

Epidemiological Report

Seroepidemiologic Study on Pertussis, Diphtheria, and Tetanus in the Fukuoka Area of Southern Japan: Seroprevalence among Persons 0-80 Years Old and Vaccination Program

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SUMMARY: In Japan, mass vaccination for diphtheria, pertussis, and/or tetanus has been mandated by the Vaccination Law since 1948. In order to evaluate the efficacy of this vaccination policy, we conducted seroepidemiological studies on pertussis, diphtheria, and tetanus among individuals aged 0-80 years. The pertussis toxin seropositive rates of the vaccine-eligible groups and vaccine-ineligible groups were 55.0 and 57.9%, respectively. The seropositive rate of each group for diphtheria antitoxin was 76.3 and 75.7%, respectively. The tetanus antitoxin seropositive rates were 91.7 and 10.5%, respectively, showing a significant difference between the two groups ($P < 0.001$). For the three diseases, variations were seen between age groups in the geometric mean antibody titers due to changes of the vaccination program. The results of this study show that natural *Bordetella pertussis* infection has occurred more frequently than expected. In order to establish the most appropriate vaccination program for the control of pertussis, diphtheria, and tetanus in Japan, further evaluation is necessary.

INTRODUCTION

The Vaccination Law was enacted in Japan in 1948, and vaccination programs involving diphtheria toxoid and a whole cell pertussis vaccine were started in 1948 and 1950, respectively. A combined diphtheria-whole cell pertussis vaccine (DwP) and a combined diphtheria-tetanus-whole cell pertussis vaccine (DTwP) were introduced in 1958 and 1968, respectively. In 1975, the adverse effects of DTwP became a major problem, so an acellular pertussis vaccine with fewer side effects was developed by Sato et al. Since the autumn of 1981, a combined diphtheria-tetanus-acellular pertussis vaccine (DTaP) containing this acellular pertussis component has been used in place of DTwP (1). Significant changes in the vaccination program have occurred with the development of better combined vaccines. So far in Japan, seroepidemiologic studies have been performed on pertussis (2,3), and on diphtheria and tetanus (4), however there has been no any seroepidemiologic study on pertussis, diphtheria, and tetanus in the same district.

In this study, we conducted a seroepidemiological investigation of pertussis, diphtheria, and tetanus in subjects aged 0-80 years in the Fukuoka area of Japan, in order to evaluate the influence of changes in the vaccination programs on the serological status of different age groups.

MATERIALS AND METHODS

Subjects: Serum samples taken from patients (0-80 years

old) at Kyushu University Hospital were stored after laboratory tests had been performed from January to May 1996. The patients' ages and sexes were the only information available regarding these serum samples. Samples from 10 males and 10 females were chosen for each age group (at 5-year intervals), and a total of 320 samples were obtained for antibody measurement. Pertussis, diphtheria, and tetanus vaccination programs for infants and children were started in Japan in 1950, 1948, and 1968, respectively. The vaccination history of patients whose antibody titers being measured could not be confirmed were grouped into a vaccine-eligible age group and a vaccine-ineligible age group according to the ages of the samples. The vaccine-eligible age groups and the vaccine-ineligible age groups were under 46 years old and over 47 years old, respectively, for pertussis, under 48 years old and over 49 years old for diphtheria, and under 28 years old and over 29 years old for tetanus.

Measurement of antibodies: Antibodies to pertussis toxin (PT) and pertussis filamentous hemagglutinin (FHA) were measured by the ball ELISA method (Wako, Tokyo) (5). The diphtheria antitoxin titer was measured by a cell-culture method employing Vero cells (6), and the tetanus antitoxin titer was measured by a passive hemagglutination test (7). PT and FHA antibody titers of 10 EU/ml or higher were judged to be positive, while the minimum protective level for diphtheria antibody and tetanus antitoxin antibody titers was considered to be 0.01 U/ml (8,9).

Statistical analysis: Differences of the seropositivity rates were compared between the vaccinated and non-vaccinated groups by chi-square analysis.

