Pertussis Vaccine Effectiveness Among Children 6 to 59 Months of Age in the United States, 1998–2001

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ABSTRACT. *Background.* **Despite the dramatic pertussis decrease since the licensure of whole-cell pertussis (diphtheria-tetanus toxoids-pertussis [DTP]) vaccines in the middle 1940s, pertussis remains endemic in the United States and can cause illness among persons at any age; >11 000 pertussis cases were reported in 2003. Since July 1996, in addition to 2 DTP vaccines already in use, 5 acellular pertussis (diphtheria-tetanus toxoids-acellular pertussis [DTaP]) vaccines were licensed for use among infants; 3 DTaP vaccines were distributed widely during the study period. Because of the availability of 3 DTaP and 2 DTP vaccines and the likelihood of the vaccines being used interchangeably to vaccinate children with the recommended 5-dose schedule, measuring the effectiveness of the pertussis vaccines was a high priority.**

Objective. **To measure the pertussis vaccine effectiveness (VE) among US children 6 to 59 months of age.**

Design. **We conducted a case-control study in the Cincinnati, Ohio, metropolitan area, Colorado, Idaho, and Minnesota.**

Participants. **Confirmed pertussis cases among children 6 to 59 months of age at the time of disease onset, with onset in 1998–2001, were included. For each case subject, 5 control children were matched from birth certificate records, according to the date of birth and residence.**

Outcome Measures. **A standardized questionnaire was used to obtain vaccination data from parents and providers. Parents/guardians were asked about demographic characteristics, child care attendance, the number of household members who stayed at the same home as the enrolled child for ≥2 nights per week, and cough illness of ≥2-week duration among these household members in the month before the case patient's cough onset. Pertussis vaccine doses among case children were counted as valid if they were received ≥14 days before the cough onset date ("valid period"). The age of the case patient (in days) at the end of the valid period was determined, and doses of vaccine for the matched control subjects were counted as valid if they were received by that age. Conditional logistic regression models were used to estimate the matched odds ratios (ORs) for pertussis according to the number of pertussis vaccine doses. The VE was calculated with the following formula: (1 − OR) × 100. Because the pertussis antigen components or amounts differed according to vaccine, the VE of 3 or 4 doses of DTP and/or DTaP was estimated according to the recorded vaccine manufacturer and vaccine type.**

Results. **All enrolled children (184 case subjects and 893 control subjects) had their vaccine history verified. The proportions of children who received 0, 1 or 2, 3, and ≥4 pertussis (DTP and/or DTaP) vaccine doses among case subjects were 26%, 14%, 26%, and 34% and among control subjects were 2%, 8%, 33%, and 57%, respectively. Compared with 0 doses, the unadjusted VE estimate for 1 or 2 pertussis doses was 83.6% (95% confidence interval [CI]: 61.1–93.1%), that for 3 doses was 95.6% (95% CI: 89.7–98.0%), and for ≥4 doses was 97.7% (95% CI: 94.7–99.0%). Among children who received 4 pertussis vaccinations, the risk of pertussis was slightly higher among those who received only 1 type of vaccine (either 4 DTP doses or 4 DTaP doses), compared with those who received a combination of DTP for doses 1 to 3 and DTaP for dose 4 (OR: 2.4; 95% CI: 1.1–5.2). Among children who received 3 or 4 DTaP vaccine doses, the risk of pertussis was slightly higher among those who received a DTaP vaccine with 4 pertussis antigen components (a vaccine no longer available), compared with those who received the DTaP vaccine with 2 pertussis antigen components (OR: 2.5; 95% CI: 1.1–5.8). Among children who received 4 doses, the risk of pertussis was 2.7 times higher for children who received dose 4 early (age of ≤13 months), compared with children who received dose 4 at an older age (age of ≥14 months) (95% CI: 1.1–6.8). For children 6 to 23 months of age, features of household structure were significant risk factors for pertussis. In a multivariate model, compared with living with an older parent (≥25 years of age), not living with an "other" household member (a relative other than a parent or sibling or a nonrelated person), and not living with a sibling 6 to 11 years of age, the risk of pertussis for children 6 to 23 months of age was 6.8 times higher if they lived with a young parent (≤24 years of age) (95% CI: 3.1–15.0), 2.5 times higher if they lived with an "other" household member (95% CI: 1.2–5.4), and 2.2 times higher if they lived with a sibling 6 to 11 years of age (95% CI: 1.2–4.3). Adjusting for these risk factors did not change the VE. Compared with control children, case children were significantly more likely to live with a household member (representing all age groups and relationships) who reported a recent cough illness with duration of ≥2 weeks (87 [52%] of 168 case subjects, compared with 79 [8%] of 860 control subjects).**

