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Effectiveness of four doses of pertussis vaccine during infancy diminished in elementary school age: A test-negative case-control study in Japan

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ABSTRACT

Objective: The Japanese national immunization program recommends that children receive 4 doses of acellular pertussis vaccine between 3 months and 2 years of age. Nevertheless, the number of pertussis cases is increasing in elementary school children aged 6–12 years. Therefore, a test-negative case-control study was conducted to assess the effectiveness of the pertussis vaccine program.
Methods: Subjects included children aged ≥3 months who visited a collaborating hospital due to pertussis-specific cough between October 2017 and November 2019. All subjects underwent diagnostic tests for pertussis, and those diagnosed as positive were regarded as cases. Subjects diagnosed as pertussis-negative were classified as controls. Vaccination history was collected using a questionnaire administered to parents with reference to immunization records. Logistic regression models were employed to calculate the odds ratio (OR) and 95% confidence interval for laboratory-confirmed pertussis.
Results: Of 187 recruited subjects (120 cases and 67 controls), questionnaire responses were obtained for 145 subjects (95 cases and 50 controls). Compared with unvaccinated subjects, the vaccine effectiveness (VE) of 4 doses was 70% among all subjects and reached to 90% with marginal significance among subjects under 6 years of age. However, among school-aged subjects, the VE was not suggestive of protection

Abbreviations: OR, odds ratio; VE, vaccine effectiveness; DTaP vaccines, acellular pertussis vaccine combined with diphtheria-tetanus toxoids; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; PT-IgG, IgG for pertussis toxin; LAMP method, loop-mediated isothermal amplification method; CI, confidence interval.

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against pertussis (VE: 8%). For vaccinees given 4 doses, the OR for developing pertussis increased significantly with longer duration since the fourth dose (compared with <4.5 years, OR of 6.0–8.2 years = 5.74; OR of ≥8.3 years = 3.88; P for trend by duration < 0.01).
Conclusion: Effectiveness of administering 4 doses of pertussis vaccine during infancy decreases with time passed since the fourth dose. This regimen does not protect school-aged children against pertussis.

1. Introduction

With the use of an acellular pertussis vaccine, pertussis was well controlled in Japan until the early 2000s [1]. However, despite high vaccine coverage (≥90% annually), surveillance focused on sentinel pediatric hospitals revealed that the number of reported pertussis cases began to increase over the last decades, particularly in adolescents and adults [2]. Therefore, in order to better characterize this trend epidemiologically, the Law of Infectious Diseases was revised to mandate reporting of all pertussis cases, including those in adults, beginning in 2018. As a result, the annual number of reported pertussis cases exceeded 10,000 in 2018, with more than half of those cases involving elementary school-aged children (i.e., 6–12 years of age). Those data also revealed that most of the affected elementary school-aged children had received 4 doses of acellular pertussis vaccine combined with diphtheria-tetanus toxoids (DTaP vaccine) during first 2 years of life [2], suggesting that the effectiveness of the pertussis vaccine is not sustained to elementary school age.

To date, the Japanese national immunization program aimed at preventing pertussis has involved administration of 4 doses of DTaP vaccine, including three primary doses at the ages of 3, 4, and 5 months and one booster dose at age 18 to 23 months. However, in many countries, such as the United States, 5 doses of DTaP vaccine are recommended during childhood (2, 4, 6, 15 to 18 months, and 4 to 6 years of age), and an adolescent booster dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) is recommended at 11 to 12 years of age [3]. As a number of studies have indicated that the effectiveness of the pertussis vaccine has declined materially by 5 years from the last dose [4–9], a consideration of the appropriate timing of the booster dose is needed in Japan. Indeed, a report on the prevalence of antibodies against pertussis in Japan indicated that the seroprotective proportion of IgG for pertussis toxin (PT-IgG) after the primary doses is highest in infants 6–11 months old, and then gradually declines, reaching its lowest level by 9 years of age [2]. Another seroepidemiologic study demonstrated that the PT-IgG titer is highest in children aged 1–2 years and then declines by the time they enter elementary school [10]. These data are consistent with the observed increase in pertussis cases in elementary school-aged children in Japan.

