学 会 等 発 表 実 績

委託業務題目「百日咳の発生実態の解明及び新たな百日咳ワクチンの開発に資する研究」

１．学会等における口頭・ポスター発表
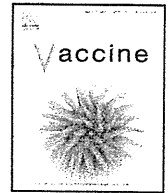
発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
百日咳の再興への対策を考える（口頭）	岡田賢司	第46回日本小児感染症学会	2014年10月	国内
百日咳ワクチンの有効性に関する症例対照研究（口頭）	岡田賢司	第18回日本ワクチン学会	2014年12月	国内
成人用百日咳ワクチン等、日本で接種がされていないワクチンの今後（口頭）	岡田賢司	第201回ICD講習会	2015年2月	国内
百日咳小児入院例の後方視的調査　口頭発表	菅　秀	第１６３回三重県小児科医会例会	2015年1月	国内
国内複数の百日咳集団発生下における百日咳ワクチン有効性に関する分析と考察	砂川富正神谷元　他	第18回日本ワクチン学会	2014年11月	国内
Cotton rat（Sigmodon hispidus)を用いたRSV自然感染時に誘導される免疫応答の検討（口頭）	山路祥晃、中山哲夫	第55回日本臨床ウイルス学会	2014年6月	国内
ムンプスウイルスF, HNタンパク発現組換え麻疹ワクチンの検討（口頭）	伊藤尚志、中山哲夫	第55回日本臨床ウイルス学会	2014年6月	国内
ワクチンの効果と免疫―ワクチンで何故免疫ができるのか（ICD講習会）	中山哲夫	第46回日本小児感染症学会	2014年10月	国内
Cotton ratを用いたRSV自然感染時に誘導される免疫応答の検討（口頭）	山路祥晃、中山哲夫	第62回日本ウイルス学会学術集会	2014年11月	国内
ヒトパピローマウイルス(HPV)ワクチン接種後の自然免疫応答―マウスモデル―	中山哲夫、柏木保代	第18回日本ワクチン学会	2014年12月	国内
本邦における小児期から青年期にかけての百日咳抗体価の分布について	康井洋介、中山哲夫、庵原俊昭	第18回日本ワクチン学会	2014年12月	国内
Bordetella pertussis fimbriae are regulated by BvgAS system and Pfim structure	大塚菜緒、柴山恵吾、蒲地一成	第88回日本細菌学会総会	2015年3月	国内
百日咳類縁菌Bordetella holmesiiの自己凝集抑制因子BipAに関する研究	平松征洋，大塚菜緒，柴山恵吾，　鈴木英里，渡邉峰雄，蒲地一成	第88回日本細菌学会総会	2015年3月	国内

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外 の別
Effectiveness of acellular pertussis vaccine in a routine immunization program: A multicenter, case-control study in Japan.	Ohfuji S, Okada K, Nakano T, Ito H, Hara M, Kuroki H, Hirota Y	Vaccine	2015	国外
Pertussis outbreak in university students and evaluation of acellular pertussis vaccine effectiveness in Japan.	Hara M, Fukuoka M, Tashiro K, Ozaki I, Ohfuji S, Okada K, Nakano T, Fukushima W, Hirota Y	BMC Infectious Diseases	2015	国外
成人百日咳の特徴と予後－臨床的診断例における検査による診断確定群と非確定群の比較－	野上裕子、岡田賢司、本荘哲、蒲池一成、岩永知秋	日本呼吸器学会誌	2014	国内
百日咳ワクチン	岡田賢司	化学療法の領域	2014	国内
主なワクチンの現状と問題点：百日咳ワクチン	岡田賢司	感染症内科	2014	国内
今後の成人ワクチン－Tdapワクチン	岡田賢司	成人の予防接種パーフェクト・ガイド	2014	国内
成人の百日咳	岡田賢司	呼吸器感染症2015 日本胸部臨床 増刊	2014	国内
百日咳	岡田賢司	感染症診療update 日本医師会雑誌	2014	国内
百日咳とパラ百日咳	岡田賢司	小児疾患診療のための病態生理Ⅰ－改訂第5版－	2014	国内
乳幼児期の予防接種の重要性	庵原俊昭	化学療法の領域	2014	国内
Production of inflammatory cytokines in response to diphtheria-pertussis-tetanus (DPT), haemophilus influenzae type b (Hib), and 7-valent pneumococcal (PCV7) vaccines.	Kashiwagi Y, Miyata A, Kumagai T, Maehara K, Suzuki E, Nagai T, Ozaki T, Nishimura N, Okada K, Kawashima H, Nakayama T.	Human vaccine & Immunother	2014	国外
Inflammatory responses following intramuscular and subcutaneous immunization with aluminum-adjuvanted or non-adjuvanted vaccines.	Kashiwagi Y, Maeda M, Kawashima H, Nakayama T.	Vaccine	2014	国外

