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Association of Childhood Pertussis With Receipt of 5 Doses of Pertussis Vaccine by Time Since Last Vaccine Dose, California, 2010

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Context In 2010, California experienced its largest pertussis epidemic in more than 60 years; a substantial burden of disease was noted in the 7- to 10-year-old age group despite high diphtheria, tetanus, and acellular pertussis vaccine (DTaP) coverage, indicating the possibility of waning protection.

Objective To evaluate the association between pertussis and receipt of 5 DTaP doses by time since fifth DTaP dose.

Design, Setting, and Participants Case-control evaluation conducted in 15 California counties. Cases (n=682) were all suspected, probable, and confirmed pertussis cases among children aged 4 to 10 years reported from January through December 14, 2010; controls (n=2016) were children in the same age group who received care from the clinicians reporting the cases. Three controls were selected per case. Vaccination histories were obtained from medical records and immunization registries.

Main Outcome Measures Primary outcomes were (1) odds ratios (ORs) for the association between pertussis and receipt of the 5-dose DTaP series and (2) ORs for the association between pertussis and time since completion (<12, 12-23, 24-35, 36-47, 48-59, or ≥60 months) of the 5-dose DTaP series. Logistic regression was used to calculate ORs, accounting for clustering by county and clinician, and vaccine effectiveness (VE) was estimated as (1 − OR) × 100%.

Results Among cases and controls, 53 (7.8%) and 19 (0.9%) had not received any pertussis-containing vaccines, respectively. Compared with controls, children with pertussis had a lower odds of having received all 5 doses of DTaP (OR, 0.11; 95% CI, 0.06-0.21 [estimated VE, 88.7%; 95% CI, 79.4%-93.8%]). When children were categorized by time since completion of the DTaP series, using an unvaccinated reference group, children with pertussis compared with controls were less likely to have received their fifth dose within the prior 12 months (19 [2.8%] vs 354 [17.6%], respectively; OR, 0.02; 95% CI, 0.01-0.04 [estimated VE, 98.1%; 95% CI, 96.1%-99.1%]). This association was evident with longer time since vaccination, with ORs increasing with time since the fifth dose. At 60 months or longer (n=231 cases [33.9%] and n=288 controls [14.3%]), the OR was 0.29 (95% CI, 0.15-0.54 [estimated VE, 71.2%; 95% CI, 45.8%-84.8%]). Accordingly, the estimated VE declined each year after receipt of the fifth dose of DTaP.

Conclusion Among children in 15 California counties, children with pertussis, compared with controls, had lower odds of having received the 5-dose DTaP series; as time since last DTaP dose increased, the odds increased, which is consistent with a progressive decrease in estimated vaccine effectiveness each year after the final dose of pertussis vaccine.

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Pertussis remains a poorly controlled vaccine-preventable disease in the United States, despite a well-established childhood vaccination program and high coverage.[1] Although infants have substantially higher rates of pertussis compared with other age groups, data from the National Notifiable Diseases Surveillance System reflect a recent increase in the number of reported pertussis cases among children aged 7 to 10 years. In 2010, this age group had the second highest incidence of pertussis in the United States.[2] The changing epidemiology raises important questions about possible waning protection from the childhood acellular pertussis vaccine series.

After the diphtheria, tetanus, and whole-cell pertussis (DTwP) vaccine was introduced in the late 1940s, a dramatic decline occurred in the number of reported pertussis cases. However, whole-cell vaccine was commonly associated with local adverse events (eg, redness, swelling, and pain at the injection site) and less commonly with more serious adverse events.[3,4] These safety concerns prompted development and licensure of diphtheria, tetanus, and acellular pertussis (DTaP) vaccines, which were recommended by the

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Advisory Committee on Immunization Practices in 1992 for childhood booster doses at 15 to 18 months and 4 to 6 years of age and in 1997 for the complete 5-dose series, including the primary doses at 2, 4, and 6 months of age.[5] In 2006, an adolescent booster dose (Tdap) was recommended at age 11 to 12 years.[6] Recent studies have demonstrated waning protection following the current 5-dose DTaP schedule, but no study, to our knowledge, has compared fully vaccinated with unvaccinated children to estimate the durability of protection afforded by the childhood series.[7,8]

