Experience with Diphtheria Toxoid–Tetanus Toxoid–Acellular Pertussis Vaccine in Japan
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In Japan, the morbidity rate for pertussis per 100,000 population was 147.6 in 1950 when whole cell pertussis vaccine was introduced but dropped to 0.2 in 1972 when routine immunization with a combined vaccine consisting of diphtheria toxoid, tetanus toxoid, and whole cell pertussis had been widely accepted. Thereafter, adverse reactions to the whole cell pertussis vaccine became a social problem and lowered the acceptance of the vaccine. As a result, the morbidity rate increased to 11.3 in 1979. Introduction of the safer yet efficacious acellular pertussis vaccine, consisting of mainly pertussis toxoid and filamentous hemagglutinin, into the routine childhood vaccination in combination with diphtheria and tetanus toxoids in 1981 increased the acceptance rate. The lowest morbidity rate, 0.1, was achieved in 1993. During the next 16 years, almost all cases were in unvaccinated or incompletely vaccinated persons. Regardless of whether whole cell or acellular pertussis vaccine was used, >90% of the reported pertussis cases were in children <10 years of age until 1990. However, since 1991, the rate of pertussis in young adults 20–44 years of age has been clearly increasing. To control pertussis, booster vaccination with diphtheria toxoid–tetanus toxoid–acellular pertussis vaccine in adults should be considered.

Pertussis, diphtheria, and tetanus are serious infectious diseases whose symptoms are mediated by bacterial toxins and are typical vaccine-preventable diseases. In Japan, diphtheria toxoid, whole cell pertussis vaccine (wP), diphtheria-pertussis combined vaccines, and tetanus toxoid were introduced in 1948, 1949, 1958, and 1960, respectively. Diphtheria toxoid–tetanus toxoid–wP combined vaccine (DTwP) was officially incorporated into the routine vaccination schedule for childhood in 1968 [1].

Since pertussis and diphtheria are contagious respiratory diseases, widespread use of DTwP resulted in herd immunity in children and a rapid decrease in cases of these two diseases, as shown in figure 1. However, wP-containing vaccines had been accepted reluctantly from the beginning because of a high frequency of local and systemic adverse reactions to the wP in spite of its significant protective efficacy against pertussis. Just at the time when pertussis was becoming a rare disease (the morbidity rate per 100,000 population calculated from the reported cases of clinical disease was 0.2–0.3 during 1971–1973), two fatal accidents following DTwP vaccination in 1974 and 1975 were widely publicized. These two fatalities and the adverse reactions associated with DTwP caused considerable concern among parents and pediatricians and became a social problem. After temporary suspension of pertussis vaccination for 2 months in 1975 to consider a countermeasure for this situation, the initial vaccination age for DTwP was raised from 3 months to 2 years. However, acceptance of DTwP decreased further, down to almost 10% in 1976 [2]. Consequently, the number of pertussis cases increased dramatically: The morbidity rate per 100,000 population increased from 0.4 in 1974 to 11.3 in 1979 [3]. Thus, introduction of a new, safer yet efficacious pertussis vaccine became an urgent social demand in Japan. At the same time, since diphtheria and tetanus toxoids vaccine (DT) was widely accepted, the incidence of diphtheria and tetanus decreased continuously.

We developed an acellular pertussis vaccine (aP) consisting mainly of two protein antigens, pertussis toxoid and filamentous hemagglutinin (FHA), and this new diphtheria toxoid–tetanus toxoid–acellular pertussis combined vaccine (DTaP) was introduced in 1981 in place of DTwP for the routine vaccination of children at age 2 years [4, 5]. Soon after the introduction of the DTaP vaccine, the acceptance rates increased to >80% in 1982 because of much less adverse reactions [2, 5]. Cases of pertussis decreased rapidly, again as shown in figure 1. The Ministry of Health and Welfare, after 7 years of safe and effective use of DTaP, recommended its use for vaccination of infants 3 months of age at a mass immunization in 1988 [2]. The number of pertussis cases reached the lowest record, 130, in 1993. During the 16 years following its introduction, >60 million doses of this DTaP vaccine have been administered to Japanese children, who have been almost completely protected from these three diseases. Almost all cases of these diseases in Japan were in unvaccinated or incompletely vaccinated persons [3, 6, 7].

Diphtheria, Tetanus, and Pertussis Immunization Schedule

Table 1 shows the routine immunization schedule recommended for diphtheria, tetanus, and pertussis vaccination and acceptance rates [2] of the vaccines in Japan. The primary
Age Distribution of Pertussis Cases

Figure 2 shows the age distribution of annual reported cases of pertussis from 1959 to 1995. Routine vaccination of infants with DTwP kept the incidence of pertussis at low levels from 1968 until 1974. After the fatalities with DTwP, there was a recurrence of pertussis. However, routine vaccination with the new DTaP, even at age 2 years, lowered the incidence again.

