Immunogenicity and Safety after Booster Vaccination of Diphtheria, Tetanus, and Acellular Pertussis in Young Adults: an Open Randomized Controlled Trial in Japan

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The recent increase of pertussis in young adults in Japan is hypothesized to be due to waning protection from the acellular pertussis vaccine. While a booster immunization may prevent an epidemic of pertussis among these young adults, little is known about the safety and immunogenicity of such a booster with the diphtheria, tetanus, and acellular pertussis vaccine (DTaP), which is currently available in Japan. One hundred and eleven medical students with a mean age of 19.4 years were randomly divided into 2 groups of 55 and 56 subjects and received, respectively, 0.2 or 0.5 ml of DTaP. Immunogenicity was assessed by performing the immunoassay using serum, and the geometric mean concentration (GMC), GMC ratio (GMCR), seropositive rate, and booster response rate were calculated. Adverse reactions and adverse events were monitored for 7 days after vaccination. After booster vaccination in the two groups, significant increases were found in the antibodies against pertussis toxin, filamentous hemagglutinin, diphtheria toxoid, and tetanus toxoid, and the booster response rates for all subjects reached 100%. The GMCs and GMCRs against all antigens were significantly higher in the 0.5-ml group than in the 0.2-ml group. No serious adverse events were observed. Frequencies of local reactions were similar in the 2 groups, although the frequency of severe local swelling was significantly higher in the 0.5-ml group. These data support the acceptability of booster immunization using both 0.2 and 0.5 ml of DTaP for young adults for controlling pertussis. (This study was registered at UMIN-CTR under registration number UMIN000010672.)

During the last few decades, the number of reported pertussis cases has increased in developed countries, despite high vaccination coverage (1). This resurgence of reported pertussis has been hypothesized to be due to several reasons, including increased awareness of pertussis; use of PCR assay for diagnosis; failure of the diphtheria, tetanus, and acellular pertussis vaccine (DTaP); and genetic changes in circulating strains of *Bordetella pertussis* (2, 3). DTaP does not confer lifelong immunity, and it has been reported to last for 4 to 12 years after infant immunization (4). A recent study demonstrated that after the fifth dose of DTaP, protection against pertussis waned during the following 5 years, and the risk of pertussis increased by an average of 42% per year (5).

The prevalence of pertussis in Japan was estimated to be 2.4 (95% confidence interval, 1.6 to 3.3) per 100,000 population in 2007 (see the National Institute of Infectious Diseases fact sheet for pertussis vaccine [in Japanese] at [http://www.mhlw.go.jp/stf/shingi/2r9852000000bx23-att/2r9852000000byfg.pdf](http://www.mhlw.go.jp/stf/shingi/2r9852000000bx23-att/2r9852000000byfg.pdf)), while the prevalence in the United States was reported to be 9.0 per 100,000 population in 2010 (3). It is difficult to compare these values, because of differences of diagnostic methods applied and case definitions for surveillance. However, the proportion of adults among recently reported pertussis cases has been increasing in Japan (see the National Institute of Infectious Diseases fact sheet), even though underreporting of adult cases was suspected due to the fact that pertussis cases were primarily reported from pediatric clinics. In Japan, children receive 4 doses of the DTaP vaccine, with 3 primary doses and a single booster dose at ages 3, 4, 5, and 18 to 23 months. Thus, a decreased protective effect of the vaccine may contribute to the increasing frequency of pertussis in the last decade on college campuses and in high schools and offices in Japan (6–10). Pertussis prevention among young adults is important because unrecognized adult pertussis is the major source of pertussis in young infants, in whom the disease can be severe and fatal (2).

The tetanus, reduced antigen content diphtheria, and acellular pertussis vaccine (Tdap) is used as a booster vaccination worldwide for adults, and its effects in adolescents and adults, as well as in specific risk groups, such as pregnant women and their newborns, health care workers, and older adults, have been reported (11–13). Since Tdap has not yet been licensed in Japan, DTaP may be available for booster immunization in the interim. Safe and effective booster immunization using DTaP in adolescents has been confirmed (14); however, little is known about the immunogenicity and safety of the DTaP vaccine in young adults. In this study, we examined the immunogenicity and safety of 0.2 and 0.5 ml of DTaP in young adults in Japan.

