times the rates of carriage that were observed in general US populations before the introduction of Hib conjugate vaccines. The continued circulation of the organism in the community, as evidenced by Hib 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 population. These findings have implications for the control of Hib disease both in the United States and developing countries around the world.

HbOC	*Haemophilus influenzae* type b oligosaccharide-CRM$_{197}$ vaccine
Hib	*Haemophilus influenzae* type b
PRP-OMP	Polyribosylribitol phosphate–outer-membrane protein conjugate vaccine
PRP-T	Polyribosylribitol phosphate–tetanus toxoid vaccine

Before the widespread use of Hib conjugate vaccines in the United States, 20,000 cases of Hib disease occurred each year, and 50% to 60% of cases were meningitis.[2] The mortality rate from Hib disease ranged from 3% to 10%, and 20% to 30% of patients had neurologic sequelae. In the past 10 years, the incidence of Hib disease in the United States has declined by 99%.[3] One of the Healthy People 2010 objectives is to eliminate Hib disease in the United States. Is this a realistic goal? Hib 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. The Hib 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 un-immunized infants.[4-6] For example, in the Navajo nation, once 50% of the children <2 years of age were immunized with polyribosyl-ribitol phosphate–outer-membrane protein conjugate vaccine, there was close to 75% reduction in the rates of

disease among non-immunized children.[7] Because of these unique features, it should be possible to eliminate the disease with the widespread use of Hib vaccines. Nevertheless, there are substantial constraints to achieving this goal.

The age distribution of Hib disease varies widely. In many European countries such as Finland, the peak incidence of Hib disease occurs between 12 and 24 months of age, and <5% of cases occur before 6 months of age.[8] In the general US population, before the use of Hib conjugate vaccines, the peak incidence of disease occurred between 6 and 11 months of age,[9] with <15% of cases occurring before 6 months of age.[10] 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.[11,12] In developing countries, the age distribution of Hib disease is similar to that of the Native American populations in the United States.[13]

From 1996 to 1997, there were only 144 cases of documented Hib disease in the United States.[3] The highest rates of Hib disease among children <5 years of age occurred among the Native American populations (12.4 vs 0.7 among the non-Hispanic 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.[10] This shift in age distribution of the disease suggests that the current vaccine programs in the United States are more effective in preventing Hib cases in infants and children >6 months of age compared with younger infants.

Among the 3 Hib conjugate vaccines that are used in the United States (PRP-OMP, Hib oligosaccharide-CRM$_{197}$ vaccine, and PRP–tetanus toxoid vaccine), only the PRP-OMP induces a significant antibody response after the first dose. In the efficacy trial conducted among the Navajo population from 1988 to 1990, PRP-OMP was demonstrated to begin protection

after the first dose.[14] Between the first dose of the PRP-OMP 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%). The other 2 vaccines have not been demonstrated to begin protection until the second dose. Thus if a susceptible infant comes in contact with the Hib organism before receiving at least 2 doses of HbOC or PRP-T, the infant may not be protected. On the other hand, both PRP-T and HbOC have been shown to induce higher antibody levels after completion of the primary series compared with PRP-OMP.[15,16] Previous studies have demonstrated that infants who receive the first dose of PRP-OMP vaccine at 2 months of age, followed by one of the other Hib conjugate vaccines, have better antibody responses after the primary series than infants who complete the series with PRP-OMP alone.[17] Thus a vaccine schedule consisting of the PRP-OMP, followed by either PRP-T or HbOC, would provide highest antibody levels both after the first dose and after the primary series. Unfortunately, the "protective levels" of Hib antibodies are not known for Hib conjugate vaccines. Therefore it is not clear that the peak antibody levels after the primary series have any clinical relevance. Because Hib conjugate vaccines induce a T-cell–dependent response even if the infant has low levels of antibodies, there should be a brisk antibody response 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 Hib during the study period.[18] These individuals had dramatic rises in levels of anti-PRP antibody levels (1.12 to 550 µg/mL and 0.2 to 61.8 µg/mL).

All of the Hib conjugate vaccines have been shown to not only protect against disease but also to reduce oropharyngeal carriage.[4-6] The rates of Hib disease among infants <12 months of age in the United States began to de-

cline before the routine immunization with Hib conjugate vaccines in this age group.[19] 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-OMP 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.[20] 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 (44%) Hib cases occurred in individuals >5 years of age—an age group for which Hib vaccination is not currently recommended.[3] 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.[21] 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 dynam-ics 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-OMP should be used for the first dose.

