Vaccine 33 (2015) 1027–1032

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effectiveness of acellular pertussis vaccine in a routine immunization program: A multicenter, case-control study in Japan

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ARTICLE INFO

Article history:
Received 11 August 2014
Received in revised form
22 December 2014
Accepted 5 January 2015
Available online 14 January 2015

Keywords:
Effectiveness
DTaP vaccine
Pertussis
Risk factors
Case-control study

ABSTRACT

In 2008, the number of pertussis cases increased substantially among Japanese adolescents, despite high coverage with acellular pertussis vaccine (DTaP). This study examined the effectiveness of DTaP vaccine in the routine immunization program in Japan. Between April 2009 and October 2012, we conducted a multicenter, case-control study, and compared the history of DTaP vaccination between 55 newly diagnosed pertussis cases and 90 age- and sex-matched controls. DTaP vaccine history was obtained by a self-administered questionnaire completed by their parents or guardians. Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of vaccination for development of pertussis.

DTaP vaccination of ≥1 dose revealed a significantly lower OR for pertussis (OR = 0.20, 95%CI, 0.04–0.97), and the OR of complete vaccination (4 doses) was 0.22 (0.04–1.05). Even after limiting subjects to those whose vaccination status could be confirmed by the immunization records, the negative associations were observed. The decreasing ORs of 4-dose vaccinees remained, even among subjects who had received the fourth dose ≥9.2 years earlier (OR = 0.11, 95%CI, 0.01–1.02).

In conclusion, DTaP vaccination had a preventive effect for pertussis. Effectiveness was observed even 9 or more years after the final dose.

1. Introduction

In Japan, the routine immunization program with pertussis vaccine was temporarily suspended in 1975 due to concern about severe adverse events such as encephalopathy [1–4]. Two months later, the immunization program was resumed, but vaccine coverage had been extremely low until acellular pertussis vaccine combined with diphtheria–tetanus toxoids (DTaP vaccines) was introduced for children over 24 months in late 1981. Afterward, the age of administration of DTaP vaccine was changed to 3 months in 1988, and vaccine coverage improved to about 90% in the late 1990s. Through these strategies, the annual number of reported pertussis cases decreased to about 10,000 in the early 2000s [3]. However, despite high vaccination coverage (i.e., over 90% in every year), the number of reported pertussis cases increased in the late 2000s. According to the age distribution of reported pertussis cases, the proportion of adolescents and adults has been increasing, and the proportion reached half in 2008 [5]. The reason why pertussis cases have been increasing among adolescents and adults is not completely clear. However, several reasons, such as improved diagnostics, the lower vaccine coverage era between 1975 and 1981, or waning immunity among those who had received DTaP vaccination in childhood, may be responsible [6,7].

Based on the present Japanese immunization program with DTaP vaccination, children receive 4 doses of DTaP, including 3 primary doses at the ages of 3, 4, and 5 months, and 1 booster

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

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http://dx.doi.org/10.1016/j.vaccine.2015.01.008
0264-410X/

dose at 18 to 23 months. On the other hand, in the United States of America, the Advisory Committee on Immunization Practices recommends 5 doses of DTaP vaccination for childhood (2, 4, 6, 15 to 18 months, and 4 to 6 years of age) and an adolescent booster dose of the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) at 11 to 12 years [8]. According to previous studies, the clinical effectiveness of DTaP vaccine for pertussis has been weakening with time after the final dose of pertussis vaccine [9–13], which suggests that an adolescent booster dose of vaccination might also be needed in Japan.

Thus, a hospital-based case-control study was conducted to examine the effectiveness of DTaP vaccine in preventing the development of pertussis in the present routine immunization program. The present study also evaluated the effect of 4-dose vaccination for pertussis separately by time since the fourth dose of DTaP.