To examine the effectiveness of the current DTaP vaccination program in Japan, a hospital-based case-control study using test-negative controls was conducted. Vaccine effectiveness (VE) was evaluated separately among different age groups, and we also examined the optimal timing of the booster dose.

2. Methods

2.1. Study design and study subjects

A multicenter case-control study using test-negative controls was conducted in Japan. We prospectively recruited all children who visited a collaborating pediatric hospital seeking treatment for pertussis-specific symptoms between October 2017 and November 2019 (i.e., the study period). Pertussis-specific symptoms were based on 2017 clinical diagnostic criteria for pertussis, as follows: for infants <1 year old, a cough with one or more symptoms (paroxysmal cough, whoop, post-tussive vomiting, or apnea); for children ≥1 year and adults, cough lasting more than 7 days with one or more symptoms (paroxysmal cough, whoop, post-tussive vomiting, or dyspnea) [11]. According to the guideline for diagnosis of pertussis [11], subjects with pertussis-specific symptoms usually undergo culture isolation of *Bordetella pertussis* or loop-mediated isothermal amplification (LAMP) assay. For culture isolation, nasopharyngeal swab samples are inoculated onto Bordet-Gengou plates or modified cyclodextrin solid medium using cefdinir [12], and incubation of samples and identification of suspected colonies are done according to standard methods [2,11]. LAMP assays are conducted using commercial kits [13]. The sensitivity and specificity of the LAMP assay kit for detecting *Bordetella pertussis* are 100% and 98%, respectively, when compared with culture isolation, and 96% and 100%, respectively, when compared with PCR tests [14]. Patients with positive results for culture isolation and/or LAMP assay are considered confirmed to have pertussis. Subjects for whom these tests could not be conducted or who had a negative result are recommended to receive serological testing for PT-IgG antibody or IgM/IgA antibody. Serologic diagnosis was defined as follows: for paired serum samples in the acute and recovery phases, at least a 2-fold increase in PT-IgG titer; for single serum samples in the acute phase, PT-IgG titer ≥ 10 EU/ml among unvaccinated subjects or ≥100 EU/ml among vaccinated subjects; or positive IgM/IgA antibody test [11]. Subjects exhibiting a positive result for at least one of these tests were regarded as cases for the purpose of this study. Subjects exhibiting negative results for these tests were regarded as controls for the purpose of this study. As the study was observational, we used the results of clinical tests conducted as part of daily medical care according to the above-mentioned guidelines [11], meaning that not every subject underwent every diagnostic test. Subjects who were too young to receive pertussis vaccine (under 3 months of age) and those with a history of diagnosed pertussis were excluded from the study.

The study protocol was approved by the ethics committees of the Osaka City University Graduate School of Medicine and the collaborating hospitals. Appropriate informed consent was obtained from each child's parent or guardian prior to participation.

2.2. Information collection

The following information was obtained by means of a self-administered questionnaire completed by each child's parent or guardian: date of birth, gender; history of pertussis; history of DTaP vaccination, number of vaccinations, vaccination dates, vaccine manufacturer, and vaccine lot number, if vaccinated; underlying illnesses (e.g., heart disease, renal disease, liver disease, diabetes mellitus, anemia, asthma, other respiratory disease, tonsillitis, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, immune-deficiency, epilepsy); and environmental characteristics, including maternal smoking during pregnancy, passive smoking in the house, preschool or school attendance, frequency of going out (per week), hand washing habits, gargling habits, frequency

of tooth brushing (per day), total room space in the home (m^2), number of family members, siblings, contact with a confirmed pertussis case during the previous month, and contact with a person with a lasting cough during the previous month. In Japan, vaccination history is typically recorded in an immunization record book maintained by individuals. Thus, we collected information as to whether the reported vaccination status was confirmed by the immunization record. Ingredients of the vaccines study subjects received are shown in the Supplementary Table [15,16]. When missing answers or illogical data were detected, research technicians conducted a telephone interview to complete the data.

