Safety and Immunogenicity of an Acellular Pertussis Vaccine in Premature Infants

Rolf L. Schloesser, MD; Doris Fischer, MD; Walter Otto, MD; Werner Rettwitz-Volk, MD; Peter Herden, PhD; and Stefan Zielen, MD

ABSTRACT. Objectives. To evaluate the safety and immunogenicity of a two-component acellular pertussis vaccine in preterm infants.

Study Design. Fifty preterm infants (25–35 weeks of gestation; mean, 30.8 weeks) and 50 term infants as a control group received a two-component acellular pertussis vaccine irrespective of their biological age and actual weight. Adverse reactions were registered by parents on a diary card and reviewed on each visit. Antibodies against pertussis toxoid (PT) and filamentous hemagglutinin (FHA) were determined with an enzyme-linked immunosorbent assay before the first and after the third vaccination.

Results. The infants of both groups showed an increase in geometric mean titers (GMT) against PT and FHA after vaccination (3 doses). There was a significant difference of antibody concentration between the preterm and the control group. The GMT for PT antibody of the preterm infants was 64.16 U/L, and for the term infants it was 98.96 U/L. The GMT for FHA was 50.92 U/L in preterm versus 86.02 U/L in the control group. Efficacy of the immunization (more than a fourfold increase of antibody concentration in each infant) was 93.5% in the preterm group with respect to PT and 82.6% with respect to FHA. The incidence of adverse reactions was low and comparable in both study groups.

Conclusion. Immunization with an acellular pertussis vaccine is safe for preterm infants. The immune response is significantly lower compared with a control group of term infants, but efficacy is high. Pediatrics 1999;103(5). URL: http://www.pediatrics.org/cgi/content/full/103/5/e60; immunization. pertussis vaccine, preterm infant, adverse effects, immunogenicity.

ABBREVIATIONS. PT, pertussis toxin; FHA, filamentous hemagglutinin; GMT, geometrical mean titer.

Official authorities recommend immunization of preterm infants at 2 to 3 months of their chronological age. Nevertheless, there is some uncertainty in clinical practice about implementing this policy because of fear of a higher incidence of adverse effects and doubt about immunogenicity and efficacy of early vaccination.1,2 In particular, immunization with whole cell pertussis vaccine is often withheld in preterm infants because of reports of apnea in these patients.3,4 On the other hand, preterm infants should have protection against pertussis by vaccination at the same time as other term infants. Infection with Bordetella pertussis in premature infants is more severe because of immaturity of the immune system and a higher incidence of chronic lung disease after mechanical ventilation.5

Previous studies on vaccination of preterm infants have been done with whole cell antigen and showed results in preterm infants that were comparable to term infant controls.6–8 Acellular pertussis vaccines have not yet been tested. They are not as reactogenic as whole cell vaccine and have good immunogenicity.9 Therefore, we conducted a study of reactogenicity and immunogenicity of acellular pertussis-vaccine in premature infants.

METHODS

The study was approved by the local ethical committee and written parental consent was obtained.

Patients

From August 1995 through August 1996, 100 infants were enrolled in our study. Fifty were term infants treated by one practitioner (W.O.); the 50 preterm infants were selected from one perinatal center (Children’s University Hospital, Frankfurt, Germany). Prematurity was defined according to the World Health Organization criteria, ie, birth before 37 weeks of gestation. Gestational age was determined by medical records (based on early ultrasound examination in pregnancy). The preterm infants were selected in sequence. Vaccination of their infants was also offered to those parents who did not agree to the study. No blood for antibody measuring was obtained before or after immunization in these cases.

We included only infants without evidence of severe neurologic damage such as complicated intracranial bleeding (grade III and IV, periventricular leukomalacia, and nontreatable convulsions). The other exclusion criteria included the usual items for immunization studies, ie, positive human immunodeficiency virus status of the mother, genetic disorders, and infection within the last 2 days before vaccination.

All infants were vaccinated with a two-component acellular pertussis vaccine (Pa-Vaccinol; Procter Gamble Pharmaceuticals [Weiterstadt, Germany]; Pa-Vaccinol is corresponding to CU-2, which is licensed for Connaught/Biken [Swiftwater, PA] in the United States as Tripedia in a 3-valent vaccine) in their lateral leg combined with HibDT (HibDT-Vaccinol; Procter Gamble Pharmaceuticals) in their contralateral site. Each volunteer of both groups received a 0.5-mL suspension of Pa-Vaccinol for each vaccination from the same lot.