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Conclusions. **Any combination of ≥3 DTP/DTaP vaccine doses for children 6 to 59 months of age was highly protective against pertussis. However, there were differences according to vaccine type (DTaP or DTP) and DTaP manufacturer. Among children who received 4 pertussis vaccine doses, a combination of 3 DTP doses followed by 1 DTaP dose had a slightly higher VE than other combinations; among children who received 3 or 4 DTaP vaccine doses, 1 DTaP vaccine performed less well. The finding that pertussis dose 4 was more effective when given to children at ≥14 months of age might be confounded if health care providers were more likely to vaccinate children at 12 months of age because of a perceived risk of undervaccination and if these same children were also at higher risk for pertussis. Household members of any age group and relationship could have been the source of pertussis, and household structure was associated with risk for pertussis for children 6 to 23 months of age. In contrast to control children in the study, 26% of case children had never been vaccinated against pertussis. Unvaccinated children are at risk for pertussis and, in a community with other unvaccinated children, can lead to community-wide pertussis outbreaks. Parents need to be educated about the morbidity and mortality risks associated with *Bordetella pertussis* infection, and they need to be encouraged to vaccinate their children against pertussis on time and with the recommended number of vaccine doses for optimal protection.** *Pediatrics* **2005;116:e285–e294. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2759;** ***pertussis, children, vaccine effectiveness.***

ABBREVIATIONS. DTP, diphtheria-tetanus toxoids-pertussis; PT, pertussis toxin; DTaP, diphtheria-tetanus toxoids-acellular pertussis; VE, vaccine effectiveness; CI, confidence interval; OR, odds ratio; CDC, Centers for Disease Control and Prevention.

Despite the dramatic decrease in pertussis since the licensure of whole-cell pertussis vaccines in the middle 1940s, *Bordetella pertussis* infection continues to be a cause of morbidity and death in the United States.[1–4] Although reported pertussis incidence has increased cyclically, with peak increases in incidence occurring every 3 to 5 years, the number of reported cases is likely to be a gross underestimate of true pertussis incidence.[4–6] In addition, cases might be reported differentially according to age; diagnosis and reporting of cases among infants is likely better because disease severity and disease-associated mortality rates are greater among infants than in older age groups.[3,4,7] In 2003, a total of 11 647 pertussis cases were reported among persons of all ages, the largest number of reported cases since 1964; 12% of reported cases were among children 6 to 59 months of age (incidence of 8 cases per 100 000 children; Centers for Disease Control and Prevention [CDC], unpublished data, 2004), who were eligible to have received ≥3 doses of a pertussis vaccine and represented the age group of interest for this study.

From the middle 1940s to 2000, whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids (diphtheria-tetanus toxoids-pertussis [DTP]) were used to vaccinate children against pertussis, diphtheria, and tetanus with a 5-dose series administered at 2 months, 4 months, 6 months, 12 to 18 months, and 4 to 6 years of age. During the 1990s, 2 whole-cell DTP vaccines (produced by Connaught Laboratories, Swiftwater, PA, and by Wyeth-Lederle Vaccines and Pediatrics, Pearl River, NY) were distributed nationally in the United States. Whole-cell DTP vaccines had been estimated to be 70% to 90% effective in preventing pertussis (≥3-week paroxysmal cough).[8–11] However, the Connaught whole-cell DTP vaccine, when administered in a 3-dose series, was found to have unexpectedly low efficacy (36–48%) in randomized controlled trials conducted in Italy and Sweden.[12,13] In contrast, the vaccine efficacy estimate for the Wyeth-Lederle DTP vaccine, administered in a 4-dose series, was 94% in a German clinical trial.[14,15]

In 1991 and 1992, 2 acellular pertussis vaccines (containing purified components of *B pertussis*) combined with diphtheria and tetanus toxoids (diphtheria-tetanus toxoids-acellular pertussis [DTaP]) were licensed for use as the fourth and fifth doses of the vaccination series among children who had received 3 doses of whole-cell DTP. On the basis of results of efficacy studies in Europe,[12–17] 5 DTaP vaccines were licensed in the United States and recommended for use among infants[18,19]; the first one was licensed in July 1996. Between 1998 and 2001, 4 licensed DTaP vaccines with differing pertussis antigen components and/or amounts were available in the United States, ie, a 1-component vaccine containing 40.0 μg of pertussis toxin (PT) (Baxter Hyland Immuno Vaccines, formerly North American Vaccine, Beltsville, MD), a 2-component vaccine containing 23.4 μg of inactivated PT and 23.4 μg of filamentous hemagglutinin (Sanofi Pasteur, formerly Aventis Pasteur, Lyon, France; the pertussis vaccine component was manufactured by BIKEN/Tanabe Corp, Osaka, Japan), a 3-component vaccine containing 25.0 μg of PT, 25.0 μg of filamentous hemagglutinin, and 8.0 μg of pertactin (GlaxoSmithKline Biologicals, Rixensart, Belgium), and a 4-component vaccine containing 3.2 μg of PT, 34.4 μg of filamentous hemagglutinin, 1.6 μg of pertactin, and 0.8 μg of fimbriae type 2 (Wyeth, formerly Wyeth-Lederle Vaccines and Pediatrics, Madison, NJ; the pertussis vaccine component was manufactured by Takeda Chemical Industries Ltd, Osaka, Japan). During 1998–2001, the 2-component, 3-component, and 4-component DTaP vaccines were distributed widely in the United States. By 2002 (after the study period), only 2 DTaP vaccines were available and widely distributed in the United States, ie, the 3-component vaccine and a newly licensed, 5-component vaccine (Sanofi Pasteur; the pertussis vaccine component is manufactured in Toronto, Canada).[19] Three of the licensed DTaP vaccines (the 1-component, 2-component, and 4-component vaccines) were no longer available.