2. Materials and methods

2.1. Selection of cases and controls

Between April 2009 and October 2012 (the study period), a multicenter, case-control study was conducted in Japan. Newly diagnosed cases of pertussis were recruited at 4 collaborating hospitals in 4 different areas of Japan: (from north to south) Chiba, Saitama, Mie, and Fukuoka. Eligible cases were newly diagnosed pertussis patients who satisfied the clinical criteria for pertussis and whose age at diagnosis was less than 30 years. The clinical criteria for pertussis were: cough lasting for more than 7 days with one or more symptoms (paroxysmal cough, whoop, or posttussive vomiting) and one of isolation of *Bordetella pertussis*, positive results by the loop-mediated isothermal amplification (LAMP) method, serodiagnosis (for paired serum samples at the acute phase and at the recovery phase, at least twofold increase of IgG antibody for pertussis toxin (PT-IgG) or fourfold increase of agglutinin titer, while for a single serum sample at the acute phase, PT-IgG of 10 EU/mL or more among unvaccinated subjects or 100 EU/mL or more among vaccinated subjects) or epidemiologically linked to a confirmed pertussis case. During the study period, a pertussis outbreak occurred in Saga University [14], where one of the investigators worked. Thus, if cases diagnosed in Saga University satisfied the clinical criteria in the present study, they also contributed to the present study.

Regarding the recruitment of control subjects, each case was asked to provide up to five friend controls, of the same age (or school grade) and sex as the case. Exclusion criteria were: presence of lasting cough for more than 1 week during the 1 month prior to case diagnosis. During the study period, however, it turned out that some cases (particularly preschool children) did not have any friends and could not provide any friend controls. Thus, not only friend controls but also hospital controls were recruited for cases who were enrolled since April 2012. Collaborating hospitals were encouraged to select up to five hospital controls among patients without pertussis, matching for age and sex.

The study protocol was approved by the ethics committees at the Osaka City University Faculty of Medicine and at the collaborating hospitals, and written, informed consent was obtained from all subjects (or their parents or guardians) 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: sex, date of birth; history of pertussis; history of DTaP vaccination, number of vaccinations, vaccination dates, vaccine manufacturer and vaccine lot number if vaccinated; underlying illnesses (heart disease, renal disease, liver disease, diabetes mellitus, anemia, asthma, other respiratory diseases, tonsillitis, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, immunodeficiency, epilepsy); history of steroid treatment for more than one month; total room space in the house (m^2); number of family members; contact with a confirmed pertussis case during the recent one month; and contact with a person with a lasting cough during the last month. In Japan, the vaccination history is usually recorded in an immunization record book maintained by individuals. Thus, the information collected about vaccination status was confirmed by the immunization record. When missing answers or illogical data were detected by research technicians, research technicians conducted a telephone interview to complete the data.

In addition, for pertussis cases, the following clinical findings were reported by the pediatricians-in-charge using a standardized questionnaire: date at symptom onset; date at diagnosis; disease symptoms (paroxysmal cough, whoop, posttussive vomiting, fever, dyspnea, and seizures); and laboratory examinations (culture isolation of *B. pertussis* and results by the LAMP method, and PT-IgG and agglutinin titers in the acute and recovery phases).

2.3. Statistical analysis

First, it was verified that the background characteristics of hospital controls were not different from those of friend controls using the chi-square test, Fisher's exact test, or the Wilcoxon rank sum test. Then, the characteristics were compared between cases and controls using the chi-square test or the Wilcoxon rank-sum test. Because some cases had no corresponding pair as controls and vice versa, not only a conditional logistic regression model but also an unconditional logistic regression model was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for pertussis. Trends for associations were assessed by assigning ordinal scores to the level of the independent variable. Variables that showed a *P*-value of less than 0.1 or that seemed to be medically related to the disease were considered potential confounders for adjustment. When unconditional logistic regression models were used, data for not only matched pairs but also unmatched pairs were analyzed, and matching variables (age and sex) were included in the models. Vaccine effectiveness (VE) was calculated as $(1 - \mathrm{OR}) \times 100$ (%).

In addition, to examine the associations between pertussis and 4 doses of DTaP vaccination according to time since the fourth dose, additional analyses were conducted. Time since the fourth dose was calculated as the number of years from the date of the fourth dose to the date of case illness onset or the date of control recruitment. In the analysis, nonvaccinees and 4-dose vaccinees were included, and 4-dose vaccinees were categorized into two or three levels according to the distribution of time since the fourth dose among controls, with the category boundaries chosen so as to make the sizes of the groups as similar as possible. The analysis used unconditional logistic regression models.