**MATERIALS AND METHODS**

**Study subjects and design.** The participants were recruited at the Saga University, located in southern Japan, where an outbreak of pertussis had...
occurred among medical students during April and May in 2010. After the outbreak, we used an enzyme-linked immunosorbent assay (ELISA) at a commercial laboratory (SRL, Tokyo) to examine antibodies against pertussis toxin (PT) in all 548 students during July and August 2010. We found that the levels of antibodies against PT among 258 students (47%) were <10 ELISA units (EU)/ml, and those among 242 students (44%) were ≥100 EU/ml. We announced the participation of these students in this study during August 2011. Students were excluded from participation if their antibody levels against PT were ≥100 EU/ml in 2010; if they had any history of diphtheria, tetanus, and pertussis; if they had received any other drug or vaccine within 30 days of entry; if they had a history of allergic reactions to any vaccine component; or if they received immunoglobulins or any blood products. Subjects were also excluded if they had acute disease or febrile illness at the time of vaccination. Overall, 111 students aged 19 to 20 years participated in this study. They had undergone primary vaccination with the DTaP vaccine in Japan during childhood. The immunization histories of 83 subjects were confirmed by checking their immunization records, whereas those of the remaining 28 subjects could not be verified because they did not submit their records.

This study (registered at UMIN-CTR under registration number UMIN000001672) was an open randomized controlled trial performed using blocked randomization for gender and prevaccination antibody levels against PT. The study subjects were stratified according to seropositivity for PT (PT-IgG, ≥10 EU/ml) or nonseropositivity for PT (PT-IgG, <10 EU/ml) in the previous year, and according to gender. Then, the subjects within each group were randomly assigned to receive 0.2 or 0.5 ml of DTaP vaccine. Serum samples were obtained before immunization and 1 month after immunization. All serum specimens were stored at −80°C until assay. All subjects were included in the safety and immunogenicity analysis.

The study was conducted in accordance with good clinical practice guidelines and the principles of the Declaration of Helsinki and Japanese regulatory requirements. The study protocol was approved by the Institutional Review Board of the Saga University Faculty of Medicine (approval number 23-14, 2011). The nature and possible consequences of the study were discussed at length with all subjects, and written informed consent for participation was obtained from all.

Vaccines. The single doses of 0.2 and 0.5 ml of adsorbed diphtheria-pertussis-tetanus combined vaccine (DTaP vaccine, lot number 42A; Kaketsuken) contained 3.2 and 8 μg of PT, 12.8 and 32 μg of filamentous hemagglutinin (FHA), ≥6.7 and ≥16.7 LU of diphtheria toxoid (D), and ≥2.7 and ≥6.7 LU of tetanus toxoid (T), respectively. This DTaP also contained 0.004 mg/ml of thimerosal, <3 mg/ml of aluminum hydroxide, and <1 mg/ml of formalin. The vaccine was administered subcutaneously in the lateral upper arm by using a 27-gauge needle of length 25 mm.

Assessment of safety. All subjects were carefully observed for anaphylactic shock for at least 30 min after vaccination. To assess for adverse reactions occurring during the initial 24 h and the 7 days immediately following vaccination, the subjects were asked to perform daily self-assessments and record their body temperature at the axillary fossa and their adverse reactions based on a standard health care diary. Adverse reactions occurring within 24 h included the following: fever (temperature of ≥38.0°C), eye hyperemia, facial edema, cough, dyspnea, dysphasia, hoarseness, and sore throat. After 24 h, the adverse local symptoms consisted of erythema, swelling, pain, warmth, and pruritus, whereas systemic reactions included fever (temperature of ≥38.0°C), headache, fatigue, cough, and sore throat. The degrees of pain, warmth, and pruritus in local reactions were measured using a 27-gauge needle of length 25 mm.