In addition, the following clinical findings were reported by the pediatrician in charge using a standardized questionnaire: date at symptom onset; date at diagnosis; results of laboratory examinations (culture isolation of *Bordetella pertussis*, LAMP, PT-IgG titer in the acute and recovery phases, and IgM/IgA antibody titer); disease symptoms (paroxysmal cough, whoop, post-tussive vomiting, fever, dyspnea, apnea, seizure, and drowsiness); pneumonia findings on chest X-ray; hospitalizations; and treatments (antibiotics, oxygen treatment, artificial ventilation, and γ-globulin administration).

2.3. Statistical analysis

Background characteristics of cases and controls were compared using the chi-square test, Fisher's exact test or Wilcoxon rank-sum test. Unconditional logistic regression models were employed to calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for pertussis. Trends for association were assessed by assigning ordinal scores to the level of the independent variable. Variables exhibiting a P-value < 0.1 (i.e., age and sex) and plausibly related to the disease (i.e., underlying illnesses) were considered potential confounders for adjustment. VE was calculated as (1-OR) × 100 (%) [17].

Analyses stratified by age category were conducted to examine age-specific VE. Category boundaries applied were preschool (i.e., under 6 years of age) or school age (i.e., ≥6 years of age).

To examine the associations between age and time passed since the fourth vaccine dose and pertussis, subjects who had received 4 vaccine doses were included and categorized into four groups according to age distribution or time passed since the fourth dose. Category boundaries were drawn so as to make the sizes of the groups as similar as possible.

To consider the limited number of study subjects, variables exhibiting a P value of <0.1 in multivariate models were considered marginally significant. All tests were two-sided. All analyses were performed using SAS software version 9.1.3 (SAS Institute, Cary, NC, USA).

3. Results

A total of 187 subjects (120 cases and 67 controls) were recruited during the study period. Responses to the questionnaire were obtained for 145 subjects (95 cases and 50 controls; response rate: 78%); therefore, 145 subjects were included in the analyses.

Table 1 shows the background characteristics of the cases and controls. Compared with controls, cases were older (median age: 8.0 years vs 6.4 years) and more likely to be female (66% vs 44%); other environmental factors were similar between the groups. Regarding clinical characteristics, the time passed between symptom onset and diagnostic evaluation was shorter for cases, and cases were more likely to exhibit post-tussive vomiting. Laboratory tests provided to the subjects did not differ between cases and controls, and the LAMP assay was the most frequently used test. A total of 83 cases (87%) received diagnostic testing using the LAMP assay, and among these, 66 (80%) had positive results. Among 29 cases who were not tested with the LAMP assay or had a negative LAMP assay result, 4 cases received the test for culture isolation, but no cases had a positive result. Among these 29 cases, 24 and 26 received serologic examination for PT-IgG antibody or IgM/IgA antibody, respectively. As a result, 13 and 24 cases had a positive result for each test. The laboratory confirmation of cases shown in Table 1 includes subjects who had undergo more than one method of diagnosis. Almost all cases received antibiotic treatment, but only 5% of cases required oxygen support.

Table 2 shows the association between pertussis vaccination and laboratory-confirmed pertussis. After adjusted for potential confounders, the OR of vaccinated subjects compared with unvaccinated subjects was 0.32, whereas the ORs of subjects who received 1–3 doses of vaccine and 4 doses of vaccine were 0.40 and 0.30, respectively (not statistically significant). However, the third tertile of age (reference category: <6.0 years old) and female sex (reference category: male) were significantly associated with pertussis (OR of subjects ≥9 years old = 3.71, P for trend by age = 0.01; OR of females = 2.54).