RESULTS

Figures 1 and 2 show the age distribution of the pertussis,

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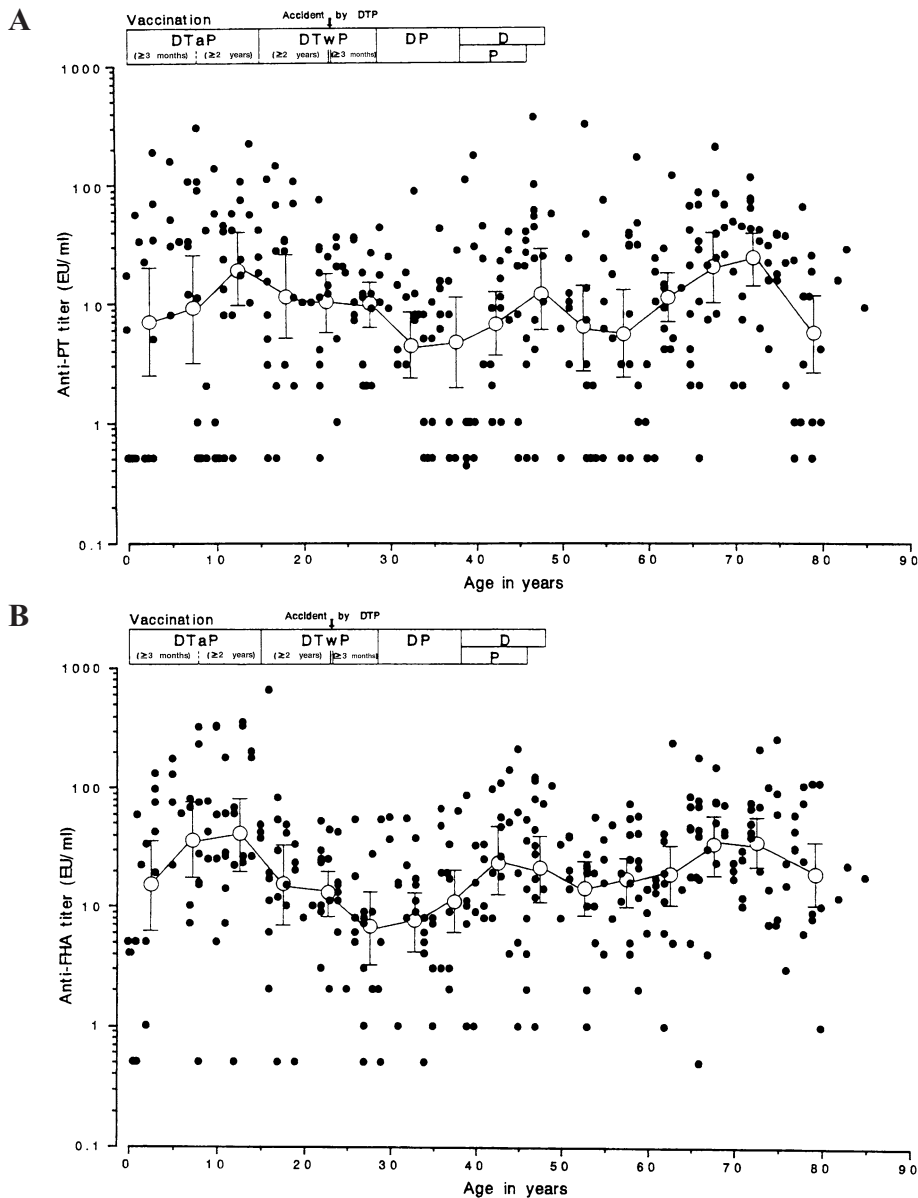


Fig. 1. Pertussis antibody titers (A: PT antibody titer, B: FHA antibody titer) in various age groups of Japanese subjects. The small solid circles indicate single subjects and the large open circles with vertical lines show the geometric mean titer \pm standard deviation.

diphtheria, and tetanus antibody titers of the 320 samples, the geometric mean antibody titer (GMT) of each age group, and the chronology of the vaccination program for diphtheria, pertussis, and tetanus in Japan. No significant sex difference in the distribution of antibody titers for the three diseases was observed in each age group (data not shown).