RESULTS

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Safety. No serious adverse events occurred during the study period. Several adverse reactions occurred, but all were transient and occurred at similar frequencies in the 2 groups (Table 3). Within 24 h after vaccination, the most frequent symptoms were cough (3.6%), dysphasia (3.6%), and sore throat (3.6%). After 24 h, local reactions were frequently observed, with few systemic reactions. The onset of local reactions is summarized in

Seroimmune response. Serum antibodies against PT, FHA, D, and T were concurrently measured by Kaketsuken. Antibodies to PT and FHA were measured using standard enzyme-linked immunosorbent assays (ELISA), and pertussis antibody titers were expressed as ELISA units (EU)/ml (15). Diphtheria antitoxin titers were examined using the micro cell culture method with Vero cells and expressed as international units (IU)/ml (16). Tetanus antitoxin titers were determined using a KPA kit (Kaketsuken, Japan) and expressed as international units (IU)/ml (17). Limits of quantification for each antibody against PT, FHA, D, and T were 1.0 EU/ml, 1.0 EU/ml, 0.005 IU/ml, and 0.005 IU/ml, respectively. Seropositive levels were defined as ≥10 EU/ml for antibodies against PT and FHA, ≥0.1 IU/ml for diphtheria antitoxin, and ≥0.01 IU/ml for tetanus antitoxin (14). A booster response for PT and FHA was defined as a postvaccination antibody concentration of ≥20 IU/ml with a prevaccination antibody concentration of <5.0 EU/ml, a postvaccination rise of at least 4 times the prevaccination antibody concentration in subjects with a prevaccination antibody concentration of 5.0 to 20 EU/ml, or at least twice the prevaccination antibody concentration in subjects with a prevaccination antibody concentration of ≥20 EU/ml. Booster responses for D and T were defined as a postvaccination antibody concentration of ≥0.1 IU/ml with a prevaccination antibody concentration of <0.1 IU/ml, or a postvaccination increase of at least 4 times the prevaccination antibody concentration with an initial concentration of ≥0.1 IU/ml (18).

Statistical analyses. The primary objective of the study was to demonstrate booster response rates of at least 80% for PT, FHA, D, and T in the two groups. The chi-square test or Fisher’s exact test was used to compare the baseline characteristics or seropositivity rates and frequency of adverse reactions between the groups. The 95% confidence interval (CI) of seropositivity rates were calculated with the exact binomial distribution for proportions. Because distributions of antibodies were skewed, all antibody calculations were done using a log scale. The Wilcoxon rank-sum test was used to compare the GMC and GMCR (GMC) between the 2 groups, while the Wilcoxon signed-rank test was used to determine the significance of the increase in antibodies after vaccination in each group. Hypothesis testing was conducted using two-sided tests, with an α value of 0.05 considered statistically significant. All statistical analyses were performed using the SAS software (version 9.1).
concentration with an initial concentration of antibody. However, none of these reactions affected the subjects’ half of the subjects. Most injection site reactions resolved within 3 days.

The severities of the local reactions are summarized in Table 5. The frequencies of severe local reactions tended to be higher in the 0.5-ml group than in the 0.2-ml group. Moreover, the frequency of local swelling was significantly higher in the 0.5-ml group than in the 0.2-ml group. Moreover, the frequency of local swelling was significantly higher in the 0.5-ml group than in the 0.2-ml group. Moreover, the frequency of local swelling was significantly higher in the 0.5-ml group than in the 0.2-ml group.

Table 4. Erythema, swelling, and pain were reported by more than half of the subjects. Most injection site reactions resolved within 3 days.

