Haemophilus influenzae Serotype b Vaccine Failure: What Is the Significance of Antibody Levels?

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(See the article by Ladhani et al on pages 372–80)

The introduction of Haemophilus influenzae serotype b (Hib) conjugate vaccine has been a major step in the prevention of meningitis, epiglottitis, and other manifestations of invasive Hib disease. Because these diseases occur mainly in children, vaccination during infancy prevents the vast majority of cases within a few years. The optimal schedule for Hib vaccination is still a matter of debate. In the United Kingdom, one of the first countries to implement Hib conjugate vaccination in the infant immunization program (in 1992), a vaccine scheme of 3 doses at 2, 3, and 4 months of age was initially applied. Together with a catch-up campaign, this caused a dramatic decrease in the incidence of invasive Hib disease. However, starting in 1999, there was an increase in the number of vaccine failures (i.e., cases of invasive Hib disease after receipt of Hib conjugate vaccine). This prompted a booster campaign in 2003 and, eventually, the introduction of a routine booster dose in the second year of life. A number of other countries had implemented such a vaccination scheme (3 doses in the first year of life and a booster in the second year) from the beginning of their Hib immunization programs [1].

In this issue, Ladhani et al [2] report an extensive and conscientious study of the antibody response to the vaccine substance polyribosylribitol phosphate (PRP), the Hib capsule, in children in the United Kingdom several years after these children experienced Hib vaccine failure. From 1992 through 2005, 388 cases occurred; the authors received a completed questionnaire from 67% and analyzed a blood sample from 167 (43%), which was probably a representative sample. The main conclusions of the study are that a significant proportion (57%) of these children have antibody concentrations below the putative long-term protection level (1.0 mg/mL) and that low antibody concentrations (<0.15 mg/mL) are independently associated with the 3 following factors: young age at Hib disease onset, underlying conditions, and surprisingly, a shorter time from Hib disease to follow-up. This last observation warrants further explanation, because normally, antibody concentrations tend to decrease after infection or immunization and would be expected to be lowest in children with a longer time from Hib disease to follow-up. The authors attribute their finding to the fact that the rate of carriage of Hib in children has decreased since the introduction of routine Hib vaccination. Reduced carriage rates mean less contact of the population with the bacterium and, thus, less natural boosting of the immune system. Therefore, it is plausible that, some years after the start of the routine vaccination, antibody levels began to decrease both in the vaccinated and in the nonvaccinated population. This could be a reason for the increase in the number of vaccine failure cases and in the incidence of invasive Hib disease in general. The authors may be correct that, in recent years, the insufficient stimulation of T and B lymphocyte memory resulted more often in low antibody levels, even after infection, than in the first years after the introduction of vaccination. However, the main laboratory parameter that would support this conclusion, an anti-PRP antibody concentration <0.15 μg/mL, was found in only 27 children (16%) with vaccine failure, and this number may be too small to draw firm statistical conclusions. This issue is still more complicated because some of the children with vaccine failure had been revaccinated after having the disease, but others were revaccinated only when their anti-PRP antibody concentration was <1.0 μg/mL; this variable was not included in the analysis.
With regard to the above conclusions, 2 questions arise. First, what does it mean that 57% of the children have anti-PRP antibody concentrations <1.0 μg/mL? Are these children prone to have a second episode of invasive Hib disease? If yes, which policy should doctors and health authorities pursue? Recurrence of invasive Hib disease is an extremely rare condition, rarer than invasive disease due to 2 other encapsulated bacteria, *Streptococcus pneumoniae* and *Neisseria meningitidis*. Recurrence of Hib disease did not occur in the cohort described by Ladhani et al [2], but it has been described, especially in a population with an extraordinary high incidence of Hib disease, such as Alaskan Natives [4]. No data are available that enable us to estimate the risk of recurrence among persons who have experienced vaccine failure. Because Hib conjugate vaccine is very well tolerated, it is common practice in the United Kingdom and in some other countries to revaccinate children after they have experienced vaccine failure. It might be advisable to revaccinate children with an anti-PRP antibody concentration <0.15 μg/mL. On the other hand, the data do not allow conclusions on the magnitude of the initial anti-PRP response in the study population. They do show that long-term antibody levels can decrease to <0.15 μg/mL. Moreover, it may be inevitable that some vaccinees will never produce sufficient antibody and that they cannot be protected optimally.

The second question is, how do these antibody concentrations in children with vaccine failure relate to those in healthy children? The study attempts to address this question by comparing the anti-PRP antibody concentrations in children with vaccine failure with those measured in population control subjects aged <16 years: one group of children that provided a blood sample during 1990–1991, before the Hib vaccination era (the unvaccinated cohort), and one from 2000, when most children would have received the Hib vaccine (the vaccinated cohort). In most age groups (2–4 years, 5–7 years, and 12–15 years), the mean antibody level in children with vaccine failure was lower than that in control subjects. Among children aged 8–11 years, antibody concentrations in children with vaccine failure were 3-fold higher than those in control subjects. However, most of these differences were not statistically significant, leading to the conclusion that antibody concentrations in children with vaccine failure do not greatly differ from those in control subjects. Among the population control subjects, a substantial number of children had an antibody concentration <0.15 μg/mL, but there is no a priori reason that they would be at risk for invasive Hib disease.

Finally, what is the cause of Hib vaccine failure? Eleven of the 167 investigated children with Hib vaccine failure had immunoglobulin A deficiency (which is higher than in the general population), but other primary immunodeficiency diseases were rare. An invasive (Hib) infection can be the first clinical sign of common variable immunodeficiency. This long-term follow-up study by Ladhani et al [2] showed that there was no recurrence of Hib disease or other major infections and that immunoglobulin levels in the majority of children were within the normal range for age, making it highly unlikely that Hib vaccine failure is attributable to common variable immunodeficiency.

This UK research group and others have been investigating several other risk factors of Hib vaccine failure, such as prematurity, covaccination with acellular pertussis and other vaccines, and differences among the Hib capsular genes [5, 6]; however, in spite of all that, the pathogenesis of Hib vaccine failure remains incompletely elucidated.

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**References**