All tests were two-sided. All analyses were performed using SAS version 9.1.3 software (SAS Institute, Cary, NC, USA).

3. Results

The sample size required to achieve statistically significant VE was calculated using the power calculation for case-control studies. The calculation was conducted assuming an α level of 0.05, a β level of 0.20, DTaP vaccination proportion in controls of 90%, and OR of vaccine of 0.20. As a result, to achieve statistically significant VE, a total sample size of 90 (30 cases and 60 controls) was needed.

Among the 72 pertussis cases and 97 controls (75 friend controls and 22 hospital controls) enrolled, 63 cases and 94 controls (73 friend controls and 21 hospital controls) responded to the questionnaire (response rate, 88% for cases and 97% for controls). However,

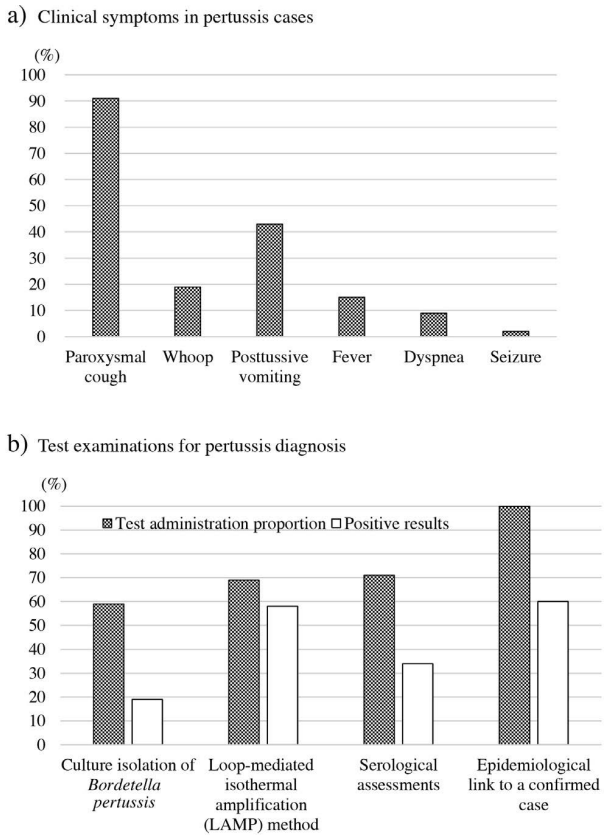

Fig. 1. *Clinical findings in pertussis cases:* (a) clinical symptoms in pertussis cases. (b) Test examinations for pertussis diagnosis.

2 friend controls were subsequently found to be ineligible because they had a history of pertussis. A further 8 cases and 4 controls had incomplete data for the variables and were thus excluded. Eventually, 55 cases and 90 controls (69 friend controls and 21 hospital controls) comprised the subjects for the analysis. Of these, 33 cases and 68 controls (56 friend controls and 12 hospital controls) maintained the matching conditions and were included in the analyses using conditional logistic regression models.

Fig. 1 shows the clinical characteristics of the pertussis cases. About 90% of cases had paroxysmal cough, whereas 19% had an inspiratory whoop and 43% had posttussive vomiting. Among the other symptoms, the proportion having fever was relatively higher (15%) than the others. The median duration from symptom onset to diagnosis was 13.0 days (range: 0–39 days). As for laboratory examinations, culture isolation tests were performed in 60% of cases, and among those, one-third had positive results. LAMP methods were used in 70% of cases, of which 84% had positive results. Among cases who underwent serological assessment (71%), about half had positive results. The number of laboratory-confirmed cases (i.e., positive results for culture isolation, LAMP methods, or serological assessment) was 39 (71%). Based on the information from the self-administered questionnaires, 60% of cases reported contact with a confirmed pertussis case during the last month, which suggested epidemiological linkage to confirmed pertussis cases.

Table 1 shows the background characteristics of the 69 friend controls and 21 hospital controls. A history of steroid treatment seemed to be more common and room space in the house seemed to be larger in hospital controls than in friend controls. Although the small sample size might contribute to the lack of significant differences, further analyses were conducted in all 55 cases and 90 controls, including both friend controls and hospital controls.