Anti-PT and anti-FHA antibody titers: Among the pertussis vaccine-eligible age groups, those aged 0-15 years were immunized with DTaP and those aged 16-28 years were immunized with DTwP. The vaccine-eligible age group (<46 years old) showed a similar distribution of PT and FHA antibody titers to the vaccine-ineligible age group (≥ 47 years old) (Fig. 1). The GMTs of PT antibody showed three peaks, which were at 11-15 years, 46-50 years, and 71-75 years, while low titers were seen at 31-35 years and 56-60 years (Fig. 1A). The age distribution of GMT values for FHA antibody showed a similar pattern to that for PT antibody (Fig. 1B).

Diphtheria antitoxin antibody titer: In the vaccine-ineligible age group (≥ 49 years old), diphtheria antitoxin

antibody titers showed lower values than in the vaccine-eligible age group (<48 years old). GMTs for diphtheria antitoxin antibody showed peaks at 6-15 years and 21-25 years, with low titers observed at 16-20 years and 41-45 years (Fig. 2A).

Tetanus antitoxin antibody titer: The tetanus antitoxin antibody titers of the vaccine-ineligible age group (≥ 29 years old) were far lower than those of the vaccine-eligible age group (<28 years old). In the vaccine-eligible age group, GMTs showed peaks at 11-15 years and 21-25 years, with a low titer at 16-20 years. In the age groups above 30 years, very low titers were observed (Fig. 2B).

Seropositivity rates for pertussis, diphtheria, and tetanus: Table 1 shows the seropositivity rates in the groups with and without vaccination for pertussis, diphtheria, and tetanus. The PT antibody seropositivity rates of the two groups were 55.0 and 57.9%, respectively, while the FHA antibody seropositivity rates were 65.6 and 79.3%, respectively. No significant difference was seen between the two groups in