In 2010, California experienced its largest pertussis epidemic in more than 60 years; more than 9000 pertussis cases were reported and 10 infants died.[9] Concordant with national trends, a substantial burden of disease (67.9 cases per 100 000) occurred in 7- to 10-year-olds despite high DTaP coverage.[2] Concern about the number of cases in California and the increasing burden of pertussis among 7-to 10-year-olds prompted a large-scale assessment of the long-standing pertussis childhood vaccination program. The objectives of the investigation were to evaluate the association between pertussis and receipt of 5 DTaP doses by time since the fifth DTaP dose.

METHODS

Study Population and Design

We examined the association between pertussis disease and receipt of the 5-dose DTaP series using a case-control design. Fifteen California counties (26%) with high pertussis incidence (>15 per 100 000) or a high pertussis case count (>100) as of August 31, 2010, agreed to participate (Alameda, Del Norte, El Dorado, Fresno, Madera, Marin, Merced, Orange, Riverside, San Diego, San Luis Obispo, Santa Clara, Santa Cruz, Sonoma, and Stanislaus counties). These counties made up 40% of California's population in 2010. One invited county declined to participate.

Cases were all suspected, probable, and confirmed pertussis cases among children aged 4 to 10 years reported in the participating counties from January 1 through December 14, 2010; controls were children in the same age group who received care from the clinicians reporting the cases. Clinicians within the participating counties who reported a pertussis case(s) to their state or local health department during the assessment period were included in the assessment; clinics were dispersed throughout the counties with clustering observed around population centers as expected.

We collected demographic information (including race/ethnicity) and vaccine histories for cases and controls from clinician offices; a standardized protocol and abstraction form were used for medical record reviews. Controls were restricted to patients with a recent clinician visit to minimize case ascertainment bias. Data collection teams were trained on control selection; 3 controls per case were selected sequentially using appointment logs from the day(s) immediately preceding the abstraction date, excluding patients whose chief concern was cough illness. Because of the expected high correlation of age with the outcome of interest (time since fifth DTaP dose), controls were not age-matched to cases.

Selected demographic information included age, sex, race, ethnicity, insurance type, eligibility for the federally funded program for underinsured children (Vaccines for Children), and date of child's first visit to the clinician office. Vaccination dates, vaccine product, type, manufacturer, and lot number were collected for all pertussis-containing vaccines where available. Clinician vaccine history information was cross-referenced with state and local immunization registries; discrepancies were reconciled using medical records as the gold standard.

Pertussis Case Classification

The Council of State and Territorial Epidemiologists case definition was used to classify probable and confirmed pertussis cases.[10] A clinical case was defined as cough for 14 days or more and at least 1 of the following symptoms: whoop, posttussive vomiting, and paroxysmal cough. A confirmed case was defined as cough plus isolation of *Bordetella pertussis* in culture or a clinical pertussis case with either a positive polymerase chain reaction (PCR) test result or epidemiologic link to a confirmed case. Clinical cases that were not laboratory-confirmed or epidemiologically linked were classified as probable cases. The California Department of Public Health case definition also includes a suspected case category.[11] A suspected case was defined as cough with positive PCR result or cough with at least 1 other sign and an epidemiologic link to a confirmed case. Cases were classified using symptom information collected by routine public health case investigations. No additional symptom information was abstracted from patient charts.

Vaccine Histories

The total number of DTaP doses received was determined for each child. To account for the time needed to elicit an immune response following vaccination, doses received less than 2 weeks prior to case illness onset or control enrollment were not included in the final dose count. For our analyses, DTaP doses were considered on schedule if doses 1 through 3 were received at younger than 1 year, dose 4 was received between ages 1 and 2 years, and dose 5 was received between ages 4 and 6 years.[5] Participants were considered unvaccinated for pertussis if their medical record included a Personal Beliefs Exemption or other documentation of unvaccinated status and if their clinician vaccination record and immunization registry entry did not include any record of pertussis-containing vaccines. If unvaccinated status could not be confirmed using these methods, individuals with no record of vaccination were excluded from the analyses.