The age distribution of the reported pertussis cases is shown in figure 3. Regardless of whether it was the DTwP or DTaP era, >90% of the reported cases were in children <10 years of age until 1990. However, after 1991, the rate of pertussis in those >10 years of age increased significantly.

Figure 4 shows the age-specific proportion of total pertussis cases in 1971, 1981, 1991, and 1995. The rate in young adults 20–44 years of age is clearly increasing in 1991 and 1995.

Figure 5 shows the age-specific proportion of reported pertussis cases in young adults 20–44 years old. The numbers of annual reported cases in this age group are almost the same in 1959–1967 and in 1991–1995, but the rates in young adults reached 7%–11% for the last 5 years (1991–1995) compared with <1% during 1959–1967. These young adults were born before 1975, when DTwP was used. Those who were born between 1967 and 1975, when the incidence of pertussis was the lowest in the DTwP era and the vaccination rates were also low (13%–57%), had less chance to be immunized with either natural infection or vaccination. It is possible that the majority of these patients were unvaccinated but had been protected by herd immunity. Children who were born after 1981, when DTaP had been officially used, are <16 years old now, and thus far they are well protected from pertussis by the DTaP vaccination schedule for children comprises four doses of DTaP. According to the present immunization law, the DTaP vaccination should be completed by 90 months of age, and the secondary vaccination is administered to 11- to 12-year-old children with only DT vaccine as a booster. After these routine vaccinations, additional boosters with diphtheria or tetanus toxoids or aP is not officially recommended. About 5 million doses of DTaP are produced annually; ~1 million doses of monovalent tetanus toxoid are produced annually, only ~30,000 doses of diphtheria toxoid for adults are manufactured every 3 years, and neither DT vaccine for adults nor monovalent aP vaccine is produced at all [1, 3, 8, 9]. Thus, most people are not vaccinated, even with either diphtheria toxoid or tetanus toxoid, after 12 years of age except under special circumstances, such as injury or travel to a country with diphtheria.

<table>
<thead>
<tr>
<th>Period</th>
<th>Vaccine</th>
<th>Age (mo) at doses 1–3*</th>
<th>Acceptance rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1968–1975</td>
<td>DTwP</td>
<td>3–12</td>
<td>40–57</td>
</tr>
<tr>
<td>1975–1981</td>
<td>DTwP</td>
<td>24–48</td>
<td>8–75</td>
</tr>
<tr>
<td>1994–present</td>
<td>DTaP</td>
<td>3–12</td>
<td>Not available</td>
</tr>
</tbody>
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NOTE. DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine; DTwP = diphtheria and tetanus toxoids and whole cell pertussis vaccine.

* A fourth dose is given 12–18 months after dose 3. Children receive a booster injection of diphtheria and tetanus toxoids at 11–12 years of age.
Figure 2. Age distribution of annual reported pertussis cases in Japan, 1959–1995. Age groups (years) are as follows: ■, 0; □, 1–2; △, 3–9; □, 10–19; □, 20–44; ■, ≥45 (based on data from the Ministry of Health and Welfare, Japan).

Figure 3. Age-specific proportion of total pertussis cases in Japan, 1959–1995. Age groups (years) are as follows: ■, 0; □, 1–2; △, 3–9; □, 10–19; □, 20–44; ■, ≥45 (based on data from the Ministry of Health and Welfare, Japan).
vaccination. Almost all patients with pertussis are unvaccinated with DTaP.

**Age Distribution of Diphtheria Cases**

The reported number of cases of diphtheria has been decreasing rapidly since introduction of the diphtheria toxoid (figures 1 and 6). Before 1980, >40% of the patients were children <10 years old. In the 10-year period 1986–1995, <10 cases were reported annually, most of which were sporadic, but small outbreaks had also occurred. However, the numbers of recent cases are too small to permit conclusions regarding an age tendency.

**Age Distribution of Tetanus Cases**

Tetanus decreased gradually but continuously from 1960, when the tetanus toxoid was introduced, until 1980. However, a small but constant number of cases has been reported every year since 1980 (figures 1 and 7). More than 80% of patients in recent years are adults aged >40. Since tetanus is not a contagious disease, people cannot benefit from herd immunity. Immunity to tetanus must be acquired individually by vaccination with tetanus toxoid, since it is not acquired by infection. Almost all of the adults >40 years old who were born before the introduction of the tetanus toxoid are unvaccinated, because adults are not routinely vaccinated in Japan.

**Seroepidemiology of Pertussis, Diphtheria, and Tetanus**

Data regarding antibody levels to pertussis antigens in a wide age group are very limited. A correlation between antitoxin levels and age is difficult to establish: >50% of almost all age groups had antibody to pertussis toxin of >10 ELISA units/mL in 1985. Among them, the young adults (18–40 years of age) had slightly lower levels of antibody to pertussis toxin and FHA. The highest titer of antibodies to pertussis toxin was <50 ELISA units/mL in young adults, compared with >200 ELISA units/mL in both younger and older age groups. Antibody titers in children and older adults are more widely scattered, from undetectable levels to >100 units/mL [10]. Recent data also showed a similar tendency of levels of antibody to pertussis toxin that is waning in young adults (data not shown).

