Control selection and confounding factors: A lesson from a Japanese case-control study to examine acellular pertussis vaccine effectiveness

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ARTICLE INFO

ABSTRACT

When using a case-control study design to examine vaccine effectiveness, both the selection of control subjects and the consideration of potential confounders must be the important issues to ensure accurate results. In this report, we described our experience from a case-control study conducted to evaluate the effectiveness of acellular pertussis vaccine combined with diphtheria-tetanus toxoids (DTaP vaccine). Newly diagnosed pertussis cases and age- and sex-matched friend-controls were enrolled, and the history of DTaP vaccination was compared between groups. Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of vaccination for development of pertussis.

After adjustment for potential confounders, four doses of DTaP vaccination showed a lower OR for pediatrician-diagnosed pertussis (OR = 0.11, 95% CI, 0.01–0.99). In addition, the decreasing OR of four doses vaccination was more pronounced for laboratory-confirmed pertussis (OR = 0.07, 95%CI, 0.01–0.82). Besides, positive association with pertussis was observed in subjects with a history of steroid treatment (OR = 5.67) and those with a recent contact with a lasting cough (OR = 4.12).

When using a case-control study to evaluate the effectiveness of vaccines, particularly those for uncommon infectious diseases such as pertussis, the use of friend-controls may be optimal due to the fact that they shared a similar experience for exposure to the pathogen as the cases. In addition, to assess vaccine effectiveness as accurately as possible, the effects of confounding should be adequately controlled with a matching or analysis technique.

1. Introduction

When using a case-control study to examine vaccine effectiveness, the selection of control subjects is a critical issue. If it failed to select adequate controls, the observed results will be biased, and lead to an erroneous conclusion. According to a description in "*Epidemiology: An Introduction*" edited by Rothman [1], "*a control group is sampled from the entire source population that gives rise to the cases. Because the control group is used to estimate the distribution of exposure in the source population, the cardinal requirement of control selection is that the controls be sampled independently of exposure status*". In other words, when considering the optimum controls, the first step is to define the source population from which the controls will be selected.

Based on the fact that all cases who develop an infectious disease must have been exposed to the pathogen, the ideal setting would one in which control subjects have a similar experience for exposure to the pathogen as the cases. More specifically, the "source population" should be defined as those who were exposed to the pathogen in question. Cases and controls should then be

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recruited from among this predefined "source population", and differences in vaccination history between the groups were compared. However, in the case of uncommon sporadic infectious diseases such as pertussis, it is particularly difficult to define a "source population" with a similar experience of exposure to the pathogen. In this case, even if traditional hospital or community controls are selected, most of them might not have had the contact with the pathogen; this would result in an underestimation of vaccine effectiveness. Therefore, in order to evaluate vaccine effectiveness as accurately as possible, it is necessary to take into account the opportunity of exposure to the pathogen when selecting controls.

In addition, when performing observational studies such as case-control studies to evaluate vaccine effectiveness, the presence of confounders is another concern. In the field of vaccine epidemiology, a confounding factor is defined as a variable which relate to vaccination and to the outcome such as infection or infectious disease development, but which is not on the intermediate from vaccination to outcome [2]. For example, age and underlying illness are generally considered to be important potential confounders that may affect the evaluation of vaccine effectiveness. If potential confounders such as these are not adequately controlled or adjusted, they will inevitably introduce a bias in the results.

In this report, we present our experience from a case-control study conducted to evaluate the effectiveness of acellular pertussis vaccine combined with diphtheria-tetanus toxoids (DTaP vaccine). In our study, friend-controls were chosen because they would have shared a similar experience for exposure to pertussis as the cases. Besides, in our study, by conducting several multivariate analyses, we became aware of several confounding factors.

2. Materials and methods

The detail of the study methods and subjects have been described elsewhere [3]. In brief, we conducted a multicenter, case-control study at five collaborating hospitals in the following five prefectures of Japan (from north to south): Chiba, Saitama, Mie, Saga, and Fukuoka. Cases were patients newly pediatrician-diagnosed with pertussis between April 2009 and October 2012, whose age at diagnosis was less than 30 years and who satisfied the following clinical criteria for pertussis: persistent cough for more than 7 days with one or more additional symptoms (paroxysmal cough, whoop, or post-tussive vomiting) accompanied by positive results for *Bordetella pertussis* isolation, positive results by the loop-mediated isothermal amplification (LAMP) method, serodiagnosis or an epidemiological link to a confirmed pertussis case. The friend-control method was adopted for the recruitment of control subjects. Each case was asked to provide up to five friend-controls who had the same age (or school grade) and sex as the case. Exclusion criteria for friend-controls were: presence of lasting cough for more than 1 week during 1 month prior to the case diagnosis.