Table 3 shows the age-specific association between pertussis vaccination and laboratory-confirmed pertussis. Among children <6 years of age, 4 doses of vaccine compared with unvaccinated subjects exhibited a marginally significantly lower OR for developing pertussis (VE 90%, P = 0.07). However, among children ≥6 years old, 4 doses of vaccine did not provide protection against pertussis, compared with unvaccinated subjects (VE 8%, P = 0.95).

In analyses focused on subjects who received 4 doses of vaccine (Table 4), the third quartile of age (8.0–10.0 years) and fourth quartile of age (≥10.1 years) exhibited significantly higher ORs for developing pertussis, compared with the first quartile of age (<6.4 years). With regard to time passed since the fourth dose of vaccine, the third and fourth quartiles also exhibited significantly higher ORs for pertussis, compared with the first quartile (<4.5 years) (6.0–8.2 years passed: OR = 5.74, 95% CI = 1.70–19.3; ≥8.3 years passed: OR = 3.88, 95% CI = 1.21–12.4). These trends were statistically significant (P for trend by age < 0.01; P for trend by time passed since the fourth dose <0.01).

4. Discussion

In the present study, administration of 4 doses of DTaP vaccine during infancy was associated with a high VE (90%) among children under 6 years of age, but 4 doses of DTaP vaccine exhibited no preventive effect against pertussis among children ≥6 years of age. In addition, the risk of developing pertussis was significantly higher among children aged ≥8 years and those in which ≥6 years had passed since the fourth dose of vaccine. Previous studies in other countries also demonstrated that older children and those in which a longer period of time had passed since the last dose of vaccine had a higher risk of developing pertussis [18–21], although the preventive effect of DTaP vaccine was highly persistent for approximately 5 years [4–9]. Therefore, the present results are consistent with these studies. Considering both our data and those of other studies [4–9,18–21], it is not surprising that there has been a resurgence of pertussis in elementary school-aged children [1].

Several studies have evaluated the effectiveness of the DTaP vaccine in Japan. A population-based, age-, sex-, and residence-matched, case-control study reported a VE of 96% (95% CI: 54–99%) for physician-diagnosed pertussis among children aged ≤6 years who received 3 or 4 doses of vaccine [22]. A hospital-based, age-, and sex-matched, case-control study reported a VE of 78% (95% CI: −5 to 96%) for physician-diagnosed pertussis among children and adolescents who received 4 doses of vaccine

Table 1
Comparison of background characteristics between cases and controls.