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Recombinant measles viruses expressing respiratory syncytial virus proteins induced virus-specific CTL responses in cotton rats.	Yamaji Y, <u>Nakayama T</u>	Vaccine	2014	国外
Virus specific cell-mediated immunity may play a role in controlling reactivated human herpes virus 6B in patients under measles induced immunosuppression.	Kumagai T, Yoshikawa T, Shiraki K, Yoshida M, <u>Nakayama T</u>, Ihira M, Asano Y.	J Med Virol	2014	国外
Humoral immune response to influenza A(H1N1) pdm2009 in patients with natural infection and in vaccine recipients in the 2009 pandemic.	Kumagai T, <u>Nakayama T</u>, Okuno Y, Kase T, Nishimura N, Ozaki T, Miyata A, Suzuki E, Okafuji T, Okafuji T, Ochiai H, Nagata N, Tsutsumi H, Okamatsu M, Sakoda Y, Kida H, Ihara T	Viral Immunol	2014	国外
Genomic diversity of mumps virus and global distribution of the 12 genotypes.	Jin L, Örvell C, Myers R, Rota PA, <u>Nakayama T</u>, Forcic D, Hiebert J, Brown KE	Rev Med Virol	2014	国外
Global population structure and evolution of Bordetella pertussis and their relationship with vaccination.	Bart MJ, Harris SR, Advani A, Arakawa Y, Bottero D, Bouchez V, Cassiday PK, Chiang CS, Dalby T, Fry NK, Gaillard ME, van Gent M, Guiso N, Hallander HO, Harvill ET, He Q, van der Heide HG, Heuvelman K, Hozbor DF, <u>Kamachi K</u>, Karataev GI, Lan R, Lutyňska A, Maharjan RP, Mertsola J, Miyamura T, Octavia S, Preston A, Quail MA, Sintchenko V, Stefanelli P, Tondella ML, Tsang RS, Xu Y, Yao SM, Zhang S, Parkhill J, Mooi FR.	mBio	2014	国外
微生物ABC 百日咳	蒲地一成	up-to-date 子どもの感染症	2014	国内

Ⅳ．研究成果の刊行物・別刷

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

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ARTICLE INFO

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.

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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

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 $(1 - OR) \times 100$ (%).

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,
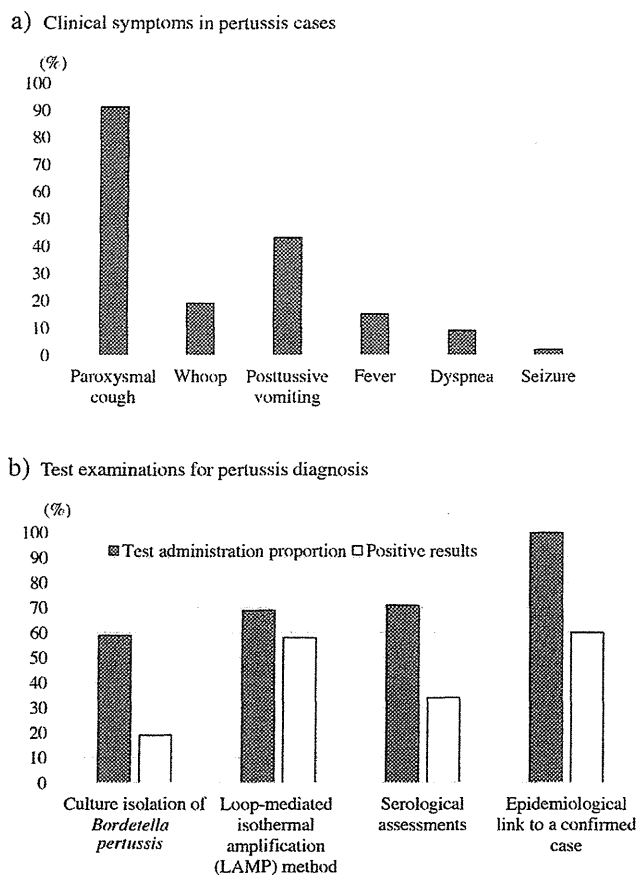
a) Clinical symptoms in pertussis cases

b) Test examinations for pertussis diagnosis

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 ≥ 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 (m²)	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 (m²)	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 (m²)	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 (m²)	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 (m²)	1 m² 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

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RESEARCH ARTICLE   **Open Access**

Pertussis outbreak in university students and evaluation of acellular pertussis vaccine effectiveness in Japan

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Abstract

Background: Recent studies worldwide have reported increasing numbers of adults diagnosed with *Bordetella pertussis* despite receiving childhood vaccinations. This study describes a pertussis outbreak at a university medical faculty campus and examines the effectiveness of diphtheria, tetanus, and pertussis (DTaP) vaccination completed during infancy in Japan.

Methods: After the outbreak, self-administered questionnaires and serum samples were collected from students on campus to determine the incidence of pertussis and underlying diseases. Pertussis was diagnosed on the basis of clinical criteria and serum anti-pertussis toxin antibody levels. Using data collected from 248 first and second grade students who had submitted copies of their vaccination records, we evaluated the effectiveness of DTaP vaccination in infancy against adult pertussis.