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 (e.g., 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; preschool or school attendance, frequency of going out (per week), hand washing habits or gargling habits at getting home, frequency of tooth brushing (per day); total room space in the house (m^2), number of family members, number of siblings;

contact with a confirmed pertussis case during the recent one month; and contact with a person with a lasting cough during the recent one month. In Japan, vaccination history is usually recorded in individually maintained Mother-Child Health Records; these books were used to confirm the information collected on vaccination status. When missing answers or illogical data were detected by research technicians, research technicians conducted a telephone interview to complete the data.

In the analyses, continuous variables except for age and the number of family members were re-categorized into two levels according to the median value of the distribution of controls. Age was re-categorized into three levels, based on the age at which most children completed DTaP vaccination (i.e., 2 years) and the age when the effects of DTaP vaccination could be continued (i.e., 10 years) [4–10]. Regarding the number of family members, a three-level category was used when considering the family structure.

The background characteristics were compared between cases and controls using the chi-square test, Fisher's exact test, or the Wilcoxon rank-sum test. To calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs) of each variables for pertussis, a logistic regression model was employed. Because some cases had no corresponding pair as controls and vice versa, main analyses were conducted in all cases and controls who responded to the questionnaire using an unconditional logistic regression model. Trends for associations were assessed by assigning ordinal scores to the level of the independent variable. In constructing the multivariate model, matching variables (age and gender) and variables that showed a p-value less than 0.1 were considered potential confounders for adjustment. Since underlying illnesses, asthma, and history of steroid treatment were strongly correlated with one another, the variable most strongly associated with pertussis (i.e., history of steroid treatment) was considered to be a prior variable to the multivariate models. Adjustment for age was conducted by including variable of the three-level age category rather than continuous age, in order to increase the statistical power. Additional analyses were then conducted to assess the effectiveness of DTaP vaccination for laboratory-confirmed pertussis. All tests were two-sided. All analyses were performed using SAS version 9.1.3 software (SAS Institute, Cary, NC, USA).

The study protocol was approved by the ethics committees at the Osaka City University Faculty of Medicine and collaborating hospitals. Written, informed consent was obtained from all subjects (or their parents or guardians) prior to participation.

3. Results

Among the 72 pertussis cases and 75 controls enrolled, 63 cases and 73 controls responded to the questionnaire (response rate: 88% for cases, 97% for controls). However, two controls were subsequently found to be ineligible because they had a history of pertussis. A further eight cases and two controls failed to provide complete data and were thus excluded. Eventually, 55 cases and 69 controls were included as subjects in the analysis. The number of laboratory-confirmed cases (i.e., positive results for culture isolation, the LAMP method, or serological assessment) was 39 (71%).

Table 1 shows a comparison of background characteristics between the 55 cases and 69 controls. Age and gender were well-matched. However, cases were less likely to have received DTaP vaccine than controls. In addition, cases had more underlying illnesses (particularly asthma), more history of steroid treatment, less frequency of tooth brushing, smaller room space in the house, and more contact with a person with a lasting cough.

A logistic regression model was employed to evaluate vaccine effectiveness for pediatrician-diagnosed pertussis (Table 2). The

Table 1
Comparison of background characteristics between cases and controls.

Variables		Cases (N = 55) n (%)	Controls (N = 69) n (%)	P value[a]
Matching variables				
Age (years)	Median (range)	9.6 (0.5–27.5)	10.3 (0.5–25.1)	0.543
	<2.0	5 (9)	3 (4)	0.197
	2.0–9.9	25 (45)	28 (41)	
	10.0+	25 (45)	38 (55)	
Sex	Male	22 (40)	23 (33)	0.443
	Female	33 (60)	46 (67)	
Vaccination status				
Number of DTaP vaccinations	0	7 (13)	3 (4)	0.061
	1–3	3 (5)	2 (3)	
	4	45 (82)	64 (93)	
Health-related conditions				
Underlying illnesses	Present	21 (38)	15 (22)	0.045
Asthma	Present	10 (18)	4 (6)	0.030
History of steroid treatment	Present	10 (18)	3 (4)	0.013
Environmental characteristics				
Preschool or school attendance	Present	50 (91)	67 (97)	0.240
Frequency of going out (per week)	<4	22 (40)	33 (49)	0.344
	4+	33 (60)	35 (51)	
Hand washing habits at getting home	Present	44 (80)	52 (75)	0.540
Gargling habits at getting home	Present	27 (49)	29 (42)	0.432
Frequency of tooth brushing (per day)	≤2	42 (76)	39 (57)	0.021
	3+	13 (24)	30 (43)	
Total room space in the house (m^2)	<100	36 (65)	34 (49)	0.071
	100+	19 (35)	35 (51)	
Number of family members	<4	20 (36)	16 (23)	0.149
	4	11 (20)	23 (33)	
	5+	24 (44)	30 (43)	
Number of siblings	Present	35 (64)	51 (74)	0.218
Recent contact with a person with a lasting cough	Present	17 (31)	8 (12)	0.008

[a] Chi-square test, Fisher's exact test, or Wilcoxon rank-sum test, where apppropriate.