The comparison of background characteristics between the 55 cases and 90 controls is shown in Table 2. Among the cases, 12 (22%) were adolescents (i.e., age 11–19 years) and 8 (15%) were adults (i.e., age $\geq$ 20 years). Regarding a history of DTaP vaccination, cases were less likely to have received DTaP vaccine than controls. In addition, cases had more underlying illnesses, more history of steroid treatment, smaller room space in the house, and more contact with a person with a lasting cough.

After adjustment for potential confounders, the OR of DTaP vaccination for development of pertussis was significantly lower in the analysis using unconditional logistic regression models (OR = 0.20, 95%CI, 0.04–0.97) (Table 3). Vaccine effectiveness was calculated to be 80% (3–96%). When considering the effect by the number of DTaP vaccinations, lower ORs were also observed not only in those with complete vaccination (4 doses), but also in those with incomplete vaccination (1–3 doses), with marginal significance. Vaccine effectiveness in those with incomplete vaccination (1–3 doses) was calculated to be 85% (−24 to 98%), and the effectiveness of complete vaccination (4 doses) was 78% (−5 to 96%). In the conditional logistic regression model (33 cases and 68 controls), the magnitudes of the ORs of vaccination were similar to those in the unconditional model, although the limited number of subjects brought about wider confidence intervals (OR of DTaP vaccination = 0.15, 95%CI, 0.01–1.80). On the other hand, a history of steroid treatment and recent contact with a person with a lasting cough showed significantly increased ORs for development of pertussis, using both the unconditional model and the conditional model. In addition, larger room space in the house showed a lower OR for pertussis.

To confirm the association between DTaP vaccination and pertussis, several sensitivity analyses were conducted using unconditional logistic regression models (Table 4). When analyzed subjects were limited to those whose vaccination status could be confirmed by their immunization records, the results were almost unchanged, since 96% of the subjects had their immunization records. In addition, when the analyzed subjects were limited to those aged less than 18 years, since subjects who enrolled from Saga University might have had a different situation on recruitment, similar ORs of DTaP vaccination were observed. When cases were limited to the laboratory confirmed cases, the ORs were almost unchanged, but the confidence intervals were wider. Even when excluding hospital controls from the analysis and comparing 55 cases with 69 friend controls, decreasing ORs were observed.

Table 5 shows the association between pertussis and 4 doses of DTaP vaccination, according to the time since the fourth dose. Unexpectedly, a decreasing OR of DTaP vaccination was observed even among subjects with a longer time since the fourth dose. ORs of 4-dose vaccinees who received the fourth dose within less than 5.8 years, 5.8–9.1 years, and 9.2 years or more were 0.24 (0.05–1.23), 0.14 (0.02–0.87), and 0.11 (0.01–1.02), respectively, all of which were marginally significant.

4. Discussion

In the present case-control study, DTaP vaccine showed effectiveness for preventing the development of pertussis. Although the limited number of study subjects and high vaccination rate in the study subjects made it difficult to detect significant vaccine effectiveness, the present results seemed to support the usefulness of DTaP vaccine in the routine immunization programs.

To date, there have been several studies on pertussis vaccine effectiveness from Japan [14–16]. One study, which was conducted in household contacts when the present immunization programs were introduced (1981–1983), indicated that DTaP vaccine had 79%

Table 1
Comparison of background characteristics between friend-controls and hospital-controls.

Variable		Friend-controls ($n=69$)	Hospital-controls ($n=21$)	P value[b]
		n (%)[a]	n (%)[a]	
Age (years)	Median (range)	10.3 (0.5–25.1)	8.7 (0.3–12.8)	0.142
Sex	Male	23 (33)	7 (33)	1.000
Number of DTaP vaccinations	0	3 (4)	0 (0)	0.486
	1–3	2 (3)	4 (19)	
	4	64 (93)	17 (81)	
Underlying illnesses	Present	15 (22)	6 (29)	0.561
History of steroid treatment	Present	3 (4)	2 (10)	0.331
Total room space in the house (m^2)	Median (range)	102.0 (25–839)	143.0 (25–285)	0.082
Number of family members	Median (range)	4.0 (1–7)	4.0 (3–7)	0.610
Room space per person (m^2)	Median (range)	25.4 (6.75–280)	28.6 (4.17–57)	0.215
Recent contact with a person with a lasting cough	Present	8 (12)	2 (10)	1.000

Abbreviations: DTaP, acellular pertussis vaccine.
[a] Data expressed as n (%) unless otherwise indicated.
[b] The chi-square test, Fisher's exact test, or the Wilcoxon rank sum test was used as appropriate.