The DTaP vaccines were not evaluated in the same clinical trial, and comparisons among the products could be made only indirectly. Because of the availability of different DTaP and DTP vaccines in the United States and the likelihood of different products being used interchangeably, estimating the effectiveness of the pertussis vaccines was a high priority. Although surveillance data showed that

approximately one quarter of reported cases were among unvaccinated children 6 to 59 months of age,[1] the vaccination status was not documented for all cases; for those case children with documented vaccination status, the vaccine type, lot, and manufacturer data were usually unavailable. Therefore, we conducted this study to measure the pertussis vaccine effectiveness (VE) in the United States among children 6 to 59 months of age, for whom maximal effectiveness might be expected because of the limited time since the last dose. We also measured the VE according to product type (ie, DTP or DTaP) and manufacturer and assessed the effect of demographic, socioeconomic, and household structure variables on the risk of pertussis.

METHODS

Patients and Study Design

The sample size needed to estimate 80 ± 10% VE was 120 case subjects, with 4 control subjects per case subject, given a ≥3-pertussis vaccine dose coverage level of 90% among control subjects. Because of expected nonresponse and the high vaccination coverage among control subjects, we sought to enroll 200 case subjects, with 5 control subjects per case subject, for an enrollment goal of 200 case subjects and 1000 control subjects.

The study was performed in the Cincinnati, Ohio, metropolitan area, Colorado, Idaho, and Minnesota. Each of these sites had demonstrated access to ≥40 pertussis cases among children 6 to 59 months of age in 1 of 4 years before the study period. Institutional review boards approved the study at the CDC and at each of the 4 sites.

Confirmed pertussis cases[20] reported to local public health officials from 1998 to 2001 among children 6 to 59 months of age were eligible for inclusion in the study. A case was confirmed with ≥1 day of cough and isolation of *B pertussis* from a clinical specimen. A case could also be confirmed with the clinical case definition (an acute cough illness lasting ≥2 weeks with paroxysms of coughing, inspiratory "whoop," or posttussive vomiting) and a positive polymerase chain reaction result for *B pertussis* DNA or direct contact (epidemiologic linkage) with a laboratory-confirmed case. Two sites (Colorado and Idaho) used internally validated polymerase chain reaction assays to detect DNA from *Bordetella* spp.[21] Both assays targeted the insertion element IS*481*.

For age-matching with case children, control children were first selected from a sample of children born on the same day as the case subjects. If needed, control subjects born 1 to 14 days (up to 2 months in 1 instance) before the case child's birth date were contacted for inclusion. Control children also had to live in the same state and region of the state or metropolitan area (eg, in the same or adjacent county or zip code area, in the case of Cincinnati) as the case child. Up to 12 attempts were made (by telephone, letter, or both) to locate and enroll each potential control child. For 2 sites, a letter from the health department was sent to the parent/guardian of potential control subjects; persons who refused to participate sent a postage-paid preaddressed letter requesting not to be contacted. For the other 2 sites, the initial contact was by telephone. To find updated contact information for potential control children when birth certificate data had incorrect or incomplete information, other sources were used, eg, telephone book, reverse directory assistance, Internet (up to 6 search engines), postmaster letter with return address requested, and a telephone call to the mother's obstetric care provider listed on the birth certificate.

Control children were excluded from the study if prior pertussis was suspected by study investigators, as determined through queries to parents/guardians or providers or review of health department pertussis case logs. Control children were also excluded if the child had moved from the region before the study period. Case children were excluded from the study if the child could not be located after the initial report to public health authorities. Both case and control children were excluded if a sibling was already enrolled in the study, if the child had been placed for adoption, or if the child had died.

The parent or guardian was queried for the following during the month before the case onset date: demographic characteristics, child care attendance, number of household members who stayed in the same home as the enrolled child for ≥2 nights per week, cough illness of ≥2-week duration among these household members during the month before the case patient's cough onset, number of health care providers, vaccination history, and, when relevant, reasons why the child had not received ≥3 pertussis vaccine doses. After parental consent was obtained, health care providers were contacted for information on the vaccination dates for all administered vaccines and the pertussis vaccine type, manufacturer, and lot number.

Statistical Analyses

Pertussis vaccine doses among case children were counted as valid if they were received ≥14 days before the cough onset date ("valid period"). The age (in days) of the case subjects at the end of the valid period was determined and, because the matched control subjects could be slightly older than the case subjects, pertussis vaccine doses received by control children were counted as valid if they were received within that valid period. Recorded vaccine lot numbers and manufacturers were compared with internal and external data sources and the availability period for each vaccine; if needed, vaccine lot number and manufacturer data were corrected to be consistent with these data sources.

A χ^2 test was used to assess statistical significance in the univariate analyses, and a P value of ≤.05 was considered statistically significant. Conditional logistic regression models were used to estimate the matched odds ratios (ORs) for pertussis according to the number of pertussis vaccine doses. VE was calculated with the following formula: $(1 - \text{OR}) \times 100$. Because prior studies had indicated that the VE for 3 or 4 doses of DTP and DTaP vaccines might differ because of pertussis antigen components and/or amounts,[18] the VE was estimated according to recorded vaccine manufacturer as well as vaccine type. Selected potential risk factors for pertussis (eg, demographic, socioeconomic, and household structure variables) were examined. These potential risk factors were also controlled for as potential confounders and as effect modifiers for the VE estimate. We also examined the VE according to age (6–23 months and 24–59 months) because older children might have less accessible vaccination records and thus could be categorized falsely as undervaccinated (eg, 1 or 2 doses), in comparison with younger children. In addition, household structure could affect children differently depending on the age of the child.