Table 2
Adjusted odds ratios of DTaP vaccination and selected variables for pediatrician-diagnosed pertussis.

Variables		Univariate		Multivariate[a]	
		OR (95%CI)	P value	OR (95%CI)	P value
Number of DTaP vaccinations	0	1.00		1.00	
	1–3	0.64 (0.07–6.06)	0.700	0.24 (0.02–2.93)	0.264
	4	0.30 (0.07–1.23)	0.094	0.11 (0.01–0.99)	0.049
		(Trend P = 0.071)		(Trend P = 0.050)	
History of steroid treatment	Absent	1.00		1.00	
	Present	4.89 (1.27–18.8)	0.021	4.66 (1.06–20.5)	0.042
Frequency of tooth brushing (per day)	≤2	1.00		1.00	
	3+	0.40 (0.18–0.88)	0.023	0.48 (0.19–1.19)	0.113
Total room space in the house (m^2)	<100	1.95 (0.94–4.04)	0.073	1.97 (0.85–4.58)	0.117
	100+	1.00		1.00	
Recent contact with a person with a lasting cough	Absent	1.00		1.00	
	Present	3.41 (1.34–8.67)	0.010	4.54 (1.55–13.2)	0.006

DTaP vaccination, acellular pertussis vaccine combined with diphtheria-tetanus toxoids; OR, odds ratio; CI, confidence interval.
[a] Model includes variables in this table and matching variables (three-level age category and sex).

crude OR of four doses vaccination was 0.30 (95%CI, 0.07–1.23) and that of 1–3 doses vaccination was 0.64 (0.07–6.06). After adjustment for the potential confounders, ORs of DTaP vaccination revealed to be lowered and the reduction in the OR of four doses vaccination was statistically significant (OR = 0.11, 95%CI, 0.01–0.99). Besides, a significant positive association with pertussis was observed in subjects with a history of steroid treatment (OR = 4.66) and those with a recent contact with a lasting cough (OR = 4.54).

When analyzed the association with laboratory-confirmed pertussis, these association were more pronounced than that with pediatrician-diagnosed pertussis (Table 3). The multivariate OR (95%CI) of four doses vaccination decreased to 0.07 (0.01–0.82),

although decreasing OR of 1–3 doses vaccination did not reach to the significant association. In addition, the associations between other potential confounders and pertussis were also emphasized. Subjects with a history of steroid treatment (OR = 5.67) and those with a recent contact with a lasting cough (OR = 4.12) seemed to be a higher risk condition for development of pertussis. Since 72% of vaccinees provided the name of vaccine manufacture, we also examined ORs of DTaP vaccination according to the vaccine manufactures. However, no obvious difference of ORs among vaccine manufactures was observed (data not shown).

To confirm these results, conditional logistic regression models were also employed. However, since only 31 cases and 56 controls

Table 3
Odds ratios of DTaP vaccination and selected variables for laboratory-confirmed pertussis.

Variables		Univariate		Multivariate[a]	
		OR (95%CI)	P value	OR (95%CI)	P value
Number of DTaP vaccinations	0	1.00		1.00	
	1–3	0.90 (0.09–8.90)	0.928	0.33 (0.02–4.40)	0.398
	4	0.29 (0.07–1.30)	0.105	0.07 (0.01–0.82)	0.034
		(Trend P = 0.062)		(Trend P = 0.029)	
History of steroid treatment	Absent	1.00		1.00	
	Present	5.68 (1.41–22.9)	0.015	5.67 (1.15–27.9)	0.033
Frequency of tooth brushing (per day)	≤2	1.00		1.00	
	3+	0.45 (0.19–1.06)	0.068	0.58 (0.20–1.63)	0.297
Total room space in the house (m^2)	<100	1.65 (0.74–3.67)	0.221	1.84 (0.70–4.81)	0.213
	100+	1.00		1.00	
Recent contact with a person with a lasting cough	Absent	1.00		1.00	
	Present	3.00 (1.09–8.26)	0.034	4.12 (1.23–13.8)	0.022

DTaP vaccination, acellular pertussis vaccine combined with diphtheria-tetanus toxoids; OR, odds ratio; CI, confidence interval.
  [a] Model includes variables in this table and matching variables (three-level age category and sex).

