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School-age children and adolescents suspected of having been to be infected with pertussis in Japan

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ABSTRACT

Many countries including Japan have adapted acellular pertussis vaccines combined with diphtheria and tetanus toxoids (DTaP). DTaP vaccine coverage is approximately >90%, but pertussis re-emergence has been observed since 2000 in Japan. In the present study, anti-pertussis antibodies were investigated among school-age children and adolescents from 2013 to 2015. The positive rate of anti-pertussis toxin (PT) antibodies was higher among children aged 12–13 years (60.0%. 95%CI; 56.0–63.9%) in 2014 and 18–19 years (73.0%. 95%CI; 61.4–82.6%) in 2013, compared with 6–7 years (47.1%. 95%CI; 40.7–53.6%). The mean PT antibody titer was higher among children aged 12–13 years (23.8 EU/ml. 95%CI; 21.9–25.8) in 2014 and 18–19 years (29.3 EU/ml. 95%CI; 23.0–35.6) in 2013, compared with 6–7 years (18.3 EU/ml. 95%CI; 15.5–21.2). Distributions of pertussis antibodies and mean titers at their same grade of school-age were similar from 2013 to 2015. Although school-age children were immunized with 4 doses of DTaP, the data suggested the decay of vaccine-acquired immunity and possibility of asymptomatic infection in school age, indicating the additional DTaP vaccination before the entry of elementary school, preventing household contact.

1. Introduction

Pertussis is a respiratory tract infection and it causes typical respiratory symptoms. Pertussis causes severe symptoms including apnea, pneumonia, and is sometimes complicated with encephalopathy in neonates. *Bordetella pertussis (B. pertussis)*, *B. parapertussis,* and *B. holmesii* are causal pathogens of pertussis. The World Health Organization reported 139,786 pertussis cases in 2014, and estimated 89,000 deaths in 2008 [1]. Two vaccines, whole-cell pertussis (wP) vaccines and acellular pertussis (aP) vaccines, combined with diphtheria and tetanus toxoids (DTwP) vaccines or (DTaP) vaccines are used against pertussis in many countries. The aP vaccines are mainly composed of PT and FHA, and some of them include pertactin and fimbriae (Fim) 2/3. Protective immunity against pertussis is induced by 4–5 doses of DTaP vaccines, and is believed to be maintained for 3–10 years after the vaccinations [2,3]. Tetanus toxoid with a reduced concentration of diphtheria toxoid and a pertussis vaccine components (Tdap) vaccine is used for adolescents and adults including pregnant woman, in some countries. Pertussis has been re-emerging in the latest two decades in countries where DTaP has been used [4–7].

In Japan, almost 100,000 pertussis patients and 10,000 pertussis-caused deaths were reported in the early 1950s [8]. The wP vaccines were used from 1950, and wP vaccines combined with a diphtheria vaccine were used from the late 1950s. The DTwP vaccine was recommended from 1968, and suspended from 1975 to 1981. The DTaP vaccine was recommended from 1981 until 2012, and then DTaP combined with inactivated polio (DTaP-IPV) vaccine has been recommended since 2012. The number of reported pertussis cases decreased following the introduction of DTwP or DTaP, and pertussis-related deaths decreased to less than 10 cases per year in the 1980s [8]. Now, three brands of DTaP-IPV are available. Two of them consist of pertussis toxin (PT) and filamentous hemagglutinin (FHA), and the other contains PT, FHA, pertactin, and Fim 2. In Japan, children aged 3 months are vaccinated with three consecutive doses for primary immunization, and with a booster vaccine 6–12 month after the 3rd dose of primary immunization. There is no licensed Tdap vaccine in Japan.

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Several pertussis outbreaks have been reported since 2007 in Japan [9–12]. In these pertussis outbreaks, many patients were adults and adolescents >10 years of age [9,13]. Kamiya et al. [14] reported that pertussis outbreaks also occurred among highly vaccinated children. The highly-vaccinated individuals were sometimes asymptomatic even when infected with *B. pertussis* [15,16]. Asymptomatic pertussis infection among highly-vaccinated individuals may cause further transmission in households, offices, universities and others [15,17].

It is not easy to clarify the burden of pertussis, including asymptomatic patients. To investigate the distribution of anti-PT IgG and anti-FHA IgG by enzyme immunoassay is useful to confirm the prevalence of pertussis infection among communities, including asymptomatic pertussis carriers and herd immunity to pertussis [18–24]. In Japan, pertussis is considered to be transmitted from school-age children because protective immunity induced by DTaP vaccine is maintained for 3–5 years [1,24–26]. However, there is no report on herd immunity among highly vaccinated school-age children through to adolescents in Japan in the re-emerging phase of pertussis.