Results: Questionnaire responses were obtained from 636 students (of 671 registered students; 95% response rate). Of 245 students who reported a continuous cough during the outbreak period, 84 (attack rate: 13.2%) were considered "probable" pertussis cases that met clinical criteria. The outbreak occurred mainly in first and second grade students in the Faculty of Medicine. Of 248 students who provided vaccination records, 225 had received 4 DTaP doses (coverage: 90.7%); the relative risk of the complete vaccination series compared to those with fewer than 4 doses or no doses for probable cases was 0.48 (95% confidence interval: 0.24-0.97).

Conclusions: Waning protection was suspected due to over time. Booster vaccination for teenagers and development of highly efficacious pertussis vaccines are needed.

Keywords: Pertussis, Outbreak, Vaccine effectiveness

Background

Although global vaccination coverage for diphtheria, tetanus, and pertussis (DTaP) remains high, recent reports of increasing pertussis cases among adolescents and adults are of concern because this population can be a source of infant infection [1]. Suggested causes for this increase include increased clinical awareness of pertussis, improved diagnostics using polymerase chain reaction (PCR), identification of mutations in the strain of *Bordetella pertussis* associated with epidemics, and decreasing antibody titers after vaccination [2-6]. Western countries have initiated tetanus, reduced-antigen-content diphtheria, and acellular pertussis (Tdap) vaccine booster programs for adolescents, adults, and other high-risk groups [1,7,8].

The number of adult pertussis cases has been increasing in Japan, with outbreaks in high schools and universities as well as workplaces successively reported in 2002 [9-13]. In response to these reports, studies have examined outbreak characteristics, genetic characteristics of *B. pertussis*, and alternative diagnostic methods. However, to our knowledge, no study has evaluated the effectiveness of the current DTaP vaccine. Japan has a different schedule to western countries for baby

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immunizations, including DTaP vaccine. Until 2012, pertussis vaccination is a triple DTaP vaccine (after 2012, DTaP-IPV), beginning at 3 months of age. To establish initial immunity, 3 times for 3 to 8 weeks apart are needed. A booster dose is given at 6 months to 12 months after the initial immunity. Thus, DTaP vaccine is usually completed by 18 months of age. The recommended number of doses is smaller than that in Western countries. In addition, Tdap booster vaccines are not administered after early adolescence in Japan. To determine the necessity for booster vaccination in early adolescence, it is important to evaluate the effectiveness of the current vaccine program in preventing pertussis after early adolescence. However, there have been a limited number of epidemiological evaluations on vaccine program effectiveness against pertussis in Japan, and these studies have focused primarily on children [14,15]. To our knowledge, no studies have examined the effectiveness of the vaccine against pertussis after early adolescence.

In April 2010, a pertussis outbreak was confirmed among students at the medical faculty campus of Saga University. After the outbreak ended, a retrospective cohort study was performed. This study describes the outbreak and examines the association between infant DTaP vaccination and incidence of pertussis.

Methods

Study populations

More than 20 students visited the health administration center at the Saga University Faculty of Medicine in April 2010 complaining of coughs that had lasted at least 2 weeks. Three of these students had throat swabs positive for *B. pertussis* by loop-mediated isothermal amplification [16]. Thus, this outbreak of cough symptoms was considered to be due to pertussis. The health administration center discouraged club activities, meetings, and ball game tournaments; promoted use of facemasks; terminated practical training for students with coughs; actively encouraged medical examinations at medical institutions; and notified students and faculty members of the outbreak by e-mail. By early July, no new cough cases were reported to the health administration center.

Just after the end of the outbreak in early July, a total of 671 students (411 and 260 from the departments of medicine and nursing, respectively) from the first through fourth grades on the faculty of medicine campus were provided an oral explanation of the purpose, content, and conditions of cooperation of the study, and asked to provide written informed consent forms with agreement to participate. Among them, 636 students (collection rate: 95%) completed a questionnaire about relevant demographic variables and clinical symptoms of cough, including duration, presence of coughing

paroxysms, whooping and vomiting after cough, medical institution visits, past history of disease, and DTaP vaccination status. They were also asked to provide serum specimens. Serum samples were obtained from 516 (77.1%) of these students; anti-pertussis toxin (PT) antibody levels were tested by enzyme immunoassay at an outside laboratory (SRL, Inc., Tokyo).

Of these, 248 first and second grade students had submitted copies of their vaccination records, including infant DTaP vaccine administration histories, from their maternity record books to the health administration center upon entering the school. In Japan, vaccination histories are recorded in maternity record books maintained by individuals.

This study design was approved by the ethical review board of the Saga Medical School Faculty of Medicine, Saga University (approval number 22–25, 2010).