Variables		Cases (N = 95)	Controls (N = 50)	P value*
		n (%)	n (%)	
Demographic variables				
Age (years)	Median (range)	8.0 (0.3–28.9)	6.4 (0.3–14.2)	0.01
Age category (tertile)	0.3–5.9	27 (28%)	21 (42%)	0.01
	6.0–8.9	30 (32%)	20 (40%)	
	9.0+	38 (40%)	9 (18%)	
Sex	Male	32 (34%)	28 (56%)	<0.01
DTaP vaccination status				
Number of vaccinations	0	7 (7%)	2 (4%)	0.66
	1–3	11 (12%)	7 (14%)	
	4	77 (81%)	41 (82%)	
Age at 4th dose	Median (range)	1.6 (0.7–10.3†)	1.6 (0.8–3.5)	0.36
Vaccine manufacture‡	A	104 (33%)	32 (20%)	
	B	69 (22%)	46 (28%)	
	C	88 (28%)	37 (23%)	
	D	47 (15%)	48 (29%)	
	E	6 (2%)	0 (0%)	
	Unknown	19	20	
Underlying illnesses	Present	22 (23%)	15 (30%)	0.37
Environmental factors				
Passive smoking	Ever	48 (51%)	20 (40%)	0.23
Frequency of going out	Median (range)	3.0 (1–7)	3.3 (1–7)	0.93
Hand washing habits	Present	66 (69%)	37 (74%)	0.57
Gargling habits	Present	33 (35%)	17 (34%)	0.93
Total room space in the house (m^2)	Median (range)	93 (30–14582)	98.5 (32.8–179)	0.86
	Unknown	3	6	
Number of family members	Median (range)	4.0 (2–8)	4 (2–6)	0.20
Siblings	Present	74 (78%)	39 (78%)	0.81
Clinical information				
Time from symptom onset to diagnosis (days)	Median (range)	14 (4–92)	23 (6–65)	0.02
	Unknown	3	31	
Symptoms	Paroxysmal cough	91 (96%)	20 (87%)	0.13
	Whoop	28 (30%)	4 (17%)	0.22
	Post-tussive vomiting	46 (49%)	7 (30%)	0.10
	Fever	12 (18%)	1 (7%)	0.44
	Dyspnea	15 (16%)	1 (4%)	0.19
	Apnea	2 (2%)	0 (0%)	1.00
Laboratory tests provided to the subjects ¶				
	Isolation of *Bordetella pertussis*	13 (13%)	5 (10%)	0.67
	LAMP	83 (87%)	42 (84%)	0.58
	Sero-diagnosis with IgG antibody	38 (40%)	17 (34%)	0.77
	Sero-diagnosis with IgM/IgA antibody	42 (44%)	19 (38%)	0.68
Methods for laboratory confirmation of pertussis ¶				
	Isolation of *Bordetella pertussis*	5 (5%)		
	LAMP	66 (69%)		
	Sero-diagnosis with IgG antibody	16 (17%)		
	Sero-diagnosis with IgM/IgA antibody	28 (29%)		
Chest X-ray findings	Pneumonia	0 (0%)	1 (4%)	0.19
Hospitalization	Present	9 (10%)	1 (5%)	0.68
Treatment	Antibiotics	93 (99%)	21 (91%)	0.09
	Oxygen support	4 (5%)	0 (0%)	1.00

* Chi-square test, Fisher's exact test, or Wilcoxon rank-sum test, where appropriate.
† One case received the fourth dose at 10.3 years. Excluding this case, the range of age at the fourth dose of vaccine was 0.7–4.0 years.
‡ Includes 333 doses for cases and 183 doses for controls, as 3 cases and 2 controls received one dose of vaccine, 2 cases received two doses, 6 cases and 5 controls received three doses, and 77 cases and 41 controls received four doses.
¶ More than one method of diagnosis might have been positive for a given subject.

[23]. A retrospective cohort study of university students reported a VE of 52% (95% CI: 3–76%) for probable pertussis among those who received 4 doses of vaccine [24]. As these studies involved age-matching or subjects within a limited age group, VE stratified by age could not be assessed in each study. However, the VE values reported in these studies appeared to decrease with increased subject age.

National vaccination programs for pertussis vary among countries [25]. Most countries recommend 3 primary doses of vaccine during infancy and at least 1 booster dose before entering school. In the United States and Canada, in addition to the 3 primary doses of vaccine during infancy, 2 booster doses are recommended at approximately 18 months and then 4 years of age. However, even the administration of 5 doses of vaccine exhibits waning effectiveness with the passage of time after the last dose [4–8], leading to the recommendation of periodic additional booster doses for adolescents and adults [3,25]. In New Zealand, which recommends 3 primary doses of vaccine during infancy and 1 booster dose at 4 years of age, a VE of $\geq$ 90% against pertussis hospitalization following the 3 primary doses is reportedly persistent through the children's fourth birthday, and the booster dose has a persistent VE $\geq$ 90% through 7 years of age [26]. These studies highlight the importance that booster doses be administered at an optimal age to provide persistent protective levels of immunity within the community.

When focusing on reducing the number of severe pertussis cases in infants too young to receive the vaccine, reducing the number of pertussis cases in members of the generation that has

Table 2
Odds ratios of DTaP vaccination and selected variables for laboratory-confirmed pertussis.