RESULTS

Study Groups

At the 4 sites, 199 confirmed pertussis cases were reported among eligible children 6 to 59 months of age; 184 (93%) subjects were enrolled. For the case subjects not enrolled, parents or guardians either could not be found ($n = 8$) or refused to participate ($n = 7$). Among 1236 eligible control children with whom contact was made, 893 (72%) were enrolled; control children did not participate because of language barriers ($n = 2$) or refusal ($n = 330$). After enrollment, 11 control children were excluded from the analysis because of unknown vaccination history.

Most (67%) pertussis cases were culture confirmed (Table 1). Among case children with available information, 96% had paroxysms, 72% had posttussive emesis, and 96% had coughed for ≥14 days. Ten (7%) children with pertussis were hospitalized. Three (30%) of these 10 hospitalized children each had a congenital abnormality; 1 child 6 months of age with hydrocephalus had received 2 pertussis vaccine doses, 1 child 20 months of age with partial trisomy 23 had received 1 pertussis vaccine dose, and 1 child 25 months of age with Jeune's syndrome had received 3 pertussis vaccine doses.

TABLE 1. Selected Characteristics of Enrolled Case Children ($n = 184$)

Characteristic	*n* (%)*
How diagnosed	
Culture	123 (67)
Polymerase chain reaction assay	47 (25)
Epidemiological linkage	14 (8)
Signs/symptoms†	
Paroxysms	133/139 (96)
Whoop	69/137 (50)
Posttussive vomiting	100/138 (72)
Apnea	52/137 (38)
Cough duration	
≥14 d†	168/175 (96)
No. of days, median (range)	40 (2–240)
10th and 90th quantiles, d	15 and 106
Hospitalization†	10/141 (7)
No. of days, median (range)	75 (21–120)
Age, mo, median (range)	14 (6–50)
Vaccination status	
0 dose	2/10 (20)
1 or 2 doses	3/10 (30)
3 or 4 doses	5/10 (50)
Age	
6–11 mo	36 (20)
12–23 mo	56 (30)
24–35 mo	35 (19)
36–47 mo	30 (16)
48–59 mo	27 (15)

* Percentage of cases with known data.
† Number with characteristic/number with data available.

Fifty percent of enrolled case children were 6 to 23 months of age, and 50% were 24 to 59 months of age. Male and female children were equally enrolled (Table 2). There were no significant differences between case and control children according to race/ethnicity. However, case children were less likely to attend day care, compared with control children ($P = .03$); case children's mothers had lower educational levels ($P < .001$), and case children were more likely to have had Medicaid or subsidized health insurance ($P < .001$). Case children also differed from control children with a greater proportion having a parent ≤24 years of age ($P < .0001$) and greater number of persons living in the household ($P < .01$). Compared with control children, case children were more likely to have ≥1 sibling 6 to 11 years of age living in the household ($P = .02$) but were not more likely to have a sibling 12 to 17 years of age living in the household ($P = .4$). In addition, compared with control children, case children were more likely to have a relative other than a sibling or parent or a nonrelated person living in their household ($P < .001$).

Cough Among Household Members

Compared with control children, case children were significantly more likely to live with a household member who reported a recent cough illness with duration of ≥2 weeks (87 [52%] of 168 case subjects, compared with 79 [8%] of 860 control subjects; $P < .001$). In addition, case children were significantly more likely to have reported contact with either a household member or nonhousehold member with an acute cough illness of ≥2-week duration (120 [70%] of 172 case subjects, compared with 121 [14%] of 878 control subjects; $P < .001$). One or more household members for case children reported a cough illness equally throughout the year (19 [46%] of 41 in the winter season, compared with 68 [54%] of 127 in the other seasons; $P = .5$). In contrast, ≥1 household member for control children was more likely to report a cough illness in the winter season (December to February), compared with the other seasons (33 [15%] of 215, compared with 46 [7%] of 599; $P < .001$).

Compared with control households, a greater proportion of persons (regardless of age group and relationship) in case households had a cough in the preceding month (Fig 1). Among the 87 case children exposed to household coughers, 44 (51%) lived with 1 coughing person and 43 (49%) lived with ≥2 coughing persons; among the 79 control children who lived with a coughing person, 57 (72%) lived with 1 coughing person and 22 (28%) lived with ≥2 coughing persons. Thus, case children were 2.5 times more likely to live with ≥2 coughing household members than were control children (95% confidence interval [CI]: 1.3–5.1; $P < .01$).

Vaccination History

Case children were undervaccinated compared with control children. The proportions of children who received 0, 1 or 2, 3, and ≥4 pertussis vaccine doses among case subjects were 26%, 14%, 26%, and 34% and among control subjects were 2%, 8%, 33%, and 57%, respectively ($P < .001$) (Table 3). Sixty-two children had not been vaccinated against pertussis (48 case subjects and 14 control subjects). The reasons for lack of vaccination were available for 39 (81%) case subjects and 10 (71%) control subjects, ie, parental refusal (without an explicit reason) for 17 (44%) case subjects and for 7 (70%) control subjects, philosophical or religious exemptions for 11 (28%) case subjects and for 1 (10%) control subject, medical contraindications for 4 (10%) case subjects and for 1 (10%) control subject, and scheduling problems for 7 (18%) case subjects and for 1 (10%) control subject. Only 1 or 2 valid pertussis vaccine doses had been administered to 26 (14%) case children and 70 (8%) control children. Of the 96 children who had received 1 or 2 valid pertussis vaccine doses, 47 (49%) were ≤7 months of age and 69 (72%) were ≤11 months of age. The reasons for undervaccination were available for 36 (37%) of the 96 case and control children. Among these 36 children, the reported reasons included parental refusal (5 children, 14%), concurrent illness (6 children, 17%), reaction to prior pertussis vaccinations (5 children, 14%), and scheduling problems (20 children, 56%).

