Acellular Pertussis Vaccines: Recommendations for Use as the Fourth and Fifth Doses

Committee on Infectious Diseases

In December 1991, the US Food and Drug Administration (FDA) licensed the first diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) for administration to children as the fourth and fifth doses of diphtheria, tetanus, and pertussis immunization. The product consists of an acellular pertussis vaccine produced by Japan’s Takeda Chemicals and diphtheria and tetanus components produced byLed-erle Laboratories, Division of American Cyanamid. It is expected that one or more additional acellular pertussis vaccine(s) will be licensed in the future.

The American Academy of Pediatrics (AAP) recommends that children routinely receive a series of five doses of vaccine against diphtheria, tetanus, and pertussis before 7 years of age. The FDA-approved DTaP vaccine (ACEL-IMUNE) is licensed for use only as the fourth and fifth doses for children who have been immunized previously with at least three doses of diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine. It is not licensed for the initial series of three doses in infants and children or for use in children younger than 15 months of age or after the seventh birthday. The following recommendations supplement previous AAP guidelines for use of whole-cell pertussis vaccines as the fourth and fifth doses and provide a follow-up to a previous AAP statement on acellular pertussis vaccines, which contains more complete background information.

BACKGROUND

The whole-cell pertussis vaccines currently used in the United States are prepared from inactivated cells of Bordetella pertussis and contain multiple antigens (Table 1). In contrast, the acellular vaccines contain one or more immunogens derived from the B pertussis organism. These antigens include an inactive form of lymphocytosis promoting factor (LPF), also known as pertussis toxin (PT), and filamentous hemagglutinin (FHA), both of which are prominent components of most acellular pertussis vaccines. Other constituents that may be included in acellular vaccines are agglutinogens. At present, no data exist that suggest that the two types differ in rates of side effects or efficacy. The recently FDA-licensed product is a T-type vaccine.

Efficacy and Immunogenicity of the Acellular Pertussis Vaccines

The acellular pertussis vaccine currently is approved only for the fourth and fifth doses because of lack of data on efficacy when used for the initial three doses for children beginning at 2 months of age. Information on the efficacy of the acellular pertussis vaccines is primarily derived from their use in Japan, the only country in which these acellular vaccines previously have been licensed, and from a large placebo-controlled vaccine trial in Sweden. Immunogenicity and safety data are available from other countries, including the United States. Acellular pertussis vaccines were licensed in Japan in 1981 and have been used exclusively for routine immunization of children beginning at 2 years of age. In 1988 the Japanese Minister of Health recommended that initiation of immunization with acellular pertussis vaccine be lowered to 3 months of age, and this recommendation has been put into effect in some areas of Japan. Data on efficacy in Japan and in the Swedish trial have been reviewed in a recent AAP statement.

Effectiveness of acellular pertussis vaccine against disease due to B pertussis in Japan has been demonstrated in children 2 years of age and older, but not in infants. A low secondary attack rate has been demonstrated in household contacts of Japanese children who had received an acellular pertussis vaccine identical in the pertussis vaccine components to that in the DTaP vaccine licensed by the FDA. In addition, two acellular pertussis vaccines (one a B-type vaccine containing PT and FHA, and another containing only PT) that were evaluated in Sweden during the period from 1985 to 1987 in a large placebo-controlled trial. Beginning with children at 6 months of age, either vaccine or placebo was administered in two doses separated by 8 to 12 weeks. Neither vaccine was of the T type recently licensed in the United States. Observed protection varied according to the definition used for pertussis cases. The greatest decrease in disease was for culture-confirmed cases that were more severe. A licensure application has been made.
for a B-type vaccine based in part on the results of this Swedish trial. The acellular pertussis vaccines have not been compared to the whole-cell pertussis vaccine in any efficacy study to date.

When used for the fourth and fifth doses in infants previously vaccinated with whole-cell pertussis vaccine, the immunogenicity of the antigens comprising the FDA-licensed DTaP vaccine was similar to that of whole-cell DTP vaccine, when concentrations of serum antibody to PT, FHA, agglutinogens, and/or the 69-kd protein were measured. In addition, antibody responses were demonstrated when this acellular pertussis vaccine was given for primary vaccination to 3 groups of children, ages 3 to 8 months, 9 to 23 months, and 24 to 30 months. However, in the Swedish trial antibody responses could not be correlated with protection against disease. Thus, antibody response to the various vaccine antigens thus far measured cannot be used to predict efficacy.

ADVERSE REACTIONS

The rates of local reactions (erythema and induration at the injection site), fever, and other common systemic symptoms (drowsiness, fretfulness, and anorexia) after receiving the DTaP inoculation have been lower than those in children of similar age following whole-cell DTP vaccination. Acellular pertussis vaccines appear to have similar rates of reactions in infants as in older children, except for drowsiness after the first dose in one trial. Whether the rare, more serious reactions occur less frequently after acellular pertussis vaccine is unclear. In Japan serious adverse events were observed in children vaccinated at 2 years of age at approximately the same low rate from 1975 to 1981 when whole-cell vaccines were used, as during the period from 1981 to 1984 when acellular vaccines were used exclusively. In a Swedish trial involving 241 children, 2 children who received a two-component (B-type) acellular pertussis vaccine as a fourth or fifth dose developed serious systemic reactions: 1 had hypotonia and the other had persistent and unusual, high-pitched crying. In a trial utilizing DTaP vaccine in infants in the United States, a hypotonic-hyporesponsive episode was noted after both DTP and DTaP vaccinations, indicating that the DTaP vaccine may not eliminate the occurrence of this reaction.