Statistical Analyses

Cases and controls were also excluded from all analyses if they had documented receipt of more than 5

Table 1. Exclusions From Estimation of Odds Ratios and Vaccine Effectiveness Overall and by Time Since Fifth DTaP Dose

Reason Excluded	No. (%) Cases (n = 1039)	No. (%) Controls (n = 3194)	*P* Value
Fewer than 5 DTaP doses recorded[a]	231 (22.2)	719 (22.5)	.58
DTaP doses were received off schedule[b]	105 (10.1)	379 (11.9)	.10
More than 5 DTaP doses recorded	15 (1.4)	40 (1.3)	.86
Tdap given ≥2 wk before enrollment	1 (0.1)	24 (0.8)	.01[c]
Received DTwP (whole-cell) vaccine	2 (0.2)	13 (0.4)	.38[c]
Case in previous year	3 (0.3)	3 (0.1)	.17[c]
Total excluded	**357** (34.4)	**1178** (36.9)	.15

Abbreviations: DTaP, diphtheria, tetanus, and acellular pertussis vaccine; DTwP, diphtheria, tetanus, and whole-cell pertussis; Tdap, adolescent booster dose.
[a] Includes participants with missing vaccination records.
[b] On-schedule definition: first 3 doses received at younger than 1 year; fourth dose received between ages 1 and 2 years; fifth dose received between ages 4 and 6 years.
[c] Calculated by Fisher exact test.

Table 2. Classification of Pertussis Cases Included in the Overall and Time Since Fifth DTaP Dose Analyses

	Cases, No. (%) (n = 682)
Confirmed	418 (61.3)
Culture	25
PCR	353
Epidemiologically linked to confirmed case	40
Probable	64 (9.4)
Suspected	174 (25.5)
PCR	168
Epidemiologically linked to confirmed case	6
Unclassified	26 (3.8)

Abbreviation: PCR, polymerase chain reaction.

DTaP doses, whole-cell vaccine (DTwP), or Tdap booster 2 or more weeks before enrollment, or if California Department of Public Health records indicated that they had had pertussis in a previous year. Vaccinated cases and controls were excluded from the analyses if they had missing vaccination records or fewer than 5 recorded DTaP doses. Statistical comparisons of demographic characteristics between cases and controls and vaccinated and unvaccinated participants were performed using the Pearson χ^2 test and a significance level of $P<.05$; the Fisher exact test was used for comparison of cells with fewer than 5 observations, and a 2-sided Wilcoxon rank-sum test was used to assess differences in age-related characteristics.

We used logistic regression to calculate odds ratios (ORs) for the association between pertussis and receipt of the 5-dose DTaP series and estimated vaccine effectiveness (VE) as $(1-\text{OR}) \times 100\%$.[12] Unvaccinated children were the reference group in all models, and standard errors were estimated accounting for the 2 levels of clustering by county and clinician. Time since fifth DTaP dose was calculated as number of months between the date of the fifth dose and the date of case illness onset or control enrollment. We calculated a Pearson product-moment correlation coefficient to assess the relationship between time since fifth DTaP dose and age at enrollment. The association between pertussis and time since completion of the 5-dose DTaP series was evaluated by assessing ORs for each year after receipt of the fifth dose: less than 12 months, 12 to 23 months, 24 to 35 months, 36 to 47 months, 48 to 59 months, and 60 months or more.[13] Sex, age at enrollment, and age at fifth dose were evaluated as potential confounders and effect modifiers.

To examine the influence of the pertussis case definition on the ORs and estimated VE, we restricted the analyses to confirmed cases only and compared the estimates with the unrestricted analyses. Additionally, we assessed the stability of these estimates by reintroducing previously excluded participants who had received at least 1 of the 5 DTaP doses off schedule and by excluding counties with a high percentage of unvaccinated participants (>5%).