Nineteen case children and 4 control children had received ≥1 DT vaccine dose. Only 4 of these 23 children received DT for the first 3 doses; all 4 parents stated that they had refused pertussis vaccination.

VE

The unadjusted VE for ≥3 pertussis vaccine doses, compared with 0 doses, was 97.1% (95% CI: 93.7–98.6%). When stratified according to age, the VE for 3 pertussis vaccine doses, compared with no vacci-

TABLE 2. Selected Characteristics of Control and Case Children

	n (%)*		Matched OR (95% CI)	P
	Case Subjects (*N* = 184)	Control Subjects (*N* = 893)		
Gender				
Male	93 (50)	462 (52)	1.0 (0.7–1.5)	.88
Female	91 (50)	431 (48)	Reference	
Race/ethnicity				
White, non-Hispanic	148 (84)	771 (87)	Reference	
Black, non-Hispanic	4 (2)	25 (3)	0.7 (0.2–2.7)	.65
Hispanic	15 (8)	39 (4)	2.2 (0.9–5.1)	.07
Other	10 (6)	51 (6)	1.2 (0.6–2.4)	.63
Missing	7	7		
Child day care attendance				
Attends ≥4 h/wk	62 (36)	391 (45)	0.6 (0.4–0.9)	.03
Does not attend	110 (64)	487 (56)	Reference	
Missing	12	15		
Insurance for enrolled child				
None	11 (7)	40 (5)	2.4 (1.1–4.9)	.02
Medicaid or subsidized	35 (21)	62 (7)	4.6 (2.7–7.9)	<.001
Private	119 (72)	785 (89)	Reference	
Missing	19	6		
Mother's education				
Less than high school	23 (14)	51 (6)	4.4 (2.3–8.4)	<.001
High school graduate	37 (23)	155 (17)	2.3 (1.4–3.9)	.002
Some college or technical school	55 (34)	253 (29)	1.9 (1.2–2.9)	.006
College graduate	46 (29)	427 (48)	Reference	
Missing	23	7		
Parent's age (≥1)				
≤24 y	41 (25)	71 (8)	3.9 (2.4–6.1)	<.001
≥25 y	126 (75)	811 (92)	Reference	
Missing	17	11		
Size of household				
2	5 (3)	8 (1)	2.9 (0.9–9.3)	
3	35 (19)	187 (21)	Reference	
4 or 5	93 (52)	567 (64)	0.8 (0.5–1.3)	
6	47 (26)	129 (14)	1.9 (1.1–3.2)	<.01
Missing	4	2		
Siblings 6–11 y of age				
None	99 (55)	573 (65)	Reference	
≥1	80 (45)	314 (35)	1.5 (1.04–2.1)	.03
Missing	5	6		
Siblings 12–17 y of age				
None	151 (84)	769 (87)	Reference	
≥1	28 (16)	118 (13)	1.2 (0.8–1.9)	.4
Missing	5	6		
Any "other" in household				
None	139 (78)	812 (92)	Reference	
≥1	40 (22)	75 (8)	3.0 (2.0–4.4)	<.001
Missing	5	6		
Any "other" 6–17 y of age				
None	162 (92)	869 (98)	Reference	
≥1	17 (9)	18 (2)	5.0 (2.5–10.2)	<.001
Missing	5	6		

* Percentage of case or control subjects with known data.

nation, was consistently high (range: 93.3–98.4%) (Table 3).

Among 558 children who received 4 valid pertussis vaccinations, dose 4 was given early in the acceptable age range for dose 4 (ie, age of ≤13 months, the acceptable age for vaccination plus a 1-month grace period) for 8 (13%) of 63 case subjects and 25 (5%) of 495 control subjects ($P = .02$). Compared with no vaccination, the VE was slightly lower for children who received dose 4 early (VE: 92.0%; 95% CI: 74.9–97.4%) than for children who received dose 4 at an older age (age of ≥14 months) (VE: 97.7%; 95% CI: 94.8–99.0%). That is, the risk of pertussis was 2.7 times higher (95% CI: 1.1–6.8) for children who received the fourth dose early, compared with children who received the fourth dose at an older age.