(i.e., 31 matched-set) maintained the initial matched combination and statistical power lowered, no meaningful result could be obtained. Therefore, a model was constructed in which age and sex (i.e., matching variables), instead of matched-set number, were included as stratified variables and other potential confounders were included as explanatory variables. As a result, the model, which included three-level age category and sex as stratified variables and other potential confounders as explanatory variables, showed that the decreasing ORs of four doses vaccinees were similarly observed for both pediatrician-diagnosed pertussis (OR = 0.12; 95%CI, 0.01–1.04) and laboratory-confirmed pertussis (OR = 0.08; 95%CI, 0.01–0.80). The ORs of other potential confounders were also similar to the results from the unconditional logistic regression model (data not shown).

4. Discussion

Although the present case-control study had a unique design that included friend controls, our results were comparable to those of previous studies [11–13]. In our study, the vaccine effectiveness of four doses vaccination was 89% (1–99%) for pediatrician-diagnosed pertussis and 93% (18–99%) for laboratory-confirmed pertussis. These results seemed to support the usefulness of DTaP vaccine in the Japanese routine immunization program.

Regarding the selection of controls, some might think that hospital controls would have been preferable, because our cases were selected from among hospital patients. However, for the uncommon sporadic infectious diseases such as pertussis, traditional hospital or general population controls might not have had contact with the pathogen. In this case, even if the controls had not been previously vaccinated, they did not develop pertussis because they had not been exposed to the pathogen. If this background characteristics had been ignored and controls selected among those subjects without exposure to pertussis, it could have resulted in an underestimation of vaccine effectiveness. Therefore, in evaluating vaccine effectiveness, particularly for uncommon infectious diseases, the use of friend-controls may be optimal due to the fact that they had shared a similar experience for exposure to the pathogen as the cases.

Besides, since this was an observational study, some background characteristics could have been unequally distributed between the comparison groups. Therefore, it is essential to consider potential confounders. In fact, although the crude ORs of vaccination did not show any significant effectiveness (vaccine effectiveness, 70%), the multivariate ORs revealed a vaccine effectiveness of 89%

for pediatrician-diagnosed pertussis (Table 2), suggesting that the effectiveness would have been underestimated by about 19%, if the effect of potential confounders had not been considered. Previous studies on the effectiveness of pertussis vaccine also suggested the importance of considering potential confounders. In most of the previous case-control studies, controls matched with cases for age, sex, and residence were selected [13–17]. In addition, the effects of other confounders (e.g., the number of family members, age of sibling, vaccination status of siblings, etc.) were controlled by conducting multivariate analyses [15–17]. Therefore, confounding factors that may influence the effectiveness of pertussis vaccine should be adequately controlled using conventional methods such as matching or analysis technique.

When four potential confounders were simultaneously considered in our analysis of vaccine effectiveness, two factors mainly contributed to affect the results as the confounders. These confounding factors also affect as risk factors of pertussis. First, subjects with a history of steroid treatment were shown to have a higher risk for pertussis. To the best of our knowledge, no previous study has reported an association between a history of steroid treatment and pertussis. However, some studies have reported a higher risk for pertussis among patients with asthma [18,19], who often receive steroid treatment. In addition, several studies have reported that steroid treatment is a risk factor for respiratory infections such as pneumonia [20] and influenza [21]. Taken together, a history of steroid treatment might be a proxy variable for severe asthma, and thus have an effect of increasing the individual risk for pertussis infection.

Second, variables related to exposure to the pathogen (i.e., having recent contact with a person with a lasting cough) were associated with an increased risk of pertussis. In light of previous studies, pertussis outbreaks often occurred in crowded environments such as schools [12,22], within families [23], or among soldiers [24]. Furthermore, some studies have reported that subjects who had recent contact with a person with a pertussis-like cough had a higher risk for pertussis infection [23–25]. These results suggest that increased susceptibility to pertussis in a crowded situation or increased opportunities on contact with possible pertussis patients is related to pertussis infection.

However, our study had the following limitations. First, due to the small sample size, there was insufficient statistical power, which made the detection of significant vaccine effectiveness and potential confounders difficult. Particularly for younger pertussis cases, however, it was very difficult to find up to five friend-controls according to this study protocol, because they did not have many friends. Thus, we could enroll only 75 controls for 72

cases at the time of enrolment. Second, the possibility of residual confounding cannot be ruled out. For example, the effect of total room space in the house was adjusted in multivariate analyses, but the two-level categorization may not have been sufficient to control for all of the confounding by the room space. In addition, the effects of other potential confounders such as social economic status were not considered.

Despite the limitations, the results of our case-control study using friend-control method indicated the effectiveness of DTaP vaccination and the effects of several confounders. These results are expected to highlight the importance both of selecting adequate controls and of controlling for potential confounders when assessing vaccine effectiveness using case-control study design.

Conflict of interest

None.

Acknowledgments

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