

Summary of Wyeth Lederle Position on DTaP-Hib Combination Vaccines

Hib conjugate vaccines have had an enormous benefit for the health of children. The most common cause of bacterial meningitis has been virtually eliminated in the US. Disease rates in the highest risk groups have declined by ~ 99% (Bisgard et al *Emerging Infectious Diseases* 4:229, 1998). Most of the cases that remain occur in unimmunized or inadequately immunized children.

This success has been achieved by three vaccines licensed in the US for infants, HbOC, PRP-T and PRP-OMP. The first two, which account for the majority of vaccine used, produce high levels of antibody after primary immunization (geometric mean concentrations usually in the 4 to 10 $\mu\text{g/ml}$ range) and after toddler boosting (GMCs in 15 to 40 $\mu\text{g/ml}$ range).

Such high levels of antibody may be substantially more than the minimum needed for protecting the individual child from invasive Hib disease. However high levels may have the added benefit of eliminating nasal carriage and reducing spread of Hib among healthy children.

In considering whether new combination vaccines containing DTaP and Hib should be introduced into the US one must consider whether the likely benefit outweighs the potential risks.

The benefit of reducing the number of injections in the crowded childhood schedule is clear for parents and immunization providers. However, it is not clear whether the large number of shots that are currently required has impeded vaccine acceptance. Immunization rates in the US are at an all time high. The decision to change from oral to inactivated polio vaccine indicates that preventing a few serious adverse events is considered more important than giving all children three extra shots.

The risk of introducing the DTaP-Hib combination vaccines is that the number of invasive Hib cases may increase above the very low number we see currently. In most studies, the DTaP-Hib combination vaccines induce significantly lower Hib antibody levels than the two vaccines given separately. The GMCs average 2 $\mu\text{g/ml}$ but range from < 1 $\mu\text{g/ml}$ to 6 $\mu\text{g/ml}$. (J. Eskola. *Lancet* 354:2063, 1999)

It has been argued recently that the reduced antibody concentration may not be important clinically because infants will be immunologically "primed" by conjugate vaccines and this will provide protection. Protection by priming infers that children whose antibody levels have declined to low or undetectable levels when they are exposed to Hib will have time (i.e., a minimum of 4 to 7 days) to develop an active response which will protect them from invasive disease. The evidence suggests that this is usually the case for Hib disease: infants whose Hib antibody levels decline to very low levels nevertheless have high levels of protection presumably due to priming. (R. Booy, et al *Lancet*, 349: 1197, 1997). However, it is also likely that the interval between exposure and invasive disease is sometimes too short to develop an active protective response. The likelihood of rapid invasion may vary by organism (? most common for meningococcus, intermediate for Hib and least

common for pneumococcus based on the tendency of these organisms to cause outbreaks), nature of exposure and host factors.

Several lines of evidence suggest that priming may not provide absolute protection against Hib.

1. In the US about 1/3 of Hib vaccine failures occurred in children who had 3 infant doses or one toddler dose which are protective and prime the immune system.
2. In the UK, where only 3 doses of Hib conjugate are given on a 2, 3, 4 month schedule, the failure rate increases from 0.8% in the first year to 2.7% in the second year to 5.3% in the 3rd year (R. Booy et al).
3. In the pre-vaccine era older children developed invasive Hib disease even though they were capable of developing a rapid antibody response to PRP. Most older children with documented Hib meningitis developed Hib antibody levels > 1µg/ml within 1 or 2 days of admission (P. Anderson, D. Ingram, personal communication).

Are the number of invasive Hib cases likely to increase in the US if DTaP Hib combinations are introduced and enter widespread use? The answer, of course, is not known but the following are reasons why this may occur.

1. More children will have waning antibody levels which may make them vulnerable to rapidly invasive Hib disease.
2. In practice, many children are incompletely immunized or receive their shots late. The current Hib vaccines appear to have sufficient immunogenicity to provide substantial protection to such children. It is not clear whether this would occur with less immunogenic vaccines.
3. Hib carriage may increase. The concentration of anti-PRP required to reduce carriage may be substantially higher than that, to protect from invasive disease (3 to 7 µg/ml, J. Eskola, Lancet, 354, 2063, 1999). As a consequence, herd immunity would be diminished and increased Hib exposure would occur for vulnerable children including unimmunized or incompletely immunized infants and immunocompromised children.

In considering the question of whether the benefit of DTaP/Hib Combos (convenience of fewer doses, potential improved vaccine acceptance) outweighs the risks (potential increased invasive Hib disease in the US after a decade of very low rates), two additional questions are relevant to this decision:

1. Can additional information be obtained to assess whether vaccines with lower immunogenicity are associated with more breakthrough Hib disease?
2. Can the benefits of fewer injections be obtained without taking this risk?

The first question may be answerable by comparing vaccine failure rates of Hib vaccines that differ in immunogenicity in the US and other countries.

The answer to the second question is clearly yes. In the near term combination vaccines which contain DTaP, IPV and Hepatitis B vaccine are likely to become available, reducing the number of injections. In the longer term, it may be possible to combine the Hib conjugate with other vaccines (e.g., pneumococcal and/or meningococcal conjugates) without reducing Hib antibody responses.