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Twenty-two infants had various diseases in their medical history, ie, retinopathy of prematurity, necrotizing enterocolitis, or chronic lung disease. The infants of the control group were healthy and without any evidence of a disease in their history.

Safety

Adverse reactions to the acellular pertussis vaccine are shown as cumulative reports in Table 2. Most of the parents (90% to 100%) did not observe redness or swelling at their children’s site of vaccination with any of the 3 doses of both vaccines. In the control group, redness or swelling >30 mm in diameter was reported in a total of 5 cases (redness, 2 infants; swelling, 3 infants). In the preterm group, 2 cases of redness >30 mm in diameter were seen, one after the first and the other after the second vaccination. No infant in this group had a local swelling on the injection site. Tenderness on pressure was reported in 2.0% to 18.4% of the cases, in 9 after the first vaccination, 4 after the second vaccination, and 2 cases each after the third vaccination. Swelling and tenderness on pressure were reported more often in the first 2 days after vaccination. The incidence of generalized adverse reactions was comparable in both study groups. Only 1 patient in the control group and 1 infant in the preterm group had fever >38.5°C on day 1 and 3 of the third vaccination. Mothers of term infants used antipyretic drugs more often. It is important to note that in no case was the study halted because of a severe adverse reaction.

Immunogenicity

There was a significant rise of geometrical mean titer (GMT) in the antibodies to PT and FHA in both groups. The GMT for PT was 4.46 U/L in the preterm group and 4.56 U/L in the control group. After the third immunization, the antibody titer rose to 64.16 U/L in the preterm group and 98.96 U/L in the control group. The difference between the two groups was significant (P < .003). The rise in GMT in the preterm group was 14-fold. The values for FHA were similar: after the last dose of vaccine, the GMT in the preterm group was 50.92 U/L and in the control group it was 86.02 U/L (P < .0001; Table 3).

Because a protective antibody titer for pertussis is not known, we cannot conclude whether vaccination has been effective in all cases. Nevertheless, there was antibody conversion and we can assume an efficient immune response to be after a more than fourfold rise as many other studies do. In the preterm group immunization was effective in 93.5% of

### Results

Forty-six preterm infants completed the study. One was excluded because a cerebral abnormality was diagnosed later. Serologic data are missing for 3 additional infants: 2 siblings moved after their second immunization and a third infant moved after his third immunization. In total, 144 vaccinations were implemented in the preterm group and 150 in the control group.

The median birth weight of the preterm infants was 1365.6 g (630–2580 g). In the group of infants weighing <1500 g (n = 36) the median birth weight was 1108 g (630–1490 g), in the group weighing >1500 g (n = 14) the median birth weight was 2028 g (1600–2580 g). The mean gestational age of the premature infants was 30.8 weeks (Table 1). At their first vaccination, the premature infants had a median age of 9.7 weeks (corrected age, 1.35 weeks). Seven preterm infants had various diseases in their medical history, ie, retinopathy of prematurity, necrotizing enterocolitis, or chronic lung disease. The infants of the control group were healthy and without any evidence of a disease in their history.

### Safety

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### Immunogenicity

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### Table 1

Characteristics of the 50 Preterm Infants Enrolled in the Study

<table>
<thead>
<tr>
<th>n</th>
<th>Birth Weight Mean, g</th>
<th>Range, g</th>
<th>Gestational Age Mean, Week</th>
<th>Range, Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>50</td>
<td>1365.6</td>
<td>(630–2580)</td>
<td>30.8</td>
</tr>
<tr>
<td>&lt;1500 g</td>
<td>36</td>
<td>1108</td>
<td>(630–1490)</td>
<td>29.5</td>
</tr>
<tr>
<td>≥1500 g</td>
<td>14</td>
<td>2028</td>
<td>(1600–2580)</td>
<td>33.9</td>
</tr>
</tbody>
</table>

* Data of the two groups of premature infants <1500 g and ≥1500 g are shown separately.
the infants with respect to PT and in 82.6% of the infants to FHA. In the control group the effectiveness was 98% and 92%, respectively. This difference was not significant (Table 4).

The serologic response to vaccination neither correlated with the weight at birth nor with the gestational age of the preterm infants. The GMT for PT of infants <1500 g was 65.16 U/L, and in infants >1500 g the GMT was 64.73 U/L. For FHA the corresponding values were 51.8 U/L and 48.7 U/L. Two preterm group infants who showed no increase in antibodies were infants of 2160 g and 2270 g, respectively.