Case definitions

Cases were categorized on the basis of 2 clinical definitions of pertussis, using clinical criteria established by the Centers for Disease Control and Prevention and the Council of State and Territorial Epidemiologists 2014 case definitions [17]. "Probable cases" had cough illness lasting ≥2 weeks with at least 1 of the following signs or symptoms: paroxysms of coughing, or inspiratory "whoop", or posttussive vomiting. "Suspected cases" met at least 1 of the 4 clinical symptoms or signs. In addition to these clinical definitions, the serological diagnosis of pertussis required serum anti-PT antibody levels after the outbreak to be higher than 100 EU/mL.

Vaccine effectiveness

The 248 students whose vaccination records could be confirmed by their maternity record books were classified into 2 groups: those who had completed the full 4-dose vaccination as recommended by the Japanese government, those who had received less than 4 vaccine doses or no doses. The attack rate (AR) of pertussis and the relative risk (RR) after 4 doses compared with less than 4 doses or no doses were calculated. The effectiveness of the vaccine was calculated using the equation:

$$(1 - [AR_{vaccinated}/AR_{unvaccinated}]) \times 100\ (\%)$$
$$= (1 - RR) \times 100\ (\%)$$

Statistical analysis

We used SAS 9.3 for Windows (SAS Institute, Cary, NC, USA) for statistical comparisons between each variable using chi-square and Fisher's exact tests. RRs after 4 doses compared with less than 4 doses or no doses and corresponding 95% confidence intervals (CIs) were obtained using the PROC FREQ procedure in the software

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package. RRs and their 95% CIs adjusted by faculty were obtained using the Mantel–Haenszel method.

Results

Description of outbreak

The population characteristics and cough statuses of 636 subjects who participated in the survey just after the outbreak were examined according to clinical diagnosis (Table 1). Among 245 students (38.5%) who presented with a cough during the outbreak period, the most common cough duration was 2 weeks or more, followed by duration of 1–2 weeks. The most common characteristic was paroxysmal cough, followed by posttussive vomiting. On the basis of the reported clinical symptoms, 84 and

161 students were classified into the probable case (mean age 20.4, range: 18–34 years) and suspected case (mean age 20.0, range: 18–30 years) groups, respectively. The number of cases was greatest in first grade students in the Department of Medicine. Of 245 students with continuous cough, 121 visited a medical institution; of these, 56 were diagnosed with pertussis by physicians. Patients with probable cases were more likely to seek treatment at a medical institution and be diagnosed with pertussis than those with suspected cases. Of the students diagnosed with pertussis, 21 had visited the infection control department at the university hospital. Pertussis DNA was detected in throat swabs obtained from 3 of these students by loop-mediated isothermal

Table 1 Characteristics of 636 survey subjects according to clinical diagnosis

Characteristics		Total (n = 636)		No symptoms (n = 391)		Suspected cases (n = 161)		Probable cases (n = 84)		P-value*
		n	(%)	n	(%)	n	(%)	n	(%)	
Department	Medicine	389	61.2	224	57.3	107	66.5	58	69.0	0.037
	Nursing	247	38.8	167	42.7	54	33.5	26	31.0	
Grade	1	164	25.8	85	21.7	54	33.5	25	29.8	0.079
	2	158	24.8	96	24.6	59	36.6	23	27.4	
	3	156	24.5	105	26.9	35	21.7	16	19.0	
	4	158	24.8	105	26.9	33	20.5	20	23.8	
Sex	Male	243	38.2	152	38.9	56	34.8	35	41.7	0.517
	Female	392	61.6	238	60.9	105	65.2	49	58.3	
	Unknown	1	0.2	1	0.3	0	0.0	0	0.0	
Continuous cough	Yes	245	38.5	0		161	100.0	84	100.0	
	Less than 1 week	38	6.0	-		38	23.6	0	0.0	<0.001
	1 week or more and less than 2 weeks	102	16.0	-		102	63.4	0	0.0	
	2 weeks or more	105	16.5	-		21	13.0	84	100.0	
Characters of continuous cough (multiple answers)	Proxysms of coughing	233	36.6	-		152	94.4	81	96.4	0.48
	Inspiratory whooping	22	3.5	-		12	7.5	10	11.9	0.247
	Posttussive vomiting	70	11.0	-		31	19.3	39	46.4	<0.0001
Medical institution	Visited	121	19.0	-		67	41.6	54	64.3	0.0008
	Diagnosed with pertussis	56	8.8	-		30	18.6	26	31.0	0.0323
Self-report DTaP vaccination status										
	No	7	1.1	5	1.3	2	1.2	0	0.0	<0.001
	1 shot	19	3.0	9	2.3	4	2.5	6	7.1	
	2 doses	19	3.0	8	2.0	3	1.9	8	9.5	
	3 doses	10	1.6	5	1.3	5	3.1	0	0.0	
	4 doses	47	7.4	20	5.1	15	9.3	12	14.3	
	Uncertain	534	84.0	344	88.0	132	82.0	58	69.0	

Clinical criteria: (1) cough illness lasting ≥ 2 weeks; (2) paroxysms of coughing; (3) inspiratory "whoop"; (4) post-tussive vomiting.
Suspected case: patient with at least 1 clinical criterion.
Probable case: patient with cough illness lasting ≥ 2 weeks with at least 1 other clinical criterion.
*Chi-square test.