Potential Risk Factors for Pertussis

On the basis of univariate analyses, we considered statistically significant variables in the multivariate model. With backward elimination, only household structure data (having a young parent [≤24 years of age], living with "others" [eg, an uncle, grandparent, or friend] in the household, and having ≥1 sibling 6–11 years of age) remained significantly associated with the risk for pertussis. Children had a higher risk of pertussis in households with a young parent and

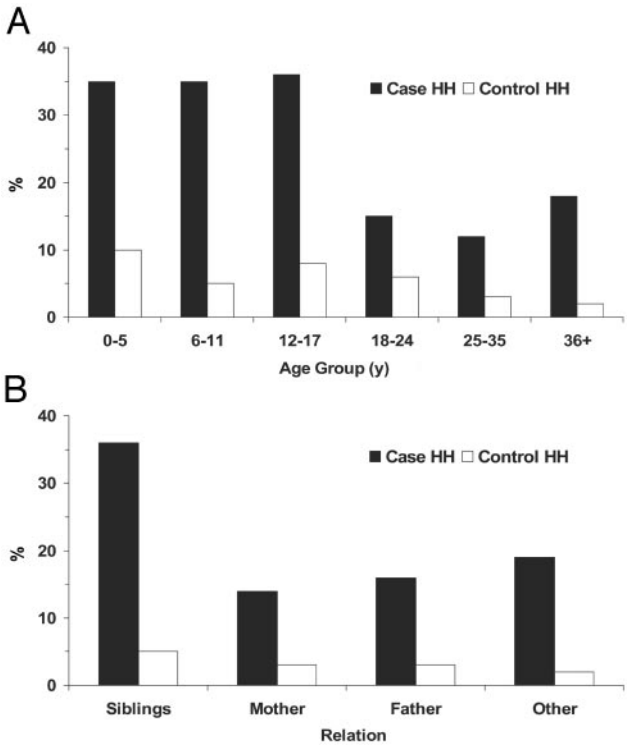

Fig 1. Distribution of household members with cough illness of ≥2-week duration in the month before the case patient's cough onset date in 168 case households (HH) and 860 control households according to age group (A) and relationship (B).

when living with "others" (Table 4). When the model was stratified according to age (6–23 months versus 24–59 months), younger case children had a higher risk for pertussis in households with a young parent, living with "others" in the households, and with ≥1 sibling 6 to 11 years of age, compared with older case children. Adjusting for these risk factors did not change the VE significantly.

Vaccine Type

Overall, the types of pertussis vaccine doses were distributed evenly; 49% were DTP, 50% were DTaP, and 1% was unknown type. Because the study was initiated in 1998, when DTaP vaccines had just become available for use among infants, a majority of older enrolled children (ie, 36–59 months of age) had received DTP for their first 3 doses, whereas a majority of younger enrolled children (ie, 6–14 months of age) had received DTaP for their first 3 doses ($P < .001$) (Fig 2).

In a model with 3 valid doses, the VE estimate for 3 DTP doses (95.5%) was not statistically different from the VE estimate for 3 DTaP doses (95.4%) or for a mixture of DTP and DTaP doses (94.5%) (Table 5). Similarly, the VE estimate for 4 DTP doses (96.7%) was not statistically different from the VE estimate for 4 DTaP doses (96.7%) or for a mixture of DTP and DTaP doses (98.0%). However, the risk of pertussis was slightly higher among children who received 4 DTP doses or 4 DTaP doses, compared with receipt of DTP for doses 1 to 3 and DTaP for dose 4 (OR: 2.4; 95% CI: 1.1–5.2).

Vaccine Manufacturer

DTP vaccine manufacturer data were available for 185 (75%) of 246 case and control children who received 3 or 4 valid DTP doses. With the exclusion of unknowns, there was no statistical difference in the risk of pertussis when 3 or 4 doses of the Wyeth-Lederle DTP vaccine were compared with 3 or 4 doses of the Connaught DTP vaccine (OR: 0.6; 95% CI: 0.2–1.6).

DTaP vaccine manufacturer data were available for 357 (92%) of 390 case and control children who received 3 or 4 valid DTaP doses. Approximately 38% of children received the 2-component DTaP vaccine, 9% of children received the 3-component DTaP vaccine, and 46% of children received the 4-component DTaP vaccine. Because few case or control subjects in our study had received the 3-component DTaP vaccine, we compared children who had received 3 or 4 doses of the 4-component DTaP vaccine with those who had received 3 or 4 doses of the 2-component DTaP vaccine. Compared with the 2-component DTaP vaccine, the 4-component DTaP vaccine was less effective (OR: 2.5; 95% CI: 1.1–5.8).

DISCUSSION

Our results indicated that, under field conditions, receipt of ≥3 pertussis vaccine doses among children 6 to 59 months of age was highly protective against pertussis, regardless of vaccine type or manufacturer. Compared with clinical trial results,[12–18] the VE estimates from this observational study were high and similar to results reported in a German case-control study.[22] In the German study, the VE estimate for the 2-component DTaP vaccine was higher for culture-confirmed cases with paroxysmal cough of ≥21-day duration (ie, more severe pertussis), compared with culture-confirmed cases with nonparoxysmal cough of ≥21-day duration (96% and 82%, respectively). Observational case-control studies might overestimate VE estimates if case children included in the study had more severe pertussis than children not included in the study who had unconfirmed and/or unreported pertussis and/or if the vaccination status of the child influenced the likelihood that a health care worker would consider a diagnosis of pertussis for a coughing child.[23] However, before the study and at each of the 4 sites, reported pertussis incidence in all age groups was above the national average (CDC, unpublished data, 1997), which suggests that health care providers at these sites might have been more aware of pertussis than health care workers at other sites and might have been more likely to test a coughing child and to report pertussis. Because the sites were geographically diverse, we think these results can be generalized to the United States. In addition, the vaccination status of case subjects in this study was similar to that of nationally reported case subjects[2] (CDC, unpublished data, 2004), and most parents of children who had never been vaccinated against pertussis gave a reason for lack of pertussis vaccination; therefore, a bias in ascertainment of vaccination status is unlikely. Lastly, although a majority of cases in the