Because the age distribution of controls showed possible nonrepresentativeness of the source population (ie, skewed younger), possibly due to well-child visits or the propensity to seek care as a function of age, we evaluated the potential effect of this age distribution on the overall and time since fifth DTaP dose estimates; 200 random samples of 1029 individuals were drawn from our control population, assuming an even age distribution of controls (n=147 in each age category from 4-10 years based on the original limiting number of 4-year-old controls). Median and 95% interval estimates (IEs) were calculated for these secondary analyses. All analyses were conducted in R software, version 2.13.0.[14]

This assessment was conducted as part of the public health response to the 2010 California pertussis epidemic and was designated a nonresearch program evaluation by both the Centers for Disease Control and Prevention Human Research Protection Office and the California Health and Human Services Committee for the Protection of Human Subjects. No cases or controls or their parents/guardians were contacted as part of the assessment.

RESULTS

The median 2010 pertussis incidence for the 15 participating California counties was 35.8 (range, 15.5-139.0) per 100 000 persons.[9] Data were collected for 1039 cases and 3194 controls from 265 clinician offices. Overall, 357 cases (34.4%) and 1178 controls (36.9%) were excluded from the analyses (TABLE 1). The proportion of cases and controls excluded was similar for all criteria except for Tdap given 2 or more weeks before enrollment; controls were significantly more likely to be excluded for this reason (24 controls vs 1 case; $P=.01$), although the numbers were small.

Of the 682 included pertussis cases, 418 (61.3%) were classified as confirmed, 64 (9.4%) as probable, and 174 (25.5%) as suspected cases (TABLE 2). The majority of confirmed (84.4%) and suspected (96.6%) cases were laboratory confirmed by PCR.

Demographic and vaccination characteristics of participants included in the analysis of time since completion of the 5-dose DTaP series are shown in TABLE 3. Cases were more likely than controls to be unvaccinated (7.8% [n=53] vs 0.9% [n=19]; $P<.001$) and female (55.0% [n=375] vs 47.5% [n=958]; $P=.001$). Cases were also older than controls ($P<.001$); the median ages of cases and controls were 9 and 7 years, respectively. The majority of both cases (68.7% [n=432]) and controls (71.9% [n=1436]) received their fifth DTaP dose at 4 years of age.

Seventy-two participants had not received any pertussis-containing vaccines. Unvaccinated participants were significantly more likely to be non-Hispanic than vaccinated participants (81.0% vs 44.9% of those with known ethnicity; $P=.001$) and 4 years of age vs older than 4 years (23.6% vs 5.8%; $P<.001$), although the median age for both unvaccinated and vaccinated participants was 7 years. All but 2 counties had 1 or more unvaccinated participants included in the analysis; the proportion of unvaccinated participants per county ranged from 0.6% to 9.4%, excluding a county with 1 unvaccinated and 2 vaccinated participants. There were no significant differences between unvaccinated and vaccinated participants by sex, race, insurance type, or Vaccines for Children eligibility. Unvaccinated children had 8.9-fold odds of being a pertussis case vs children who had received all 5 doses of DTaP (95% CI, 4.9-16.1).[15]

Overall and time since fifth DTaP dose estimates are shown in TABLE 4. Compared with controls (n=2016), children with pertussis (n=682) had a lower odds of having received all 5 doses of DTaP (OR, 0.11; 95% CI, 0.06-0.21 [estimated VE, 88.7%; 95% CI, 79.4%-93.8%]). When children were categorized by time since completion of the series, using an unvaccinated reference group, children with pertussis compared with controls were less likely to have received their fifth dose within the prior 12 months (19 [2.8%] vs 354 [17.6%]; OR, 0.02; 95% CI, 0.01-0.04 [estimated VE, 98.1%; 95% CI, 96.1%-99.1%]). This association was evident with longer time since vaccination, with ORs increasing with time since the fifth dose. At 60 months or longer (range, 60-83 months; n=231 cases [33.9%] and n=288 controls [14.3%]), the OR was 0.29 (95% CI, 0.15-0.54 [estimated VE, 71.2%; 95% CI, 45.8%-84.8%]). The estimated relative decline in VE was 27.4% from less than 12 months to 60 months or longer since fifth DTaP dose. Adjusting for sex did not measurably change the estimates (overall OR, 0.11; 95% CI, 0.06-0.20 [estimated VE, 89.0%; 95% CI, 79.6%-94.1%; relative decline in VE, 26.8%]).