A recent serological survey of levels of antibody to diphtheria toxin in Japan showed that half of the adults 30–50 years of age had less than the protective level of antitoxin (<0.01 neutralizing unit/mL); >80% of younger (<30 years) and older (>50 years) age groups had antitoxin levels of >0.01 neutralizing unit/mL, although the young age group had higher antitoxin
Figure 5. Percentage of total reported cases of pertussis in Japan, 1959–1995, that are in young adults (20–44 years old) (based on data from the Ministry of Health and Welfare, Japan).

Figure 6. Age distribution of reported annual diphtheria cases in Japan, 1959–1995. Age groups (years) are as follows: ■, 0–4; □, 5–9; △, 10–19; ●, 20–44; □, ≥45 (based on data from the Ministry of Health and Welfare, Japan).
titers than did the older group [11a]. The young age group must have acquired the antitoxin from vaccination, but adults >50 years of age, who were born in the prevaccine era, may maintain the protective level of antitoxin by additional subclinical or nonsymptomatic infection. Although it seems that toxicogenic diphtheria strains have almost disappeared from the population in Japan, this may not be true. To understand the immunologic and microbiological situation in Japan, a more precise survey must be necessary. However, to prevent disease in adults as well as in children, the importance of vaccination of adults must be emphasized [12].

Unlike the situation with pertussis and diphtheria, in the case of tetanus, a correlation between incidence and antitoxin levels is clear. Almost all of the adults >40 years old have no detectable antibody to tetanus [9, 11].

Discussion and Summary

The seroepidemiological situation of diphtheria and pertussis in Japan is similar. The existence of significant antitoxin levels in older persons suggests that the pertussis and diphtheria pathogens are still widespread in the Japanese population and cause mild respiratory symptoms in persons with waning immunity and give a natural booster to adults. However, the numbers of adults lacking antigenic stimuli from vaccination or from natural exposure will be increasing. Adults who were not vaccinated or vaccinated >10 years ago might be susceptible to infection with pathogenic Bordetella pertussis and Corynebacterium diphtheriae.

The recent significant increase of pertussis in young adults must be warning against limiting the recent pertussis vaccination schedule to only children. Because many young adults, such as parents, nurses, or schoolteachers, have more opportunities for contact with infants and young children, they must become a major reservoir for transmission to nonimmunized infants and children if they are infected with pertussis. To control pertussis more effectively (as well as diphtheria), vaccination of adults, especially these young adults, with DTaP should be important.

According to Swedish reports on adverse reactions in adults to the Japanese acellular pertussis vaccines JNIH 6 (pertussis toxoid plus FHA) and JNIH 7 (pertussis toxoid) [13, 14], the adverse reactions to both acellular pertussis vaccines were much less than those elicited by whole cell vaccines in adults, and JNIH 7 had a lower rate of reactions than did JNIH 6.

A comparative survey shows the incidence of serious adverse reactions, such as encephalopathy, convulsions, and sudden death, to DTwP and DTaP in Japan [15]. From 1970 to 1974, when DTwP was given to infants 3 months of age, the incidence of such severe reactions became lower with the DTaP vaccine or from natural exposure will be increasing. Adults who were not vaccinated or vaccinated >10 years ago might be susceptible to infection with pathogenic Bordetella pertussis and Corynebacterium diphtheriae.

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The U.S. Food and Drug Administration approved two types of aP vaccine manufactured by two Japanese companies in 1991, and the DTaP vaccine in the United States has been administered in children since then [16].
Concerning the purity of the protective antigens, aP is the most purified and well-characterized antigen in the DTaP vaccine. Diphtheria and tetanus toxoids contain ~10%–40% unknown proteins as contaminants. Although there are no data to show whether these unknown antigens in the diphtheria and tetanus toxoids products add to or detract from their efficacy, there is a tacit understanding that diphtheria or tetanus toxoid alone is sufficient as the vaccine. However, for the aP vaccine developed in Japan that consists of mainly pertussis toxoid plus FHA (94%–100%), other minor contaminant antigens, such as pertactin (0–4%), have been claimed by some to be important protective antigens. This looks back to the complex vaccine era rather than to simpler vaccine development. On the basis of our experience with 60 million vaccinations with purified DTaP in Japan, we are confident that two components, pertussis toxoid and FHA, are sufficient pertussis vaccine antigens to control pertussis. If the purpose of the vaccine is not eradication of B. pertussis organisms but the control of pertussis disease, as in the case of DT [3], the vaccine with pertussis toxoid alone might be sufficient. For adult immunization, development of a vaccine composed of diphtheria, tetanus, and pertussis toxoids might be a promising step toward a simpler and purer vaccine.

References