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amplification, leading to a definitive laboratory diagnosis of pertussis. Most students (534 of 636) could not remember their vaccination status.

The epidemic curve based on the date of cough onset is shown in Figure 1. The number of individuals with cough symptoms increased rapidly from early April and decreased after peaking from April 19 to 25. No prophylaxis antibiotics were administered during this time.

Figure 2 shows the distribution of anti-PT antibody titers in 516 students from whom serum was collected after the outbreak, according to grade. Among them 24 subjects' anti-PT antibody levels were greater than 100 (EU/mL), and the percentage of them was highest in first grade students.

Evaluation of vaccine effectiveness

Among entire population, 248 first and second grade students whose infant vaccination records could be confirmed by maternity record books were examined according to clinical diagnosis (Table 2). Probable cases were more common in the Department of Medicine. No significant associations were found between grade, sex, and underlying disease and incidence of pertussis. The percentage of students diagnosed with pertussis who had also received the full recommended DTaP vaccination course in infancy was notably low (12.5%). The AR of probable cases per vaccination status was 33% in unvaccinated students and 13.8% in students who had received all 4 doses, indicating that ARs were lowest in students who had received the recommended number of vaccine doses.

There were no statistically significant differences in the department, grade, sex, or underlying diseases compared to the completeness of the infant vaccination series. A significantly higher proportion of individuals who did not receive 4 doses of DTaP reported coughing

paroxysms. While the clinical characteristics of cough varied, the proportion of students with anti-PT antibody levels greater than 100 EU/mL after the outbreak were similar between those who did and those who did not receive a full vaccine dose (see Additional file 1: Table S1). We examined the RR of the DTaP vaccine for those who had received the government-recommended number of vaccinations in infancy (Table 3). When outcome was defined as probable cases based on the clinical criteria, the RR for students with 4 doses compared to those with fewer than 4 doses or no doses was 0.48 (95% CI: 0.24–0.97); after adjusting for the impact of department the effectiveness was estimated to be 52% (95% CI: 3–76). Similarly, when outcome was defined as meeting at least 1 of the 4 clinical criteria in both probable and suspected cases, the adjusted RR was 0.70 (95% CI: 0.51–0.98). When outcomes were defined as serological diagnosis of pertussis after the outbreak (anti-PT antibody levels greater than 100 EU/mL) or diagnosed at medical institutions, the RRs were 0.64 (95% CI: 0.16–2.52) and 0.74 (95% CI: 0.21–2.61), respectively; no statistically significant protective effect of complete vaccination were detected using these outcome definitions.

Discussion

The outbreak in this study occurred mainly in first and second grade students on the university campus, with peak incidence in April. Welcoming parties for new pupils or invitations to club activities before and after entrance ceremonies likely contributed to the spread of infection. The outbreak ended without administration of preventive antibiotics. Measures such as self-restraint of club activities, meetings, and ball game tournaments, termination of practical trainings, and active intervention by the health administration center to encourage examination at medical institutions appeared to effectively limit
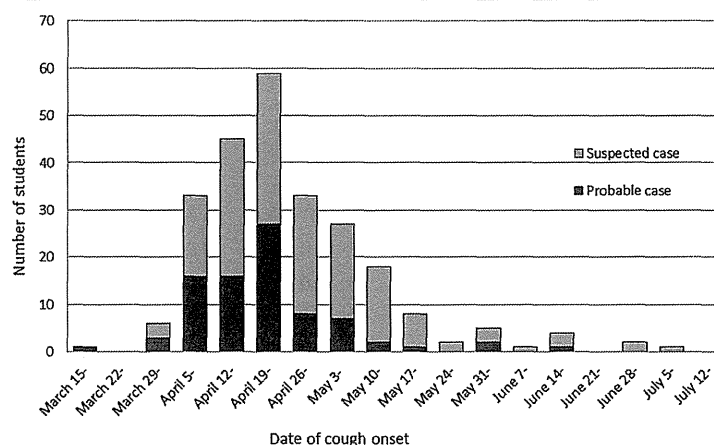

Figure 1 Epidemic curve based on date of cough onset. Dark gray and light gray bars indicate suspected and probable cases, respectively.

