Toward Global *Haemophilus influenzae* Type b Immunization

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(See the article by Russell et al. on pages 1593-9)

*Haemophilus influenzae* type b (Hib) conjugate vaccines, consisting of the type b capsular saccharide covalently linked to a protein carrier or a bacterial protein membrane complex, were put into clinical use in the late 1980s. Prior to the introduction of these conjugate vaccines, Hib was the leading cause of meningitis, epiglottitis, and other life threatening bacterial infections in infants and young children in the US and other industrialized countries [1]. Since their introduction, the incidence of Hib disease in the US has decreased by 98% among children <5 years of age. A similar decrease has been achieved in the 21 other relatively affluent countries that had introduced the Hib vaccine into their immunization programs as of 2000 [2]. The significance of these accomplishments was appropriately recognized in 1996, when John Robbins, Rachel Schneerson, David Smith, and Porter Anderson, Jr., were jointly awarded the Lasker Award in Clinical Medical Research for developing Hib conjugate vaccines. Indeed, the near elimination of Hib disease in industrialized countries is arguably the major success story in pediatrics in the last 2 decades. Moreover, borrowing similar technology, conjugate vaccines for pneumococcal disease have been introduced with similarly impressive results. Meningococcal conjugate vaccines have had success in England and seem poised for expanded development and deployment.

Due to the success of the Hib program in industrialized countries and the global burden of Hib disease, the World Health Organization (WHO) has encouraged the introduction of Hib vaccines worldwide [3]. Despite this, the majority of the world’s children still remain unvaccinated. The reasons for this poor rate of coverage in most developing countries are several: the lack of clear definitions, in many nations, of the epidemiology of Hib disease; a lack of agreement as to the disease burden threshold that should compel universal vaccination; and the expense of Hib conjugate vaccines.

Prior to the introduction of any new vaccine, it is important to demonstrate a clear need for the intervention. Defining the incidence of Hib disease in developing countries has been difficult. There are several reasons for this difficulty. The bacteriology of Hib has remained challenging for many clinical microbiology laboratories, thus hindering the easy recognition of Hib as an etiologic agent. Optimal growth conditions require media supplemented with nicotinamide adenine dinucleotide and hemin, and they are not always available. Additionally, in many countries, antibiotics are frequently given to patients prior to diagnostic testing, and, in some locales, clinical practice for patients with presumed meningitis does not dictate routine lumbar punctures. Moreover, many children may not have access to medical facilities. Even if they reach a hospital or clinic, diagnostic capabilities are often not available [4, 5].

For these reasons, Hib disease may often be undetected. When this occurs, resistance to the need for an Hib vaccination program is understandable, because of a belief that there is a relatively low burden of Hib disease. This belief, whether correct or not, has influenced decision making in many areas of the world, particularly in Asia. It does seem clear, however, that Hib disease is present throughout many parts of Asia [2, 5, 6] and, most likely, throughout the world. The principal appears to be “the harder one looks, the more Hib disease one finds.” The additional issue of what prevalence threshold is sufficient for commitment to a vaccination program is an important one that will need to be addressed by individual public health authorities.

Another important issue is that the epidemiology of Hib disease in many developing countries appears to differ from that in industrialized countries. In some developing countries, the incidence of in-
vasive Hib disease is higher than it was in the prevaccine era in the US. In such instances, the age-specific incidence of Hib disease is shifted to younger children, with a substantial proportion of cases occurring in children <6 months of age. Epiglottitis may be rare, and pneumonia may be more frequent than meningitis, with varying pneumonia/meningitis ratios depending on locale [7]. This is of importance, because proving the etiology of nonbacterial pneumonia is often impossible, despite the importance of pneumonia as a leading cause of death in children in the developing world.

How to better define the scope of Hib disease? In The Gambia, Mulholland et al. [7], in effect, used an Hib vaccine as a probe to define the prevalence of Hib disease. In a double-blind, randomized study, infants received 3 doses of Hib vaccine or of a placebo. The vaccine was efficacious in preventing 95% of proven, invasive Hib disease. Surprisingly, the vaccine also had efficacy (21%) against radiologically defined pneumonia, which was an unexpected effect. These data implied that ~20% of cases of pneumonia in young Gambian children were probably due to Hib, a rate higher than had been believed by most experts [7].

Using a vaccine to define disease prevalence, however, is not a pragmatic approach. To answer the need for a less costly approach, the WHO developed the Hib Rapid Assessment Tool (RAT). The Hib RAT protocol requires reliable data on the rate of meningitis and pneumonia and an estimate of the ratio of Hib meningitis to Hib pneumonia. With the use of 2 methods outlined in the WHO Hib RAT protocol, Russell et al. [8] calculated the incidence of Hib disease in several Pacific island countries. They demonstrated that the incidence of Hib meningitis in these countries was higher than the worldwide average. The RAT methodology had also been separately validated in Fiji, where it was used to evaluate the incidence of Hib both before and after introduction of the vaccine [9]. These studies are of importance because they provide evidence that a quick and simple tool to assess Hib disease burden in developing countries works in a reliable way. Furthermore, they demonstrate that Hib is a significant problem in all of these countries and underline the need for a vaccination program.

Even when the need can be demonstrated, however, another major obstacle to worldwide vaccination has been the cost. Cost-effectiveness analyses indicate that introduction of the Hib vaccine is economically sound, even though manufacturing conjugate vaccines is a costly process. Indeed, the current cost of a single dose of an Hib vaccine is greater than the current cost, in some developing countries, of completely immunizing a child with 1 dose of bacillus Calmette-Guérin vaccine; 3 doses of poliovirus live oral vaccine; 3 doses of diphtheria, tetanus, and pertussis vaccine; and a dose of measles vaccine; this prohibits the use of Hib vaccine in the poorest developing countries [2, 4, 10]. Fortunately, the Global Alliance for Vaccines and Immunizations (GAVI) has recognized Hib as an “underutilized vaccine.” As of July 2003, GAVI estimated that, in conjunction with the Vaccine Fund, ~4.3 million children in developing countries have received Hib vaccines with its assistance since 2000 [11].

GAVI, however, cannot do the job alone. Vaccine manufacturers will have to help. Vaccines must be sold to poorer countries at lowered prices. Additionally, research to investigate the possibility of using a lower number of injections to achieve protection or a smaller antigen dose for each injection should be funded. Combining Hib with other vaccines may at least decrease administrative costs and, therefore, the cost of an Hib vaccination program. Additionally, forming vaccine manufacturing partnerships with manufacturers in developing countries or enabling countries to manufacture their own vaccines, as has been initiated by the Serum Institute of India, are other avenues for exploration of the development of Hib immunization programs at lower cost [2, 4].

Providing access to Hib conjugate vaccines—and to pneumococcal and meningococcal conjugate vaccines—for all of the world’s children will require greater compassion, cooperation, and creativity. As Peltola [2, pg. 313] stated in 2000, “Safe and efficacious Hib vaccines should no longer be the privilege of certain peoples: preventing 38,000 cases a year among more than 2 million (a meager 1.7%, perhaps less) is just the beginning.”

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References