**DISCUSSION**

A variety of studies have demonstrated the efficacy of different vaccines in premature infants. With respect to diphtheria, tetanus, and polio, the immunogenic response was comparable to a control group of term infants. With hepatitis B immunization an adequate antibody titer could be reached when the infants were older than 1 month. Immunization with *Haemophilus influenzae* type B antigen showed lower antibody titers in the preterm group than in the control group. In studies with pertussis vaccine no significant difference was found between preterm and term infants with regard to seroconversion. All these studies were done with whole cell vaccine, and success of immunization was proven by various laboratory tests. Pullan and Hull also used an enzyme-linked immunosorbent assay technique to analyze antibodies against pertussis. They found a slight difference in antibodies of preterm versus term infants, but there was no difference in efficacy.

In our study, a two-component acellular pertussis vaccine was used for the first time in immunization of premature infants. Contrary to other investigations, we found a significant difference in antibodies against PT and FHA between preterm and control infants. However, there was an increase in antibodies of 95.4% and 97.5%, respectively, in preterm infants. In contrast to diphtheria and tetanus immunization, in which a protective antibody level has been determined, such levels for pertussis immunizations are unknown. In addition, the concentration of antibodies does not correlate with the efficacy of immunization. However, the lower antibody concentration after the third vaccination could be important for the long-term protection, so that a forth immunization should be discussed and studied in preterm infants.

The lower titers of antibodies against acellular pertussis as well as *H influenzae* can be explained by an impaired immunologic competence of premature infants. A further reason could be the smaller muscle mass of these infants. Lower antibody concentration for FHA were also found with subcutaneous vaccination when compared with intramuscular injections.

A special immunization schedule with a delayed third vaccination could be beneficial. Conway et al showed that antibody levels against pertussis were higher after the third immunization, when given at 10 months of age. However, antibodies might be lower in the time between second and third immunization and the risk of pertussis disease could be higher in this vulnerable phase.

**TABLE 3.** Geometric Mean Titer [U/L] for PT and FHA Antibodies of 46 Preterm and 50 Term Infants Before (Baseline) and After Third Vaccination (Postvaccination)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Time</th>
<th>Statistics</th>
<th>Preterm Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GMT</td>
<td>min-max</td>
<td>P</td>
</tr>
<tr>
<td>Anti-PT</td>
<td>Baseline</td>
<td>4.46</td>
<td>4–40</td>
<td>(3.91, 5.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% CI</td>
<td></td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>Postvaccination</td>
<td>64.16</td>
<td>12–206</td>
<td>(51.39, 80.10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>min-max</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Anti-FHA</td>
<td>Baseline</td>
<td>5.19</td>
<td>3–26</td>
<td>(4.2, 6.42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% CI</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postvaccination</td>
<td>50.92</td>
<td>8–153</td>
<td>(42.28, 61.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>min-max</td>
<td>P</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GMT, geometric mean titer; PT, pertussis toxoid; FHA, filamentous hemagglutinin; CI, confidence interval.

**TABLE 4.** Efficacy of Immunization*

<table>
<thead>
<tr>
<th></th>
<th>PT</th>
<th>FHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Preterm (total)</td>
<td>43 (46)</td>
<td>93.5</td>
</tr>
<tr>
<td>&lt;1500 g</td>
<td>32 (33)</td>
<td>96.9</td>
</tr>
<tr>
<td>≥1500 g</td>
<td>11 (13)</td>
<td>84.6</td>
</tr>
<tr>
<td>Control</td>
<td>49 (50)</td>
<td>98</td>
</tr>
</tbody>
</table>

Abbreviations: PT, pertussis toxoid; FHA, filamentous hemagglutinin.

* Efficacy was assumed when a fourfold increase in antibody concentration was reached. Infants are documented who did have such an increase. Differences between preterm and control group was not significant (Fisher’s exact test).
have described apnea in premature infants after vaccination with whole cell pertussis vaccine. In our study we found none of these adverse reactions. Further studies should be instigated to show whether preterm infants with neurologic disease could profit from acellular pertussis vaccine.

CONCLUSION

In summary, immunization with an acellular pertussis vaccine is safe for preterm infants. The antibody concentration is lower compared with a term infant control group; however, seroconversion is noted in most of these infants. More studies are needed to show clinical efficacy of immunization with acellular pertussis vaccine in premature infants.

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