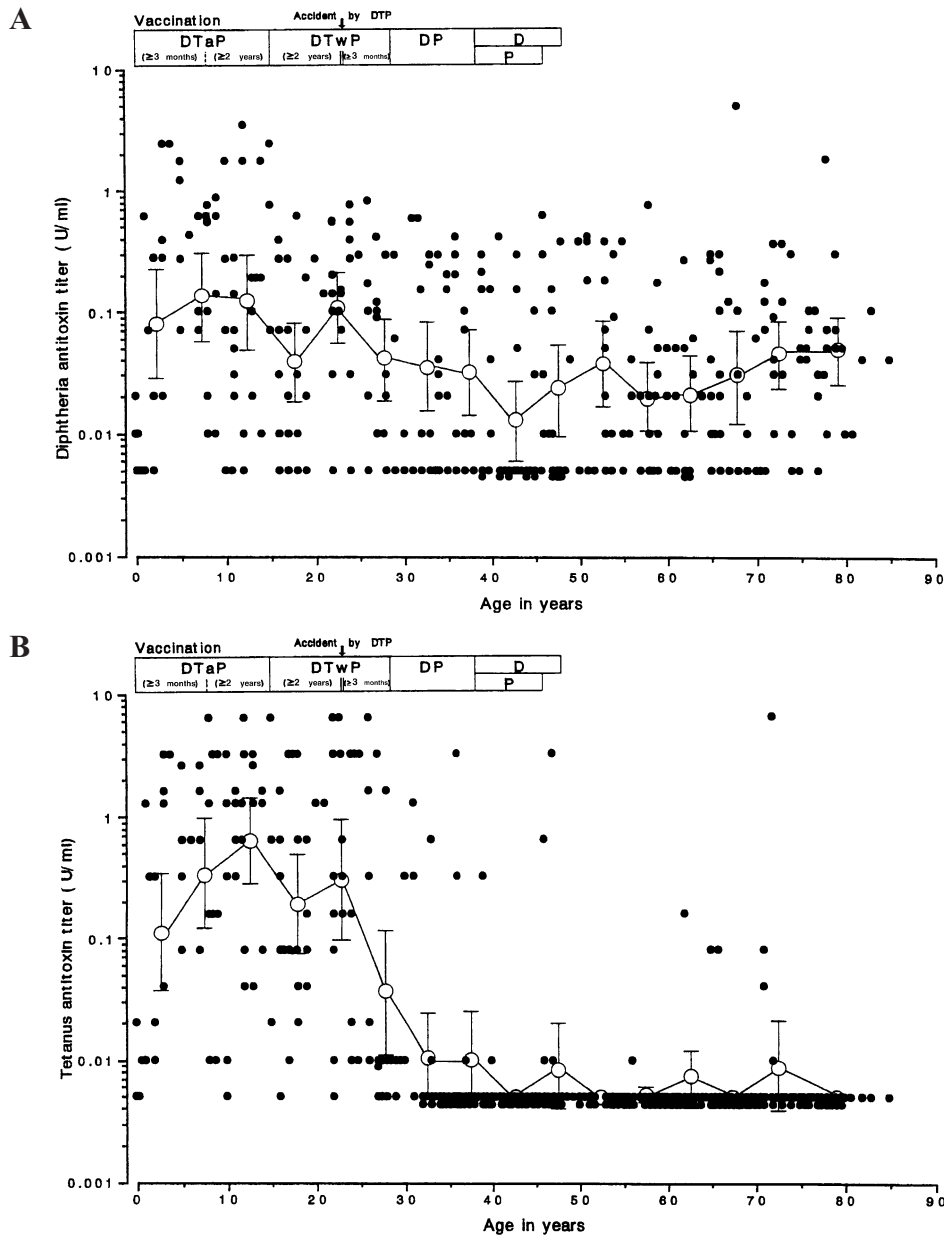


Fig. 2. Antitoxin titers for diphtheria (A) and tetanus (B) in various age groups of Japanese subjects. The small solid circles indicate single subjects and the large open circles with vertical lines show the geometric mean titer \pm standard deviation.

Table 1. Seropositive rates in the vaccine-eligible age groups and the vaccine-ineligible age groups

		Seropositive rate	
		Vaccine-eligible age groups ^{1),2),3)}	Vaccine-ineligible age groups
Pertussis ¹⁾	PT	55.0% (99/180)	57.9% (81/140)
	FHA	65.6% (118/180)	79.3% (111/140)
Diphtheria ²⁾		76.3% (122/160)	75.7% (106/140)
Tetanus ³⁾		91.7% (110/120)*	10.5% (21/200)

* $P < 0.001$.

¹⁾: Vaccine-eligible age groups for pertussis: 0-46 years old (positive antibody: ≥ 10 EU/ml).

²⁾: Vaccine-eligible age groups for diphtheria: 0-48 years old (minimal protective unit: ≥ 0.01 U/ml).

³⁾: Vaccine-eligible age groups for tetanus: 0-28 years old (minimal protective unit: ≥ 0.01 U/ml).

regard to both antibodies. The diphtheria antitoxin seropositivity rates were 76.3 and 75.7%, respectively, and no significant difference was observed between the two groups. However, the tetanus antitoxin seropositivity rates were 91.7

and 10.5%, respectively, showing a significant difference between the two groups ($P < 0.001$).

DISCUSSION

When the antibody profiles for pertussis, diphtheria, and tetanus were compared between the vaccine-eligible age groups and the vaccine-ineligible age groups in Fukuoka (southern Japan), no difference of pertussis antibody titers was observed between the two groups. However, the vaccine-ineligible age group had lower diphtheria antitoxin antibody titers (without a significant difference) and had significantly lower tetanus antitoxin antibody titers. For each disease, there were fluctuations of the GMTs between age groups due to changes in the vaccination programs.

In Japan, vaccination with DTaP is scheduled to be completed by no later than 6-7.5 years old. Therefore, the highest antibody titers for pertussis were expected to be found in the 0-5 years of age group or 6-10 years of age group. However, the peak GMTs for PT and FHA antibodies were not actually observed at 0-10 years old, but were seen in the 11-15 age group. PT antibody is produced only by infection with *Bordetella pertussis*, whereas FHA antibody can be produced by infection with other *Bordetella* spp. (10,11) or with *Haemophilus influenzae* (12). Because both PT and FHA titers peaked at 11-15 years, there might be a booster effect due to natural *B. pertussis* infection in this age group. In 1989, Takayama et al. (2) reported that the highest GMTs for PT and FHA antibodies were found in the 15-17 years of age group in Tokyo. In 1994, Konda et al. (3) studied nine prefectures in Japan, and found that the PT antibody-positive rate tended to increase from the age of 9 to 19 years among the vaccinated population. They suspected that both symptomatic and asymptomatic infections with *B. pertussis* were occurring in this age group. Cattaneo et al. (13) also reported that peak GMT values for PT and FHA antibodies were observed among adolescents in the United States, suggesting that recent natural infection with *B. pertussis* had occurred in this age group. The current study showed a similar seroepidemiological pattern for pertussis to that obtained by previous studies conducted in different areas and different periods. Because of vaccination programs targeting infants and toddlers, the incidence of typical whooping cough has decreased remarkably in industrialized countries. However, it is considered that *B. pertussis* still circulates in these societies, especially in the adult population. Therefore, it may be time to discuss the need for the administration of pertussis vaccine to adults.

