Haemophilus influenzae Type B (Hib) Antibody Responses in Children Given Diphtheria-Tetanus-Acellular Pertussis-Hib Combination Vaccines

To the Editor—Goldblatt et al. [1] reported that the individual responses to the different vaccine antigens among a group of infants given a diphtheria-tetanus toxoid–acellular pertussis toxin–Haemophilus influenzae type b (DTaP-Hib) conjugate (polyribosylribitol phosphate–tetanus toxoid [PRP-T]) combination vaccine were positively correlated, so that infants with a high antibody response to 1 antigen tended to have a high response to the others and vice versa. They speculate that this may reflect individual variation in the degree of age-dependent maturation of the immune system.

We studied 2 cohorts of infants in successive years; the first was given diphtheria-tetanus toxoid–pertussis toxoid (DTP)-Hib vaccine containing whole-cell pertussis toxin (DTPwP-Hib vaccine) [2], and the second was given DTaP-Hib vaccine containing a 2-component pertussis vaccine component (Aventis Pasteur, Lyon, France) [3, 4]. In both series, the Hib vaccine was a tetanus conjugate (PRP-T; Pasteur Mérieux), and doses of tetanus and diphtheria toxoids were identical. Like Goldblatt and colleagues, we observed positive correlations between the responses to PRP and other vaccine antigens in both groups (table 1), and, like them, we noted a closer correlation between the anti-PRP response and the anti-tetanus response than between other antigen pairs, which was statistically significant in both series. This difference was particularly marked in the DTPwP-Hib group.

However, we question the explanation of this phenomenon proposed by Goldblatt et al. [1]. The tendency to find positive correlations for responses to nearly all antigen pairs supports the idea of a “general” ability to respond, which varies in size consistently for all antigens from one individual to another, but this cannot explain the closer relationship between the responses to the 2 tetanus toxoid–containing vaccine components. Dagan and colleagues [5] have also reported a significant positive correlation between anti-PRP and anti-tetanus responses in mixing studies involving DTPwP-Hib combinations containing PRP-T, and they failed to show any significant correlation between anti-Hib and anti-diphtheria responses. They offer several hypothetical immunological mechanisms to explain their observations [5].

The variety and unpredictability of mixing effects observed to date in clinical studies involving protein-polysaccharide conjugate vaccines [6] suggest that a single, simple explanation will not emerge and that physicochemical, demographic, age, and dose-regimen effects may all be operating. However, the consistent observation of a positive correlation in the size of individuals’ antibody responses to these related antigens, together with a reduction in response to both Hib and tetanus components when DTP and PRP-T vaccines are combined in the same syringe [7–10], suggests that an antigen-specific immunological mechanism is also operating. The positive correlation between tetanus and Hib antibody responses argues against carrier-induced epitopic suppression operating through competition between antigens [6], but it may instead reflect variation in the efficacy of T cell help when related antigens are combined at the same injection site.

Table 1. Pearson’s correlation coefficients between anti-PRP-T antibody responses and antibody responses to other antigens, as shown at 5 months of age in infants given 3 doses of a combined DTP-Hib (PRP-T) vaccine at 2, 3, and 4 months of age.

<table>
<thead>
<tr>
<th>Anti-PRP-T and antibody responses to combination DTP-Hib vaccines</th>
<th>Pearson’s correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertussis toxoid</td>
<td>Filamentous hemagglutinin</td>
</tr>
<tr>
<td>Combination with whole-cell pertussis vaccine (n = 143)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Combination with acellular pertussis vaccine (n = 130)</td>
<td>+0.34a</td>
</tr>
</tbody>
</table>

NOTE. PRP-T, polyribosylribitol phosphate–tetanus toxoid; DTP-Hib, diphtheria-tetanus toxoids–pertussis–Haemophilus influenzae type b; ND, not determined.

References


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Reply

To the Editor—The only point of clarification that we would like to make relates to the assertion by Finn et al. [1] that, in our previous report [2], we tried to explain the significant correlation between reduced responses to Haemophilus influenzae type b (Hib) and tetanus vaccines by individual variations in the degree of age-dependent maturation of the immune system. This was a general comment, and, in fact, in paragraph 4 of our original discussion, we highlighted that the most marked responses to vaccine antigens other than Hib were to tetanus. The correspondence by Finn et al. is, essentially, a rebuttal of an assertion that we did not make. We also do not understand the reference to Hib and tetanus being related antigens, because they are quite distinct chemically.

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Role of Fas/FasL in Systemic Candidiasis

To the Editor—Netea et al. [1] reported that MRL/lpr mice, which lack a functional Fas molecule, have higher rates of survival than do control animals after systemic challenge with the yeast Candida albicans. We also have studied the role of Fas/FasL in systemic candidiasis, with different results. B6.MRL-Fas(h) and B6Smn.C3H-Fasl(h) mice, obtained from the Walter and Eliza Hall Institute (Melbourne), were bred under conventional conditions at the John Curtin School of Medical Research (Canberra), which also supplied the C57Bl/6J controls. The mice were inoculated intravenously with a sublethal dose of C. albicans (strain 3630 from the Mycology Reference Laboratory, Royal North Shore Hospital, Sydney) at age 8–10 weeks and were killed on day 5 after infection; the fungus burden in brain and kidney was determined by plating on Sabouraud agar. Tissue samples were processed for histologic examination. Compared with control mice, B6.MRL-Fas(h) mice showed a small but significant decrease in the number of colonies recovered from the brain but not the kidney (table 1); however, there were no detectable differences in the severity of tissue lesions (data not shown).

Several variables may have contributed to the discrepancy between the 2 experiments. First, our mice were bred under conventional, rather than pathogen-free, conditions. Second, we used a sublethal dose of C. albicans, in contrast to Netea et al. [1], who reported substantial mortality in both experimental and control groups. However, autoimmune disease in homozygous MRL/Mp mice occurs at age 8 weeks, and 50%

Table 1. Fungal burden in the brain and kidney of Fas and FasL mutant mice.

<table>
<thead>
<tr>
<th>Mouse strain</th>
<th>No.</th>
<th>Brain</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>B6.MRL-Fas(h)</td>
<td>5</td>
<td>4.85 ± 0.09*</td>
<td>5.86 ± 0.14</td>
</tr>
<tr>
<td>B6Smn.C3H-Fasl(h)</td>
<td>5</td>
<td>5.10 ± 0.06</td>
<td>5.43 ± 0.16</td>
</tr>
<tr>
<td>C57Bl/6J</td>
<td>8</td>
<td>5.26 ± 0.10</td>
<td>5.89 ± 0.12</td>
</tr>
</tbody>
</table>

NOTES. Data are mean ± SEM of log10 cfu/g tissue.

* Significantly less than C57Bl/6J (P < .05).