Variables			Univariate OR (95%CI) P	Multivariate* OR (95%CI) P
DTaP vaccination†		None	1.00 (ref.)	1.00 (ref.)
		Received	0.52 (0.11–2.62) 0.43	0.32†(0.06–1.78) 0.19
	Number of vaccinations	0	1.00 (ref.)	1.00 (ref.)
		1–3	0.45 (0.07–2.81) 0.39	0.40 (0.06–2.75) 0.35
		4	0.54 (0.11–2.70) 0.45	0.30 (0.05–1.70) 0.17
			(Trend P = 0.66)	(Trend P = 0.18)
Age (years)	Tertile	0.3–5.9	1.00 (ref.)	1.00 (ref.)
		6.0–8.9	1.17 (0.52–2.61) 0.71	1.30 (0.49–3.42) 0.60
		9.0+	3.28 (1.30–8.27) 0.01	3.71 (1.27–10.8) 0.02
			(Trend P = 0.01)	(Trend P = 0.01)
Sex		Male	1.00 (ref.)	1.00 (ref.)
		Female	2.51 (1.24–5.06) 0.01	2.54 (1.21–5.33) 0.01
Underlying illnesses		Absent	1.00 (ref.)	1.00 (ref.)
		Present	0.70 (0.33–1.52) 0.37	0.76 (0.34–1.73) 0.52

DTaP vaccination, acellular pertussis vaccine combined with diphtheria-tetanus toxoids; OR, odds ratio; CI, confidence interval.
* Model includes number of DTaP vaccinations, age categories (tertiles), sex, and underlying illnesses.
† The ORs were obtained from the model in which DTaP vaccination status was replaced by the number of DTaP vaccinations.

Table 3
Adjusted odds ratios* of DTaP vaccination for laboratory-confirmed pertussis, according to age category.

Variables		0.3–5.9 years			6.0 years or more		
		Cases (N = 27) n (%)	Controls (N = 21) n (%)	OR (95%CI) P	Cases (N = 68) n (%)	Controls (N = 29) n (%)	OR (95%CI) P
DTaP vaccination†	None	5 (19%)	1 (5%)	1.00 (ref.)	2 (3%)	1 (3%)	1.00 (ref.)
	Received	22 (81%)	20 (95%)	0.12†(0.01–1.33) 0.08	66 (97%)	28 (97%)	0.93†(0.07–11.8) 0.96
Number of vaccinations	0	5 (19%)	1 (5%)	1.00 (ref.)	2 (3%)	1 (3%)	1.00 (ref.)
	1–3	10 (37%)	7 (33%)	0.16 (0.01–2.05) 0.16	1 (1%)	0 (0%)	Not applicable
	4	12 (44%)	13 (62%)	0.10 (0.01–1.20) 0.07	65 (96%)	28 (97%)	0.92 (0.07–11.7) 0.95
				(Trend P = 0.07)			(Trend P = 0.78)

DTaP vaccination, acellular pertussis vaccine combined with diphtheria-tetanus toxoids; OR, odds ratio; CI, confidence interval.
* Model includes number of DTaP vaccinations, sex, and underlying illnesses.
† The ORs were obtained from the model in which DTaP vaccination status was replaced by the number of DTaP vaccinations.

Table 4
Association between age and time passed since the fourth vaccine dose and laboratory-confirmed pertussis among subjects who received 4 vaccine doses.