The immunity gap in the 16-20 years-of-age group regarding diphtheria antitoxin antibody titers in the current study was considered to be due to a far lower vaccination rate with DTwP because of concern about serious adverse events (1). This interpretation was also supported by the similar immunity gap observed for tetanus antitoxin antibody. In several industrialized countries, immunity gaps exist for diphtheria antibody, but the age groups of these gaps are different depending on the age of initial immunization and the prevalence of natural infection after the introduction of the vaccination program. In these countries, including Japan, vaccination programs have led to a marked decrease in the incidence of diphtheria, which in turn has caused a decrease of circulating toxigenic *Corynebacterium diphtheriae* organisms, resulting in less natural boosting of antibody levels and an increase of susceptible adults (14). Our results showed an immunity gap for diphtheria in the 41-45 years-of-age group. This might have been due to the waning of acquired immunity secondary to vaccination without any booster effect of natural infec-

tion. Alternatively, this might be explained by the influence of a lower vaccination rate after the cessation of vaccination when the Kyoto diphtheria catastrophe occurred in 1948 in Japan (15). The age groups (over 45 years) who were not immunized against diphtheria also had a high titer of diphtheria antitoxin antibody, but this was considered to be the effect of inapparent or apparent natural diphtheria infection. Similar seroepidemiologic findings have also been observed in several other countries (8,14,16).

The peak GMT of tetanus antitoxin antibody was observed in the 11-15 years-of-age group. This was due to the effect of inoculation with diphtheria-tetanus (DT) toxoid at 11-12 years old. The antibody titer became far lower in the age group over 30 years old. Almost none of the adults tested had an antibody titer higher than the minimal protective level. In Japan, the vaccination program for tetanus using DTwP was started as recently as in 1968. The vaccine-eligible age group born after this time showed an antibody response to the vaccine, while no antibody was observed in the vaccine-ineligible age group. Twenty-one subjects in the vaccine-ineligible age group were positive for tetanus antitoxin antibody. This might have been the result of inoculation after trauma, or may have been due to blood transfusion and transfusion of blood products such as γ -globulin, but the histories of these subjects were unknown. Similar seroepidemiologic findings have also been observed in different areas of Japan (4).

In the present study, the seronegative rates for PT and FHA (pertussis), diphtheria, and tetanus among adults (≥ 20 years old) were 48.0, 30.4, 27.1, and 76.6%, respectively. Therefore, the vaccination of this seronegative adult population should be considered. However, what vaccines should be used and at what age vaccination should be performed be carefully investigated. In the United States, all adults are recommended to have a booster dose of tetanus-diphtheria toxoid every 10 years. Routine health screening of 11- to 12-year-olds has been established and booster vaccination with measles-mumps-rubella vaccine (MMR), varicella, and hepatitis B vaccine as well as booster Td vaccination are recommended (17). In Japan, the final vaccination with DT toxoid is administered at 11-12 years old, with no further booster vaccination recommended thereafter. After switching from DTwP to DTaP vaccine in 1981, the immunogenicity of the vaccines used in Japan has been greatly improved and antibodies to diphtheria and tetanus persist until 11-12 years old when booster vaccination with DT is performed (18). However, natural *B. pertussis* infection might occur more frequently than expected in the 11-15 years-of-age group and might be a potential source of infection for infants and toddlers. In order to prevent infection with pertussis in this age group, DTaP rather than DT toxoid might be the best choice for booster vaccination. Edwards et al. (19) reported a sufficient antibody response in adults after using one-fourth of the current dose of DTaP for booster vaccination and showed no difference in the adverse effects arising from Td toxoid. However, further evaluation might be necessary to establish the most appropriate booster vaccination program for the control of diphtheria, pertussis, and tetanus in Japan.

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