RECOMMENDATIONS

1. All infants should be immunized with five doses of pertussis vaccine beginning at 2 months of age, or as soon as possible thereafter unless contraindicated or unless the fourth dose was given after the fourth birthday. The initial series of three doses should be given with the whole-cell preparation as part of the DTP series. Insufficient data are available at present regarding the use of acellular pertussis vaccines in the primary series. Whole-cell pertussis vaccine is the only product recommended for use for primary immunization, including immunization of children who are only partially immunized by the age of 15 or more months.

2. The new acellular vaccine should be used only for the fourth and fifth doses for children older than 15 months and younger than 7 years of age. Either acellular or whole-cell pertussis vaccines may be used for the fourth and fifth doses. However, the occurrence of minor adverse effects, such as fever and local reactions, would be expected to be appreciably less with acellular pertussis vaccine.

3. The schedule for administration of pertussis vaccine, regardless of whether acellular or whole-cell vaccine is used, is unchanged (Table 2).

4. In children who are partially immunized because of an accepted contraindication occurring within 7

### TABLE 1. Licensed Pertussis-Containing Vaccines*

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Type</th>
<th>Antigens</th>
<th>Trade Name</th>
<th>Licensed by FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connaught Laboratories (Swiftwater, PA)</td>
<td>Whole-cell</td>
<td>Many</td>
<td>DTP adsorbed, USP</td>
<td>All doses</td>
</tr>
<tr>
<td>Lederle Laboratories (Pearl River, NY)</td>
<td>Whole-cell</td>
<td>Many</td>
<td>Tri-Immunol</td>
<td>All doses</td>
</tr>
<tr>
<td>Lederle Laboratories</td>
<td>Acellular</td>
<td>Pertussis toxin</td>
<td>ACEL-IMUNE</td>
<td>Fourth and fifth doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Filamentous hemagglutinin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agglutinogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>69-kd protein (perfractin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massachusetts Public Health Biologics Laboratories</td>
<td>Whole-cell</td>
<td>Many</td>
<td></td>
<td>All doses</td>
</tr>
<tr>
<td>Michigan Department of Public Health</td>
<td>Whole-cell</td>
<td>Many</td>
<td></td>
<td>All doses</td>
</tr>
</tbody>
</table>

* Abbreviations: DTP, diphtheria and tetanus toxoids and whole-cell pertussis; FDA, Food and Drug Administration; USP, United States Pharmacopeia.

### TABLE 2. Recommended Diphtheria, Tetanus and Pertussis Vaccination Schedule for Children Younger Than 7 Years of Age*

<table>
<thead>
<tr>
<th>Dose</th>
<th>Age</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 mo</td>
<td>DTP</td>
</tr>
<tr>
<td>2</td>
<td>4 mot</td>
<td>DTP</td>
</tr>
<tr>
<td>3</td>
<td>6 mot</td>
<td>DTP</td>
</tr>
<tr>
<td>4</td>
<td>15–18 mo†</td>
<td>DTaP or DTP</td>
</tr>
<tr>
<td>5</td>
<td>4–6 yrs§</td>
<td>DTaP or DTP</td>
</tr>
</tbody>
</table>

* Abbreviations: DTP, diphtheria and tetanus toxoids and whole-cell pertussis; DTaP, acellular pertussis vaccine.
† Prolonging dose interval does not require restarting the series.
§ Give 6 to 12 months after third dose.
* Give before child's seventh birthday and before the child enters kindergarten or elementary school; not necessary if fourth dose administered after the fourth birthday.
days following DTP vaccination, no further pertussis vaccine, either whole-cell or acellular, is generally recommended. In such cases, DT should be substituted for each of the remaining DTP doses.

5. Simultaneous administration of DTaP and other appropriate vaccines is acceptable. Based on studies using whole-cell DTP, the simultaneous administration of DTaP vaccine with oral poliovirus vaccine, inactivated polio vaccine, measles-mumps-rubella vaccine, *Haemophilus influenzae* type b conjugate vaccine, and/or hepatitis B vaccine should not result in differences in side effects or antibody responses from those that occur when the vaccines are administered separately.

6. Erythromycin prophylaxis should be given to all appropriate contacts, regardless of immunization status, who have been exposed to an individual with pertussis disease (as recommended in the 1991 Report of the Committee on Infectious Diseases [Red Book]).

**FUTURE DEVELOPMENTS**

Other acellular pertussis vaccines may soon be approved for use in children for the fourth and fifth doses. Studies are currently in progress to assess the safety and immunogenicity of acellular pertussis vaccines when administered to infants as the primary series. Several of these vaccines are scheduled for efficacy trials beginning early this year. In addition, vaccines that combine the diphtheria and tetanus toxoids and acellular pertussis vaccine with other antigens are being developed.

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