Table 2
Comparison of background characteristics between cases and controls.

Variable		Cases ($n=55$)	Controls ($n=90$)	P value[b]
		n (%)[a]	n (%)[a]	
Age (years)	Median (range)	9.6 (0.5–27.5)	9.7 (0.3–25.1)	0.912
Sex	Male	22 (40)	30 (33)	0.417
Number of DTaP vaccinations	0	7 (13)	3 (3)	0.061
	1–3	3 (5)	6 (7)	
	4	45 (82)	81 (90)	
Underlying illnesses	Present	21 (38)	21 (23)	0.056
History of steroid treatment	Present	10 (18)	5 (6)	0.015
Total room space in the house (m^2)	Median (range)	70.0 (24.75–200)	104.0 (25–839)	0.024
Number of family members	Median (range)	4.0 (1–7)	4.0 (1–7)	0.613
Room space per person (m^2)	Median (range)	21.7 (8.0–140)	25.9 (4.17–280)	0.039
Recent contact with a person with a lasting cough	Present	17 (31)	10 (11)	0.003

Abbreviations: DTaP, acellular pertussis vaccine.
[a] Data expressed as n (%) unless otherwise indicated.
[b] The chi-square test, Fisher's exact test, or the Wilcoxon rank sum test was used as appropriate.

Table 3
Adjusted ORs of DTaP vaccination and selected variables for pertussis: unconditional and conditional logistic regression models.

Variable		Unconditional model		Conditional model	
		n (%) or median; cases/controls	OR (95%CI) P value	n (%) or median; cases/controls	OR (95%CI) P value
DTaP vaccination	None	7 (13)/3 (3)	1.00 (ref.)	4 (12)/3 (4)	1.00 (ref.)
	Received	48 (87)/87 (97)	0.20 (0.04–0.97) 0.045	29 (88)/65 (96)	0.15 (0.01–1.80) 0.133
Number of vaccinations	1–3	3 (5)/6 (7)	0.15 (0.02–1.24) 0.078	1 (3)/5 (7)	0.12 (0.01–1.91) 0.133
	4	45 (82)/81 (90)	0.22 (0.04–1.05) 0.057 (Trend $P=0.098$)	28 (85)/60 (88)	0.20 (0.01–4.73) 0.319 (Trend $P=0.249$)
History of steroid treatment	Present	10 (18)/5 (6)	3.98 (1.17–13.6) 0.027	6 (18)/4 (6)	8.23 (1.25–54.3) 0.029
Total room space in the house (m^2)	1 m^2 Increased	70.0/104.0	0.99 (0.98–0.99) 0.036	74.0/108.5	0.98 (0.96–0.99) 0.019
Number of family members	1 Person increased	4.0/4.0	1.12 (0.81–1.55) 0.486	4.0/4.0	1.85 (0.93–3.68) 0.080
Recent contact with a person with a lasting cough	Present	17 (31)/10 (11)	4.62 (1.73–12.4) 0.002	10 (30)/7 (10)	4.44 (1.10–18.0) 0.037

Abbreviations: CI, confidence interval; DTaP, acellular pertussis vaccine; OR, odds ratio.

Table 4
Adjusted odds ratios of DTaP vaccination for pertussis: several sensitivity analyses using unconditional logistic regression models[a].