Worldwide, 500,000 deaths are estimated to occur as a result of Hib disease each year.[22] 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

1. Singleton R, Bulkow LR, Levine OS, Butler JC, Hennessy TW, Parkinson A. Experience with the prevention of invasive *Haemophilus influenzae* type b disease by vaccination in Alaska: the impact of persistent oropharyngeal carriage. J Pediatr 2000;137:313-20.
2. Cochi SL, Broome CV, Hightower AW. Immunization of US children with *Haemophilus influenzae* type b polysaccharide vaccine: a cost-effectiveness model of strategy assessment. JAMA 1985;253:521-9.
3. Bisgard KM, Kao A, Leake J, Strebel

PM, Perkins BA, Wharton M. *Haemophilus influenzae* invasive disease in the United States, 1994-1995: near disappearance of a vaccine-preventable childhood disease. Emerg Infect Dis 1998;4:229-37.

4. Takala AK, Eskola J, Leinonen M, et al. Reduction of oropharyngeal carriage of *Haemophilus influenzae* type b (Hib) in children immunized with an Hib conjugate vaccine. J Infect Dis 1991;164:982-6.

5. Takala AK, Santosham M, Almeido-Hill J, et al. Vaccination with *Haemophilus influenzae* type b meningococcal protein conjugate vaccine reduces oropharyngeal carriage of *Haemophilus influenzae* type b among American Indian children. Pediatr Infect Dis J 1993;12:593-9.

6. Adegbola RA, Mulholland EK, Secka O, et al. Vaccination with a *Haemophilus influenzae* type b conjugate vaccine reduces oropharyngeal carriage of *Haemophilus influenzae* type b among Gambian children. J Infect Dis 1998;177:1758-61.

7. Moulton LH, Chung S, Croll J, et al. Estimation of the indirect effect of Hib conjugate vaccine in an American Indian population. Int J Epidemiol 2000;29. In press.

8. Takala AK, Eskola J, Peltola H, Makela H. Epidemiology of invasive *Haemophilus influenzae* type b disease among children in Finland before vaccination with *Haemophilus influenzae* type b conjugate vaccine. Pediatr Infect Dis J 1989;8:297-302.

9. Broome CV. Epidemiology of *Haemophilus influenzae* type b infections in the USA. Pediatr Infect Dis J 1987;6:779-82.

10. Ward J, Leiberman JM, Cochi SL. *Haemophilus influenzae* vaccines. In: Plotkin SA, Mortimer EA, editors. Vaccines. 2nd ed. Philadelphia: WB Saunders Co; 1994. p. 337-86.

11. Losonsky GA, Santosham M, Sehgal VM, Zwalen A, Moxon ER. Haemophilus influenzae disease in the White Mountain Apaches: molecular epidemiology of a high risk population. Pediatr Infect Dis J 1984;3:539-47.

12. Coulehan JL, Michaels RH, Hallowell C, et al. Epidemiology of *Haemophilus influenzae* type b disease among Navajo Indians. Public Health Rep 1984;99:404-9.

13. Funkhouser A, Steinhoff MC, Ward J. *Haemophilus influenzae* disease and immunization in developing countries. Rev Infect Dis 1991;13(Suppl 6):S542-554.

14. Santosham M, Wolff M, Reid R, Hohenboken M, Bateman M, Goepp J, et al. The efficacy in Navajo infants of a conjugate vaccine consisting of Haemophilus influenzae type b polysaccharide and Neisseria meningitidis outer-membrane protein complex. N Engl J Med 1991;324:1767-72.

15. Bulkow LR, Wainwright RB, Letson GW, et al. Comparative immunogenicity of four *Haemophilus influenzae* type b conjugate vaccines in Alaska Native infants. Pediatr Infect Dis J 1993;12:484-92.

16. Decker MD, Edwards KM, Bradley R, Palmer P. Comparative trial in infants of four conjugate *Haemophilus influenzae* type b vaccines. J Pediatr 1992;120:184-9.

17. Greenberg DP, Lieberman JM, March SM, et al. Enhanced antibody responses in infants given different sequences of heterogeneous *Haemophilus influenzae* type b conjugate vaccines. J Pediatr 1995;126:206-11.

18. Heath PT, Bowen-Morris J, Griffiths D, et al. Antibody persistence and *Haemophilus influenzae* type b carriage after infant immunization with PRP-T. Arch Dis Child 1997;77:488-92.

19. Adams WG, Deaver KA, Cochi SL, et al. Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. JAMA 1993;269:221-6.

20. Kauppi M, Saarinen L, Kayht H. Anticapsular polysaccharide antibodies reduce nasopharyngeal colonization by *Haemophilus influenzae* type b in infant rats. J Infect Dis 1993;167:365-71.

21. Dowdle WR, Hopins DR. The eradication of infectious diseases report of the Dahlem Workshop on the Eradication of Infectious Diseases, Berlin, March 16-22, 1997. Chichester: John Wiley & Sons; 1998.

22. Levine OS, Wenger J, Perkins YB, Rosenstein N, Schuchat A. *Haemophilus influenzae* type B infection. Bull WHO 1998;76(Suppl 2):131-2.