Variables		Cases (N = 77) n (%)	Controls (N = 41) n (%)	OR* (95%CI) P
Age (years)				
	0.3–6.3	13 (17%)	17 (41%)	1.00 (ref.)
	6.4–7.9	18 (23%)	12 (29%)	1.96 (0.69–5.58) 0.21
	8.0–10.0	23 (30%)	6 (15%)	4.77 (1.45–15.7) 0.01
	10.1+	23 (30%)	6 (15%)	4.79 (1.50–15.4) < 0.01
				(Trend P < 0.01)
Time passed since the fourth dose (years)				
	<4.5	14 (18%)	16 (39%)	1.00 (ref.)
	4.5–5.9	16 (21%)	14 (34%)	1.33 (0.47–3.71) 0.59
	6.0–8.2	26 (34%)	5 (12%)	5.74 (1.70–19.3) < 0.01
	8.3+	21 (27%)	6 (15%)	3.88 (1.21–12.4) 0.02
				(Trend P < 0.01)

OR, odds ratio; CI, confidence interval.
* Adjusted for sex, and underlying illnesses.

more contact with infants is important. A study examining the association between social contact patterns and respiratory symptoms among infants <1 year old reported that mothers had the longest contact with their infant children, and contact with school-aged children was a major risk factor for respiratory symptoms in infants [27]. A survey of household contacts of infants with laboratory-confirmed pertussis showed that the mother was the probable source of infection in 38% of infants with pertussis, followed by siblings (31%) and the father (10%) [28]. A study of household contacts of infants with pertussis in China indicated that half of cases involved clear exposure to a household member with a persistent cough, including siblings (23.4%) and parents (18.4%) [29]. These studies suggest that contacts with not only the mother but also school-aged siblings is a major risk factor for infant pertussis. Taken together, these data suggest that it may be desirable to recommend a booster dose of vaccine for pregnant women and for children before they enter school, as is already the case in some other countries.

The present study had several limitations. First, the small number of study subjects lowered the statistical power of the analyses.

In the analysis stratified by age, however, the number of children ≥6 years old who failed to exhibit a protective effect of the vaccine was larger than the number of children <6 years of age who clearly exhibited high VE. Therefore, the inability to detect a preventive effect of vaccination in children ≥6 years old was not likely due to insufficient statistical power. Second, other unconsidered confounding factors might have affected the present results. Third, subjects in test-negative case-control studies are usually treated as cases or controls based on the results of laboratory diagnosis, but the timing of laboratory tests among controls in the present study was relatively late compared to that among cases. This could have resulted in some misclassification, in which some pertussis cases might have been classified as test-negative controls due to the timing of the laboratory tests. In addition, the sensitivity and specificity of the laboratory tests might have affected the case or control status. As the present study utilized the results of laboratory tests that were conducted according to guidelines for the diagnosis of pertussis [11], it was found that 83 cases (87%) and 42 controls (84%) had undergone testing with the LAMP assay, which has high sensitivity (96–100%) and high specificity (98–100%) [14]. Therefore, misclassification due to the accuracy of applied laboratory tests, if any, would be relatively small. Moreover, misclassification associated with the accuracy of the laboratory tests, if small, would lead to the dilution of the study results, and thus, the validity of the study results would not be affected. On the other hand, the present study had a number of strengths. First, as the laboratory tests were applied to patients meeting standardized criteria of pertussis-specific symptoms, the possibility of selection bias that can generally occur in medical settings was minimized. Second, since 2018, all pertussis cases in Japan have been reported to the surveillance system, and the use of LAMP assays for diagnostic purposes has been covered by medical insurance. Therefore, subjects with pertussis-specific symptoms have ready access to laboratory tests for pertussis, which may have resulted in an unbiased registration in the present study.

In conclusion, the present study demonstrated that the VE of 4 doses of DTaP vaccine declines with increasing time passed since the fourth dose and that passage of ≥6 years since the fourth dose is associated with increased susceptibility to pertussis. Our findings suggest the strategy for pertussis vaccination in Japan should be reconsidered. This issue will require careful and ongoing consideration of epidemiology, VE, vaccine safety, and cost-effectiveness. Also, to achieve adequate control of pertussis within the community, it would be helpful to develop a vaccine that provides a longer-duration-protective effect.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.11.035.

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