Analyzed subjects	≥1 Dose of DTaP vaccination (ref. none)	4 Doses of DTaP vaccination (ref. none)
	OR (95%CI) P value	OR (95%CI) P value
All subjects (55 cases/90 controls)	0.20 (0.04–0.97) 0.045	0.22 (0.04–1.05) 0.057
Limited to subjects whose vaccination status could be confirmed by immunization records (52 cases/88 controls)	0.21 (0.04–0.99) 0.049	0.22 (0.05–1.08) 0.063
Limited to subjects aged less than 18 (43 cases/73 controls)	0.22 (0.04–1.18) 0.077	0.22 (0.04–1.25) 0.088
Laboratory confirmed cases vs. all controls (39 cases/90 controls)	0.25 (0.05–1.39) 0.114	0.28 (0.05–1.62) 0.156
All cases vs. friend controls (55 cases/69 controls)	0.30 (0.06–1.42) 0.130	0.29 (0.06–1.38) 0.120

Abbreviations: CI, confidence interval; DTaP, acellular pertussis vaccine; OR, odds ratio.
[a] Adjusted for history of steroid treatment, room space in the house, number of family members, recent contact with a person with a lasting cough, and matching variables (age and sex).

Table 5
Adjusted xORs of 4-dose vaccines for pertussis, according to time since the fourth dose.

Variable	Cases (n = 51)[a]	Controls (n = 84)	Unconditional model[b]
	n (%)	n (%)	OR (95%CI) P value
Number of vaccinations, Time since the fourth dose for 4-dose vaccinees			
0 Doses	7 (14)	3 (4)	1.00 (Ref.)
4 Doses, <7.7 years	22 (43)	41 (49)	0.22 (0.04–1.07) 0.060
4 Doses, 7.7–24.2 years	22 (43)	40 (48)	0.18 (0.03–1.13) 0.067 (Trend P = 0.124)
0 Doses	7 (14)	3 (4)	1.00 (Ref.)
4 Doses, <5.8 years	17 (33)	28 (33)	0.24 (0.05–1.23) 0.087
4 Doses, 5.8–9.1 years	12 (24)	27 (32)	0.14 (0.02–0.87) 0.035
4 Doses, 9.2–24.2 years	15 (29)	26 (31)	0.11 (0.01–1.02) 0.052 (Trend P = 0.057)

Abbreviations: CI, confidence interval; DTaP, acellular pertussis vaccine; OR, odds ratio.
[a] Since one case did not provide the time of the fourth dose vaccination, the case was not included in the analysis.
[b] Adjusted for history of steroid treatment, room space in the house, number of family members, recent contact with a person with a lasting cough, and matching variables (age and sex).

effectiveness for decreasing the secondary attack rates in children aged 0 to 6 years [15]. Another population-based case control study, which was conducted during a non-epidemic period (1999–2001), showed that the effectiveness of 3 or 4 vaccinations for physician-diagnosed pertussis was 96% (95%CI: 54–99%) among children aged less than 6 years [16]. In the other retrospective cohort study among university students, which was conducted just after the pertussis outbreak ended (2010), the reported vaccine effectiveness was 52% for probable pertussis [14]. Taken together, the observed effectiveness might be higher in a study during a non-epidemic period than during an outbreak.

In addition, effectiveness might vary according to the age distribution in the study subjects. Previous studies reported the possibility that DTaP vaccine effectiveness was waning by time since the final dose [9–13]. In the present study, however, there was no waning in effectiveness by time since the final dose, and effectiveness was observed even 9 years or more after the final dose, as shown in Table 4. Although the reason for the discrepancy across studies was not clear, the following explanations could be considered: (1) lower statistical power to detect waning effectiveness in the present study; and (2) the present study's results might be affected by the previous booster effects from undiagnosed natural infection in the community. Particularly with respect to the latter explanation, Okada et al. reported that 58% of the unvaccinated population had PT-IgG antibody of 10 EU/mL or more, and 79% had pertussis filamentous hemagglutinin antibody of 10 EU/mL or more, which suggested the presence of undiagnosed natural infection [17]. Furthermore, a pertussis epidemic had sporadically occurred during the late 2000s in Japan. Thus, the present results may have been affected by the previous booster effects from undiagnosed natural infection. In fact, subjects with incomplete vaccination (1–3 doses) also had 85% effectiveness for preventing pertussis in the present study. When we consider that the effectiveness of incomplete vaccination might be explained by the previous booster effects from undiagnosed natural infection, this seems reasonable.