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Table 2. Antibody GMCS, seropositive levels, and booster responses after DTaP vaccinations

Table 3. Adverse reactions after vaccination

DISCUSSION

In this randomized clinical trial comparing 0.2 ml to 0.5 ml of DTaP vaccine in young adults, we showed that effective immunogenicity for PT, FHA, D, and T was achieved in both groups. All
subjects in the two groups demonstrated sufficient booster responses against all vaccine antigens. None of the severe adverse reactions observed required medications. The total number and onset of local and systemic reactions between the 2 groups were similar, although the frequency of severe local swelling was significantly higher in the 0.5-ml group ($P < 0.05$). Thus, both doses of DTaP may provide adequate booster immunization in young adults in Japan, where the Tdap vaccine has not yet been licensed.

Clinical trials evaluating the duration of protective immunity provided by 3 or 4 doses of DTaP against pertussis demonstrated that protective immunity was sustained for 5 to 6 years after immunization (19, 20). The immunization schedule of DTaP in Japan consists of 4 doses in young children during 4 to 23 months of age and 1 dose of DT during 11 and 12 years of age. Thus, in our study participants, 17 to 18 years had elapsed since their last immunization. In our study, the prevaccination antibody seropositivity rates against pertussis were around 40% for PT and 70 to 80% for FHA, which are lower than those reported in Japanese adolescents (14) and Finnish young adults (21). In the former study, seropositivity rates against pertussis were 52 to 59% for PT and 79 to 86% for FHA among the adolescents, who were immunized for pertussis about 10 years prior (14). In the latter study, seropositivity rates at 10 years after the fifth dose of Tdap were 61.3% for PT and 100% for FHA (21).

Since immunogenicity to vaccination is influenced by the prevaccination antibody level, vaccination history, doses of vaccine components, and laboratory where the antibodies were measured, it is difficult to compare immunogenicity between previous studies using Tdap and the present study. With regard to the prevaccination antibody level, we observed antibody levels against PT and FHA that were lower than those in previous studies (14, 21). Thus, immunogenicities in our subjects may have been lower than those of the previous studies if the components of the vaccine were the same. The 0.5 ml of DTaP vaccine (Kaketsuken) contains the same dose of PT and higher doses of FHA, D, and T than Boostrix Tdap (13) and higher doses of PT, FHA, D, and T than

### TABLE 4 Onset of local reactions

<table>
<thead>
<tr>
<th>Local reaction</th>
<th>Vaccine dose (ml)</th>
<th>Day of onset</th>
<th>Total no. (%) with indicated reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>0.2</td>
<td>10 (18.2)</td>
<td>14 (25.5)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>9 (16.1)</td>
<td>14 (25.0)</td>
</tr>
<tr>
<td>Swelling</td>
<td>0.2</td>
<td>6 (10.9)</td>
<td>15 (27.3)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>8 (14.3)</td>
<td>15 (26.8)</td>
</tr>
<tr>
<td>Pain</td>
<td>0.2</td>
<td>11 (20.0)</td>
<td>14 (25.5)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>15 (26.8)</td>
<td>17 (30.4)</td>
</tr>
<tr>
<td>Hotness</td>
<td>0.2</td>
<td>7 (12.7)</td>
<td>10 (18.2)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>8 (14.3)</td>
<td>10 (18.3)</td>
</tr>
<tr>
<td>Itching</td>
<td>0.2</td>
<td>8 (14.5)</td>
<td>10 (18.2)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>6 (10.7)</td>
<td>12 (21.4)</td>
</tr>
</tbody>
</table>