2. Materials and methods

2.1. Subjects

This study was conducted from 2013 to 2015. History of pertussis and pertussis vaccination was taken by questionnaire to students of nursing schools and universities, and to the parents of elementary school and junior high school students. The candidates of the study participants consisted of 504 subjects at first grade elementary school students, 1313 subjects of junior high school students, and 200 subjects of nursing school and university students, as shown in Table 1. Among them, 502 elementary school students, 1291 junior high school students, and 190 nursing school and university students participated in the study. Participants with a pertussis history were one elementary school students (0.19%), 12 junior high school students (0.93%), two nursing school students (2.33%), and none of the university students. Of the participants with blood samples, 490 elementary school students, 1260 junior high school students, and 150 nursing school and university students had a definite history of pertussis vaccination without a pertussis history. Most participants received more than three or four doses of DTaP without a pertussis history: 480 elementary school students, 1229 junior high school students, and 144 nursing school and university students were candidates for statistical analysis. Five of the elementary school students, 23 of the junior high school students, and 5 of the university students had received pertussis vaccinations more than 5 times in foreign countries in which they previously lived.

2.2. Serological examination

Serum samples were stored at −20 °C until assay in the Kitasato Institute for Life Sciences. Anti-PT IgG and anti-FHA IgG antibodies were measured by enzyme immunoassay (anti-pertussis EIA antibody SEIKEN, DENKA SEIKEN, Tokyo, Japan) as the manufacture instructions. Standard sera were provided from DENKA SEIKEN (anti-pertussis antibody control FHA SEIKEN or PT SEIKEN, DENKA SEIKEN, Tokyo, Japan). Antibody titers of 10 EU/ml or higher were considered positive, and below 10 EU/ml were considered negative.

2.3. Statistical analysis

Statistical analysis was performed using SPSS version 24 (SPSS Inc., Chicago, Illinois, United States). For statistical analysis, titers <10 EU/ml were converted to 5 EU/ml. Positive rate and serum antibody titers were evaluated as the arithmetic mean with 95% confidence intervals (95%CI). To evaluate the distribution of antibody titers, distribution curves of cumulative relative frequency were used with titers categorized as follows: <10 EU/ml, <20 EU/ml, <30 EU/ml, <40 EU/ml, <50 EU/ml, <60 EU/ml, <70 EU/ml, <80 EU/ml, <90 EU/ml, <100 EU/ml, and ≥100 EU/ml.

The study was approved by the Research Ethics Committee of Keio University and the Ethics Committee of the National Mie hospital. Informed consent for the study was signed by the students of the nursing school and university, and the parents of elementary school and junior high school students.

3. Results

3.1. PT antibodies in the participants who received 3 or 4 doses of DTaP

The results of PT antibodies are shown in Fig. 1. Positive rates of anti-PT IgG were 47.1% (95%CI: 40.7–53.6%) at the 1st grade of elementary school (aged 6–7 years), 60.0% (95%CI: 56.0–63.9%) at 12–13 years of age in 2014, and 73.0% (95%CI: 61.4–82.6%) at 18–19 years of age in 2013 (Fig. 1A). In 2015, those were 37.4% (95%CI: 31.2–43.9%) at 6–7 years of age, 61.3% (95%CI: 57.3–65.2%) at 12–13 years of age, and 75.7% (95%CI: 64.0–85.2%) at 18–19 years of age (Fig. 1B).

The arithmetic averages of anti-PT IgG were 18.3 EU/ml (95%CI: 15.5–21.2) at the 1st grade of elementary school (aged 6–7 years) in 2014 and increased to 23.8 EU/ml (95%CI: 21.9–25.8) at 12–13

Table 1
The participants and their history of anti-pertussis vaccinations.

School	Elementary		Junior high		Nursing	University
Year	2014	2015	2014	2015	2013	2015
Total number of 1st grade students	252	252	653	660	86	114
Participants	252	250	646	645	86	104
Blood samples of participants	249	243	641	638	86	104
Participants with a pertussis history	1	0	7	5	2	0
Pertussis vaccinations of blood samples provided participants without a pertussis history						
0	1	1	0	0	0	0
1	2	1	1	2	0	0
2	0	0	4	1	0	1
3	4	6	24	34	6	4
4	238	232	593	578	68	66
5	2	3	8	14	0	4
6	0	0	0	1	0	1
Unknown	1	0	4	3	10	28

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