As for the other associated factors, the present study suggested that subjects with a history of steroid treatment had a higher risk for pertussis (Table 3). To the best of our knowledge, no study has reported the association between history of steroid treatment and pertussis. However, some studies showed a higher risk for pertussis in patients with asthma [18,19], who often receive steroid treatment. In addition, several studies reported that steroid treatment was a risk factor for respiratory infections such as pneumonia [20] and influenza [21]. Taken together, it is therefore plausible that a history of steroid treatment also increased the individual risk for infection with other respiratory pathogens such as pertussis.

In the present study, living in a smaller room space and having recent contact with a person with a lasting cough were also related to pertussis, independent of vaccination status or history of steroid treatment. Although the present study included friend controls, the proportion of "having recent contact with a person with a lasting cough" was only 12% in friend controls, suggesting that contact with present study cases (i.e., physician-diagnosed pertussis) was not common among friend controls. This might be partly explained by the fact that most of the present study cases were absent from school after symptom onset. In the light of previous studies, pertussis outbreaks often occurred in crowded situations such as in schools [14,22], families [15], or soldiers [23]. Furthermore, some studies reported that subjects who had contact with a person with a pertussis-like cough had a higher risk for pertussis infection [23–25]. Thus, the present results agreed with the previous findings. These results suggest that increased susceptibility to pertussis in a crowded situation or increased opportunities on contact with possible pertussis patients would be related to pertussis infection.

The present case-control study had a unique design that included friend controls. However, some might think that hospital controls would have been preferable, because cases were selected from hospital patients. To examine vaccine effectiveness, however, it is very important to consider the likelihood of exposure to the pathogen, which is a necessary cause for infectious disease. Particularly in the case of pertussis, disease occurrence is sporadic, which is different from common infectious diseases such as influenza. For pertussis, traditional hospital controls or general population controls might not have had contact with the pathogen. Vaccine effectiveness should be estimated under the assumption that controls have a similar potential for exposure to the pathogen as cases. It is therefore considered that friend controls would be among the most suitable controls in terms of sharing a similar potential for exposure to the pathogen as cases. However, friend controls might have similar background characteristics to those of cases, such as socioeconomic status, religious beliefs, and even probably vaccination status, which might contribute to the underestimation of VE. We considered that underestimation of VE, if any, would not affect the plausibility of the study results, and therefore decided to use friend controls.

When interpreting the present results, however, the following limitations should be considered. First, insufficient statistical power due to the small sample size is obviously important. This limitation made it difficult to detect significant vaccine effectiveness. However, pertussis cases in Japan have decreased substantially not only at the collaborating hospitals in the present study, but also in all parts of Japan during the study period [5]. Thus, it was thought

that obtaining more subjects would be impossible. Second, there may be concern that changing the protocol with respect to control selection during the study period might have had some effect on the present results. Of particular concern was that hospital controls might not have had contact with the pathogen, but the proportion of "recent contact with a person with a lasting cough" was found to be similar between friend controls and hospital controls. On the other hand, hospital controls were younger and had more underlying illnesses with steroid treatment than friend controls, which might have affected to the results. To consider the effect of including hospital controls during the study period, however, when analyses were limited to friend controls and cases, the ORs of DTaP vaccination were almost unchanged, and 95% CIs became wider, suggesting that including hospital controls increased statistical power (Table 4). Third, the present results were obtained after adjustment for potential confounders (i.e., history of steroid treatment, total room space in the house, number of family members, recent contact with a person with a lasting cough), but the effects of other confounding factors, such as socioeconomic status, birth order, and school attendance, could not be considered.

In conclusion, the present results support that DTaP vaccination in the routine immunization program in Japan had a preventive effect against infection with pertussis. Effectiveness was observed even 9 or more years after the fourth dose. However, observed effectiveness in the present study might have included not only genuine vaccine effectiveness, but also the effects of previous booster effects from undiagnosed natural infection in the community. To consider whether adding a booster dose of vaccination for adolescents is needed, results from descriptive epidemiological studies of pertussis outbreaks, seroepidemiologic studies, and further large-scale studies about vaccine effectiveness, if possible, are needed.

Acknowledgments

This study was supported by a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labor and Welfare, Japan (H23-SHINKO-IPPAN-017).

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