TABLE 3. Number of Doses and Unadjusted Pertussis VE, Stratified According to Age

	n (%)		VE, %	95% CI
	Case	Control		
Age 6–23 mo	*N* = 92	*N* = 445		
0 dose	20 (22)	11 (2)	Reference	
1 dose	8 (9)	9 (2)	50.5	−71.1 to 86.3
2 doses	12 (13)	53 (12)	80.1	41.3 to 93.2
3 doses	41 (44)	275 (62)	93.3	83.1 to 97.4
4 doses	11 (12)	97 (22)	95.1	85.1 to 98.4
Age 24–59 mo	*N* = 92	*N* = 448		
0 dose	28 (30)	3 (1)	Reference	
1 dose	5 (5)	3 (1)	93.5	19.4 to 99.5
2 doses	1 (1)	5 (1)	99.4	87.3 to 99.9
3 doses	6 (7)	22 (5)	98.4	86.0 to 99.8
4 doses	52 (57)	398 (88)	99.3	95.0 to 99.9
5 doses	0	17 (4)	100	
All	*N* = 184	*N* = 893		
0 dose	48 (26)	14 (2)	Reference	
1 dose	13 (7)	12 (1)	70.8	13.9 to 90.1
2 doses	13 (7)	58 (6)	89.5	71.3 to 96.2
3 doses	47 (26)	297 (33)	95.6	89.7 to 98.0
4 doses	63 (34)	495 (55)	97.4	94.2 to 98.8
5 doses	0	17 (2)	100	

TABLE 4. VE Adjusted According to Household Structure Variables and Stratified According to Age

	Age 6–23 mo		Age 24–59 mo		All Ages	
	OR or VE	95% CI	OR or VE	95% CI	OR or VE	95% CI
OR						
Either parent ≤24 y of age	6.8	3.1 to 15.0	2.2	0.8–6.0	4.4	2.4–7.9
Any "other" household member	2.5	1.2 to 5.4	1.9	0.7–5.2	2.3	1.3–4.1
Any sibling 6–11 y of age	2.2	1.2 to 4.3	1.1	0.6–2.0	1.5	0.9–2.3
VE, %						
Pertussis vaccine dose 1	46.0	−147 to 88.2	95.8	41.1–99.7	74.6	14.3–92.5
Pertussis vaccine dose 2	79.6	24.6 to 94.5	99.4	88.7–99.9	90.7	72.0–96.9
Pertussis vaccine dose 3	91.7	74.5 to 97.3	98.5	86.6–99.8	95.1	87.8–98.1
Pertussis vaccine dose 4	96.4	86.4 to 99.0	99.3	94.8–99.9	97.5	94.1–98.9
Pertussis vaccine dose 5			100		100	

Analyses included 167 case subjects and 808 control subjects.

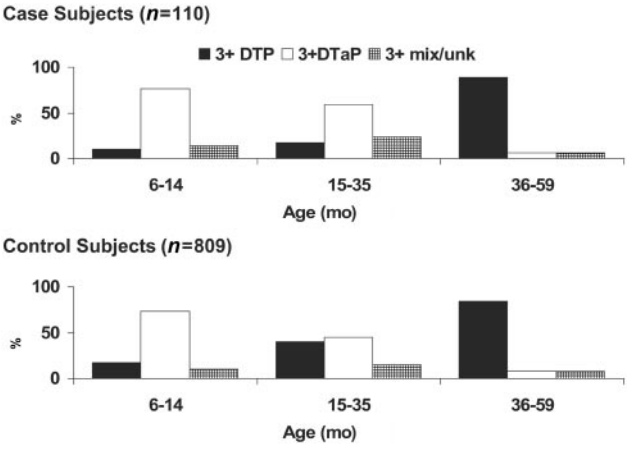

Fig 2. Type of pertussis vaccination, according to age, for case and control children who received ≥3 doses. mix/unk indicates mixture/unknown.

study were confirmed through isolation of *B pertussis*, unless laboratory confirmation of pertussis cases differed according to vaccine type or manufacturer, there would be little effect on comparisons between these groups.

It was speculated that DTaP vaccines with more components are more protective than vaccines with fewer components.[24–26] In this study, we found that, although both DTaP vaccines were effective, the 4-component DTaP vaccine seemed to perform slightly less favorably than the 2-component DTaP vaccine. The 2 products differed substantially in composition; for example, the PT content of the 4-component vaccine (3.2 μg of PT) was smaller than the PT content of the 2-component vaccine (23.4 μg of PT). After 3 doses were administered to children, anti-PT IgG antibody levels were significantly lower for the 4-component DTaP vaccine, compared with the 2-component DTaP vaccine.[27] Additionally, although the 2-component DTaP vaccine performed slightly better than the 4-component vaccine, it is interesting to note that three studies indicated that the presence of IgG antibodies to PT, fimbriae type 2, and pertactin is correlated with protection against pertussis.[24–26] Because of marketing decisions, distribution of both the 4-component DTaP vaccine and the 1-component DTaP vaccine in the United States were discontinued in 2000.[28]