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Figure 2 Distribution of serum pertussis toxin antibodies in 516 students after the outbreak, according to grade. Black, gray, black with dots, and gray with dots bars indicate first, second, third, and fourth grades, respectively.
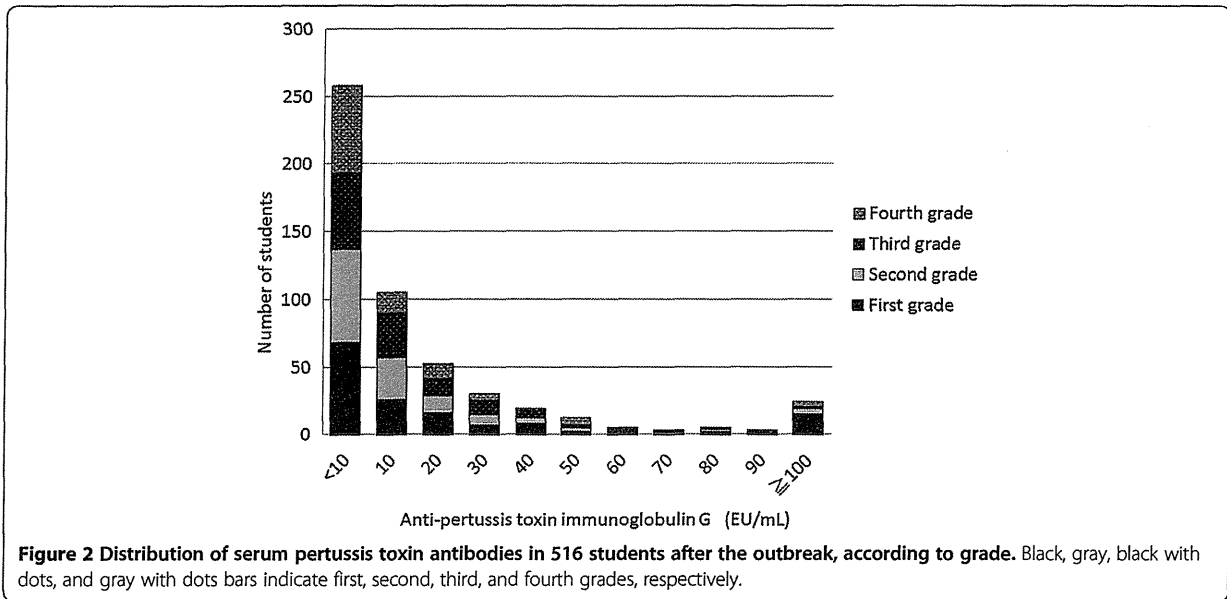
Table 2 Comparison of underlying disease and DTaP vaccination according to clinical diagnosis in 248 students with confirmed vaccination records

Characteristics		Total	No symptom (n = 133)		Suspected case (n = 77)		Probable case (n = 38)		P-value*
		(n = 248)	n	(%)	n	(%)	n	(%)	
Department	Medicine	156	76	57.1	51	66.2	29	76.3	0.0075
	Nursing	92	57	42.9	26	33.8	9	23.7	
Grade	1	133	64	48.1	47	61.0	22	57.9	0.1652
	2	115	69	51.9	30	39.0	16	42.1	
Sex	Male	102	53	39.8	30	39.0	19	50.0	0.4784
	Female	146	80	60.2	47	61.0	19	50.0	
History	Allergic rhinitis	59	35	26.3	18	23.4	6	15.8	0.4032
	Anemia	30	15	11.3	9	11.7	6	15.8	0.7474
	Food Allergy	12	7	5.3	3	3.9	2	5.3	0.8979
	Heart disease	2	2	1.5	0	0.0	0	0.0	0.4182
	Liver disease	1	1	0.8	0	0.0	0	0.0	0.6479
	Renal disease	4	4	3.0	0	0.0	0	0.0	0.1724
	Diabetes	1	1	0.8	0	0.0	0	0.0	0.6479
	None	90	48	36.1	32	41.6	10	26.3	0.2778
Vaccination record for DTaP vaccine									
	No	3	1	0.8	1	1.3	1	2.6	0.0742
	1 shot	4	2	1.5	2	2.6	0	0.0	
	2 doses	2	0	0.0	0	0.0	2	5.3	
	3 doses	14	5	3.8	5	6.5	4	10.5	
	4 doses	225	125	94.0	69	89.6	31	81.6	

DTaP: diphtheria, tetanus, and pertussis.
*Chi-square test or Fisher's exact test.

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Table 3 Relative risks of history of DTaP vaccination for pertussis according to case definition

Definition of pertussis	Number	Case	Attack rate (%)	Relative risk	(95% CI)	Relative risk[a]	(95% CI)
Probable cases							
Less than 4 doses or no doses	23	7	30.4	1		1	
4 doses	225	31	13.8	0.45	(0.23-0.91)	0.48	(0.24-0.97)
Probable + Suspected cases							
Less than 4 doses or no doses	23	15	65.2	1		1	
4 doses	225	100	44.4	0.68	(0.49-0.95)	0.70	(0.51-0.98)
Anti- PT antibody titers after outbreak ≥ 100EU/mL							
Less than 4 doses or no doses	23	2	8.7	1		1	
4 doses	225	13	5.8	0.64	(0.16-2.76)	0.64	(0.16-252)
Diagnosed as pertusis at medical institutions							
Less than 4 doses or no doses	23	2	8.7	1		1	
4 doses	225	17	7.6	0.87	(0.21-3.53)	0.74	(0.21-2.61)

DTaP: diptheria, tetanus, and pertussis; CI: confidence interval; PT: pertussis toxin.
Clinical criteria: (1) cough illness lasting ≥ 2 weeks; (2) paroxysms of coughing; (3) inspiratory "whoop"; (4) post-tussive vomiting.
Probable case: a patient who met cough illness lasting ≥ 2 weeks with at least 1 item in the other clinical criteria.
Suspected case: a patient who met at least 1 item in the above 4 clinical criteria.
[a]Adjusted by department using the Mantel-Haenszel method.

the outbreak. In addition, approximately 1 week of university holidays owing to consecutive holidays in May might also have reduced the spread of infection.