### TABLE 5 Degrees of local reactions

<table>
<thead>
<tr>
<th>Type of reaction $^a$</th>
<th>Vaccine dose (ml)</th>
<th>Absence of reaction</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Risk ratio (95% CI) $^b$ for severe local reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness</td>
<td>0.2</td>
<td>16 (29)</td>
<td>5 (13)</td>
<td>26 (67)</td>
<td>8 (21)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>23 (41)</td>
<td>5 (15)</td>
<td>17 (52)</td>
<td>11 (33)</td>
<td>1.35 (0.59–3.10)</td>
</tr>
<tr>
<td>Swelling</td>
<td>0.2</td>
<td>23 (42)</td>
<td>8 (24)</td>
<td>22 (67)</td>
<td>2 (6)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>23 (41)</td>
<td>6 (18)</td>
<td>18 (55)</td>
<td>9 (27)</td>
<td>4.42 (1.00–19.54)</td>
</tr>
<tr>
<td>Pain</td>
<td>0.2</td>
<td>21 (38)</td>
<td>23 (68)</td>
<td>10 (29)</td>
<td>1 (3)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>18 (32)</td>
<td>22 (58)</td>
<td>13 (34)</td>
<td>3 (8)</td>
<td>2.95 (0.32–27.47)</td>
</tr>
<tr>
<td>Warmth</td>
<td>0.2</td>
<td>32 (58)</td>
<td>20 (87)</td>
<td>3 (13)</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>29 (52)</td>
<td>21 (78)</td>
<td>6 (22)</td>
<td>1.96 (0.52–7.46)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.2</td>
<td>28 (51)</td>
<td>14 (52)</td>
<td>12 (44)</td>
<td>1 (4)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>31 (55)</td>
<td>6 (24)</td>
<td>16 (64)</td>
<td>3 (12)</td>
<td>2.95 (0.32–27.47)</td>
</tr>
</tbody>
</table>

$^a$ Degrees of redness and swelling: mild (<2.0 cm), moderate (2.0 to 4.9 cm), or severe (≥5.0 cm). Degrees of pain, warmth, and pruritus: mild (sensed, but not anxious about), moderate (anxious), or severe (needs medication).

$^b$ CI, confidence interval.
the Adacel Tdap (12), which is used abroad (14) (Table 6). However, immunogenicities against PT in this study were sufficient despite 0.2 ml of DTaP, results which are very similar to those of previous reports (12–14, 21).

The most common local reactions reported in our study were erythema, swelling, and pain. The frequencies of these reactions were similar to those reported in Japanese adolescents aged 11 to 12 years (14) who had received 0.2 or 0.5 ml of DTaP. Compared to randomized clinical trials for Tdap, the frequency of injection site pain was similar, whereas there were more cases of erythema and swelling in our study. The frequencies of pain, swelling, and erythema in American adults who were vaccinated with the Adacel Tdap (12) were 65.7%, 21%, and 24.7%, respectively, and in those who had the Boostrix Tdap (13) were 61.0%, 21.1%, and 17.6%, respectively. These discrepancies in the frequencies of erythema and swelling between Japan and the United States may be due to the mode of injection. In the United States, Tdap is injected intramuscularly, while DTaP vaccine was administered subcutaneously in this study. The frequencies of other adverse reactions in this study did not differ from those in the clinical trials of Tdap (12, 13).

Several studies have examined the effects of vaccine antigen contents on immunogenicity and reactogenicity, and although immunogenicities differed between the studies, all demonstrated that local reactions can be reduced by decreasing the amount of antigen (14, 18, 22, 23). Knuf et al. assessed DTP vaccines with reduced amounts of antigens in the fourth dose in the second year in Germany and reported that the immunogenicity was adequate, whereas reduced amounts of antigen induced lower antibody concentrations (22). Hendriks et al. examined IgG responses in children following revaccination at age 4 and found that a booster vaccine with higher pertussis antigen levels induced higher antibody levels than a vaccine containing low antigen levels (23). Okada et al. compared 0.2 and 0.5 ml of DTaP in children aged 11 to 12 years in Japan and observed that GMC and seropositivity rates were similar between the groups (14). Blatter et al. reported that GMCs for anti-PT and anti-FHA were approximately 2-fold higher in the Boostrix group than in the Adacel group 1 month after vaccination, and these differences remained apparent even 1 year after vaccination, although the magnitudes of difference decreased (18). It is difficult to know which dose is appropriate for booster vaccinations. On one hand, a lower dose might be suited to booster vaccinations, as it induces seropositivity levels of antigens with a lower rate of local reactions. On the other hand, a higher dose might be better if it induces not only higher immunogenicity but also longer persistence of this immunogenicity. Studies have demonstrated that antibody concentrations 1 month after vaccination strongly predicted antibody persistence (24) and hence, a higher dose vaccine may contribute to longer persistence of the antibody. However, to our knowledge, there is no study that has compared the long-term persistence of antibodies induced by various doses of antigens.