We found that a majority of case children reported contact with a person with an acute cough illness in the month before onset. The estimates of a potential source of pertussis in this study might have been higher than estimates from other transmission source

TABLE 5. Distribution of 3 or 4 Valid DTP and DTaP Doses and VE, Compared With No Vaccination

	No. (%)		VE, %	95% CI
	Case Subjects	Control Subjects		
Only 3 valid doses	$N = 47$	$N = 297$		
All DTP	8 (17)	53 (18)	95.5	87.3–98.4
Mixture of DTP and DTaP	5 (11)	26 (9)	94.5	81.1–98.4
All DTaP	34 (72)	210 (71)	95.4	88.7–98.2
Unknown	0	8 (3)		
Only 4 valid doses	$N = 63$	$N = 495$		
All DTP	25 (40)	160 (32)	96.7	91.9–98.7
Mixture of DTP and DTaP*	17 (27)	190 (38)	98.0	95.0–99.2
All DTaP	20 (32)	126 (25)	96.7	90.8–98.8
Unknown	1 (1)	19† (4)		

* Of mixtures, 81% were 3 DTP doses (doses 1–3) and 1 DTaP dose (dose 4).
† Sixteen (84%) of 19 control children received 3 DTP doses (doses 1–3) and 1 unknown dose.

studies[29,30] because it could have included persons who were infected at the same time as the case child. Recall of a cough illness among household members by the parents/guardians of case subjects might have been more likely than that in control households. Given these limitations, it is of interest that contacts representing all age groups and relationships could have been the source of pertussis for the case children (Fig 1).

We found significant differences in the household structure among case and control children. Although we were unable to assess the risk of pertussis associated with living with a child <6 years of age because of study design, we found that children 6 to 23 months of age were at increased risk of pertussis through living with ≥1 sibling 6 to 11 years of age. In 2 previous studies, household composition and maternal age were found to be risk factors for pertussis.[31,32]

The study design contributed to other potential limitations of our study. Control children might not have been representative of the general population because, to have been contacted successfully, control children had to have been a resident of the study area since birth. Case children, however, could have migrated into the study area. Parents of control children were more likely to have completed a college education and to have private insurance for their children, compared with parents of case children; therefore, differences between case and control households might have been overaccentuated, compared with the general population. Because data were not available about potential control parents/guardians who refused to participate in our study, we cannot make inferences about how nonresponse could have affected the findings. To explore whether there might have been a bias in selecting control children, we compared vaccination coverage level data for the study control children with 1997 data from the National Immunization Survey.[33] At the 4 sites, among survey children 24 months of age, National Immunization Survey data estimated that 2% of children had never been vaccinated against pertussis, 93% had received ≥3 doses of DTP/DTaP, and 77% had received 4 doses of DTP/DTaP (Q. Li, unpublished data, 2003). Although our data are not directly comparable with the National Immunization Survey data (because of the age at the assessment of vaccination), a similar proportion of control children in our study (2%) had never been vaccinated against pertussis, whereas a greater proportion of control children 24 to 59 months of age enrolled in the study (98%) (Table 3) had received 3 or 4 doses of a pertussis vaccine.

In contrast to control children in the study, 26% of case children had never been vaccinated against pertussis, a proportion similar to that documented with surveillance data.[2] Unvaccinated children are at risk for pertussis and, in a community with other unvaccinated children, can give rise to community-wide pertussis outbreaks.[34,35] Parents need to be educated about the morbidity and mortality risks associated with *B pertussis* infection[1–4,7] and encouraged to vaccinate their children against pertussis.

In this study, 60% of pertussis cases were among children who had received ≥3 pertussis vaccine doses. Although protective against death and severe morbidity,[3,7,36] pertussis vaccines are imperfect; after receipt of ≥3 doses, vaccinees can still become infected and symptomatic after significant exposure to *B pertussis*. The apparent protective effectiveness of 1 or 2 doses of a pertussis vaccine might have been a result of measurement error or the small number of children in that stratum. As was shown in the clinical trials, 3 pertussis vaccinations provided more protection than did 2 pertussis vaccinations.[18,36]

This study was not designed to examine the issue of whether receipt of 4 pertussis vaccinations was more protective than receipt of only 3 pertussis vaccinations, because of the narrow age range between 6 months of age (when dose 3 should be administered) and 15 months of age (when dose 4 should be administered).[18,37] The design of the study allowed for examination of the timing of administration of dose 4; we found that pertussis dose 4 was more effective when given to children ≥14 months of age. According to the US pertussis vaccination recommendations, the fourth dose should be given at 15 to 18 months of age but may be given as early as 12 months if the child is not likely to return for a visit at the recommended age.[18,37] Therefore, this finding

might be confounded if health care providers were more likely to vaccinate children at 12 months of age because of a perceived risk of undervaccination and if these same children were also at higher risk of pertussis, and additional study is warranted. We also found that the VE estimate was slightly higher for a mixed schedule of DTP for doses 1 to 3 and DTaP for dose 4, compared with either 4 doses of DTaP or 4 doses of DTP (Table 5), but DTP vaccines are no longer available in the United States.

Data from this study and other studies[3,7,13–18,36] illustrate that pertussis vaccination with any licensed product protects children against pertussis. Children need to be vaccinated with a pertussis vaccine promptly at 2 months, 4 months, 6 months, 15 to 18 months, and 4 to 6 years of age[37] for optimal protection against pertussis.

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