The vaccine effectiveness was 52% for probable cases meeting the clinical criteria for pertussis when students with fewer than 4 or no shots was defined as the reference. It is difficult to directly compare these results with other studies because booster vaccination recommendations vary by country [1,7,8,18], studies use different case definitions [1,18,19], vaccine effectiveness decreases with age-associated decreases in vaccine-induced antibodies [5,20,21], and study subject characteristics may also differ considerably between studies. We report a vaccine effectiveness lower than the 96% effectiveness reported by case–control studies of children in Japan with 3 or more vaccine doses compared to unvaccinated children [15], and about 80% reported by a meta-analysis study of children who received 4 vaccine doses [18]. Considering that the mean age in our study population was 20.4 years, the length of time since the last vaccination may contribute the lower vaccine effectiveness. This observation suggests that replacing the conventional diphtheria and tetanus toxin vaccine administered in adolescence to DTaP might be necessary in Japan. In addition, complete vaccination in infancy is essential, since incomplete vaccination did not show protective effects against pertussis in this study.

In other countries, the DTaP vaccine is administered in early childhood, and a Tdap booster vaccination is administered after early adolescence. Therefore, there are limited reports on the effectiveness of the DTaP vaccine in adolescents and adults. In a case–control study performed during an outbreak at a military school in France, the vaccine effectiveness rates among biologically confirmed cases where 5 and 4 DTaP vaccinations were administered was 32% and 22%, respectively [20]. This study also found that effectiveness decreased as the period from the last vaccination increased. On the other hand, 2 case–control studies in adolescents and adults after Tdap booster vaccination reported an effectiveness around 60%; these studies defined patients diagnosed with pertussis by PCR as cases and patients with pertussis-like symptoms but negative by PCR as controls [22,23]. In our study, the effectiveness of the DTaP vaccine was higher than that in a previous report from a US military school and slightly lower than that of Tdap effectiveness. However, because the vaccination series is completed by 2 years of age in Japan, 16 years or more had passed since the last vaccination. We also defined cases based on clinical criteria. Other reasons for these disparate results may be due to the effects of boosters administered during a pertussis outbreak in Japan in 2008 and 2009 [9-13]. Other reasons may include a higher rate of completed vaccine courses: in our study population, the vaccination coverage, or the percentage of the study population that had received 4 vaccine doses, was 94%. Differences in vaccine components [24,25] and vaccination methods (subcutaneous injection in Japan vs. intramuscular injection in the US) may also have contributed to differences in reported results.

Generally, the more precisely defined the outcome, the higher the diagnosis sensitivity [19], and detected effectiveness. In our study, the vaccine effectiveness against probable cases was higher than against suspected cases.

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However, differences in vaccine effectiveness were not detected by serologically or medically diagnosed cases. In our study, patients with serum anti-PT antibody titers greater than 100 EU/mL at the end of July were considered positive for pertussis, although we could not perform examinations with paired sera to compare levels during the acute phase to the recovery phase of pertussis. Anti-PT antibodies have been reported to decrease particularly rapidly [26], so a patient with pertussis might not show as positive if antibody levels had fallen below this threshold. If many subjects with pertussis were not detected by serological testing, misclassification might occur. Medically diagnosed cases might be confounded by health-related behavior. Not all probable cases visited medical institutions; thus, outcomes were likely biased.

This study had several limitations. First, pertussis was diagnosed only on the basis of clinical criteria. The clinical definition of probable case includes a continuous cough for 14 days or more. In this study, promotion of active interventions and medical examinations at medical institutions occurred during the early phase of the outbreak for the purpose of infection control; as a result, the average cough duration decreased, leading to potential misclassification. Second, we could confirm vaccination records for only half of the study participants. Although misclassification of the vaccination category could be avoided by including only those participants whose maternity record books could confirm vaccination status, the sample size would be quite small. However, since the outbreak of pertussis occurred mainly in first and second grade students in our study, we believe that statistically significant differences in vaccine efficacy could be detected. Third, the past history of pertussis in the study participants is unknown. Since outbreaks of pertussis in high school students have also been recently reported in Japan [12], some students may have been infected with pertussis before entering the university. It is generally believed that a history of pertussis is protective against future pertussis owing to antibodies acquired by natural infection. Inclusion of subjects with a history of pertussis in the group that had not received 4 vaccinations in infancy could lead to underestimated vaccine effectiveness. Finally, hygiene behaviors might confound the association between the vaccination record and onset. For example, if those who did not receive recommended infant vaccinations were also not taught appropriate hygiene behaviors, they might not take prophylactic actions against infection, such as washing hands, wearing facemasks, and avoiding crowds during the pertussis season. However, if these differences exist, the effects are minimal, because vaccine effectiveness was not detected when we examined the association between measles vaccination with pertussis in the subjects of this study (Additional file 2: Table S2).