In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends a Tdap vaccine booster dose for all adolescents aged 11 to 18 years, ideally at 11 to 12 years, and for adults aged 19 to 64 years who have not received a dose since 2005 (25, 26). In 2010, ACIP further recommended a booster dose of Tdap for unvaccinated adults aged 65 years and older who are in close contact with an infant aged < 12 months (27). In 2012, ACIP approved the use of Tdap for all adults aged 65 years and older (28). In comparison, no additional DTaP vaccine after a single booster dose in childhood is recommended in Japan. We suspected that the lack of immunization with DTaP during adolescence at 11 to 12 years of age may be the leading cause of the recent resurgence of pertussis among young adults in Japan. To reduce the incidence of infant death as a result of severe pertussis, vaccination among pregnant women may have a greater impact than vaccination among adolescents; however, alteration of vaccination schedules is very difficult. Therefore, adolescents in Japan are currently expected to receive a low dose of DTaP instead of DT (14). However, this may increase the susceptibility to pertussis among adults, including pregnant women, because the immunity induced by DTaP decreases with time. In addition to vaccination in adolescents, repeat booster vaccinations of DTaP may be required to substantially reduce or eliminate the incidence of pertussis. With regard to longer persistence of immunity, a higher dose of booster vaccination may be suitable. Furthermore, the development of a more immunogenic and efficacious pertussis vaccine that requires considerably fewer doses and induces long-term durable protective immunity is required (29).

The present study had several limitations. First, although our relatively small sample size was sufficient to evaluate immunogenicity, it was less than ideal for the detection of adverse events. However, much larger clinical trials investigating Tdap have also not reported serious adverse events (12, 13). Second, study subjects were restricted to young adults only. In the present study, we enrolled students who were exposed to a pertussis outbreak in the previous year and did not exclude individuals who had been exposed to pertussis or had contact with pertussis patients. This may have influenced the vaccination response, although we excluded subjects who developed pertussis in the previous year, after which no outbreak was noted. A healthy group of individuals who were not previously exposed to pertussis would be a better cohort to assess the actual vaccination response in a population experiencing waning immunity from the last vaccination in infancy. However, several outbreaks of pertussis have been reported at college and university campuses in the current decade, and therefore, we consider individuals in this age group as one of the target populations for control of pertussis in Japan. In addition, booster immunization is considered essential at any age in those who have not received it previously. Further studies in other age groups and specific risk groups, such as pregnant women, their newborns, and health care workers, are needed.

In conclusion, 0.2 and 0.5 ml of the DTaP vaccine can induce

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer</th>
<th>PT (µg)</th>
<th>FHA (µg)</th>
<th>Pertactin (µg)</th>
<th>Fimbriae (µg)</th>
<th>D (Lf)</th>
<th>T (Lf)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP, 0.5 ml</td>
<td>Kaketsuken</td>
<td>8</td>
<td>32</td>
<td></td>
<td></td>
<td>≥16.7</td>
<td>≥6.7</td>
</tr>
<tr>
<td>DTaP, 0.2 ml</td>
<td>Kaketsuken</td>
<td>3.2</td>
<td>12.8</td>
<td></td>
<td></td>
<td>≥6.7</td>
<td>≥2.7</td>
</tr>
<tr>
<td>Tdap, 0.5 ml</td>
<td>GlaxoSmithKline Biological</td>
<td>8</td>
<td>8</td>
<td>2.5</td>
<td></td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Tdap, 0.5 ml</td>
<td>Sanofi Pasteur</td>
<td>2.5</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>
antibodies in young adults without severe adverse reactions that affect their daily ordinary activities; thus, both doses can be used for booster immunizations to control pertussis in Japan.

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