Conclusions

An outbreak of pertussis was observed in a population in which the majority of individuals had completed the DTaP vaccine course as infants. The AR was higher in students who did not complete the full infant DTaP vaccine course. The vaccine effectiveness was an estimated 52%, lower than that described in previous reports of children, mostly likely because of decreasing antibody levels in the long period of time since their last DTaP dose. These results suggest the necessity for booster vaccination for teenagers and development of highly efficacious pertussis vaccines.

Additional files

Additional file 1: Table S1. Characteristics of 248 students with Confirmed DTaP Vaccination History according to Completeness of Infant Vaccination.

Additional file 2: Table S2. Relative Risks for Pertussis by History of Measles Vaccination According to Case Definition in 248 Students with Confirmed Vaccination Records.

Authors' contributions
MH, KO, TN, SO, and YH designed the study. MH, MF, and IO participated in data collection. MH, KT, KO, TN, SO, WF and YH participated in data analysis and interpretation and wrote the report. All authors reviewed the data and approved the final report.

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成人百日咳の特徴と予後

—臨床的診断例における検査による診断確定群と非確定群の比較—

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成人百日咳の特徴と予後

—臨床的診断例における検査による診断確定群と非確定群の比較—

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要旨：2009年2月から2013年2月までに，咳持続期間と症状から臨床的百日咳の診断基準に合致した症例 33例（男性11例，女性22例，平均年齢42.0±16.5歳）を対象にLAMP法，百日咳毒素抗体検査等を施行 し，百日咳と確定診断できた症例が14例，確定できなかった症例が19例であった．百日咳確定群は咳持続 期間が非確定群に比して有意に長く，高熱がないことが特徴であり，炎症反応上昇を認めなかった．さらに 確定群では吸入ステロイド使用例や感染後に咳喘息や喘息を発症した症例が多くみられた．
キーワード：成人百日咳，気道過敏性，マクロライド，LAMP法
　　　　　　Adult pertussis, Bronchial hyperresponsiveness, Macrolide,
　　　　　　Loop-mediated isothermal amplification method

緒　言

　百日咳は，グラム陰性桿菌である百日咳菌 *Bordetella pertussis* によって引き起こされる急性の気道感染症であ る．百日咳菌は，気道上皮細胞，主として線毛細胞に付 着して百日咳毒素を産生し，その結果激しい咳を生じる とされている．典型的にはカタル期（1〜2週間），痙咳 期（4〜8週間），回復期（1〜2週間）という経過をとる が，痙咳期における連続性の咳嗽（staccato）や，吸気 時の笛声音（whooping）が特徴的である．元来乳幼児の 疾患として知られていたが，最近では成人においても増 加していることが報告[1]され，注目を集めている．成人 の百日咳感染は，症状がワクチン未接種の乳幼児のよう に典型的ではなく，そのため診断に苦慮し，適切な治療 がなされない場合が多くみられる[2]．成人の百日咳は乳 幼児の感染源となっている場合があり，ワクチン未接種 の乳児が百日咳に感染すると無呼吸や肺炎などを合併し 重篤となる危険性が高い．よって成人百日咳を早期診断 し，抗菌薬を早期に投与することは重要であると思われ

る．

　成人百日咳の診断において，咳嗽に関するガイドライ ン第2版では，臨床的診断と検査による確定診断をフ ローチャートに示している[3]．

　今回我々は，臨床的百日咳の診断基準に合致した症例 のなかで，検査により百日咳と確定できた症例（以下確 定群）と，検査で百日咳と確定できなかった症例（以下 非確定群）に分けて，その臨床的特徴と治療，予後につ いて比較検討したので報告する．

対象と方法

　2009年2月から2013年2月までに，咳を主訴に国立 病院機構福岡病院内科を受診し，咳嗽に関するガイドラ イン第2版で臨床的に百日咳と診断された症例，すなわ ち14日間以上続く咳のうち，「発作性の咳き込み」，「吸 気性笛声」，「咳き込み後の嘔吐」のいずれか1つ以上伴っ た症例33例（男性11例，女性22例，平均年齢42.0± 16.5歳）を対象とした．

　対象症例には，百日咳確定のため，鼻咽頭ぬぐい液を 検体として loop-mediated isothermal amplification （LAMP）法および培養，百日咳毒素（pertussis toxin： PT）に対する抗体価（抗PT抗体価），凝集素価（山口 株：流行株K抗原：1.3.6）の測定を行った．抗PT抗体 価は酵素免疫測定法（enzyme-linked immunosorbent assay：ELISA法），凝集素価は細菌凝集反応により測定 した．LAMP法はKamachi[4]らの方法により，国立感染 症研究所で測定した．なお，単血清を用いた凝集素価法 は診断精度が低いとされているため，本研究ではペア血

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