Age at enrollment was strongly correlated with time since fifth DTaP dose ($r=0.95$; $P<.001$); including age in the time since fifth DTaP dose model offset the decline in estimated VE (estimated $VE_{<12\ \text{months}}$, 97.3% [95% CI, 93.4%-98.9%]; estimated $VE_{\geq 60\ \text{months}}$, 85.4% [95% CI, 76.4%-90.9%]; OR for age, 1.22 [95% CI, 1.05-1.41]). The analyses based on repeated random

Table 3. Selected Characteristics of Participants Included in the Estimation of Odds Ratios and Vaccine Effectiveness Overall and by Time Since Fifth DTaP Dose

Characteristics	No. (%) Cases (n = 682)	No. (%) Controls (n = 2016)	*P* Value
Sex			
Female	375 (55.0)	958 (47.5)	.001
Male	307 (45.0)	1053 (52.2)	
Missing data	0 (0.0)	5 (0.2)	
Age at enrollment, y			
4	23 (3.4)	147 (7.3)	<.001[a]
5	40 (5.9)	360 (17.9)	
6	56 (8.2)	366 (18.2)	
7	97 (14.2)	342 (17.0)	
8	104 (15.2)	313 (15.5)	
9	148 (21.7)	255 (12.6)	
10	214 (31.4)	233 (11.6)	
Race			
Black	10 (1.5)	43 (2.1)	.58
White	134 (19.6)	400 (19.8)	
Other/≥1 race	44 (6.5)	127 (6.3)	
Missing data	494 (72.4)	1446 (71.7)	
Ethnicity			
Hispanic	132 (19.4)	436 (21.6)	.29
Missing data	425 (62.3)	1229 (61.0)	
Insurance type			
Private	475 (69.6)	1392 (69.0)	.19
Medi-Cal	121 (17.7)	416 (20.6)	
Missing data	86 (12.6)	208 (10.3)	
Vaccines for Children program eligibility			
Yes	101 (14.8)	345 (17.1)	.42
Missing data	309 (45.3)	843 (41.8)	
Unvaccinated			
Yes	53 (7.8)	19 (0.9)	<.001
Age at fifth dose, y (n = 2626)			
4	432 (68.7)	1436 (71.9)	.11[a]
5	194 (30.8)	546 (27.3)	
6	3 (0.5)	15 (0.8)	

[a] Calculated using the Wilcoxon rank-sum test.

Table 4. Odds Ratios for Pertussis Disease Associated With Receipt of 5 DTaP Doses and Estimated Vaccine Effectiveness for Each Year Following the Complete DTaP Series

	Primary Analysis[a]				Secondary Analysis[b]		
Estimated VE Model	Cases, No. (n = 682)	Controls, No. (n = 2016)	OR (95% CI)	Estimated VE, % (95% CI)	Controls, No.	OR (95% IE)	Estimated VE, % (95% IE)
Overall No. of doses							
0	53	19	1 [Reference]	1 [Reference]	11	1 [Reference]	1 [Reference]
5	629	1997	0.11 (0.06-0.21)	88.7 (79.4-93.8)	1018	0.13 (0.08-0.16)	87.2 (83.6-91.9)
Time since fifth dose, mo							
0 doses	53	19	1 [Reference]	1 [Reference]	11	1 [Reference]	1 [Reference]
<12	19	354	0.02 (0.01-0.04)	98.1 (96.1-99.1)	230	0.02 (0.01-0.02)	98.3 (97.8-98.9)
12-23	51	391	0.05 (0.02-0.09)	95.3 (91.2-97.5)	158	0.07 (0.04-0.09)	93.4 (91.1-96.0)
24-35	79	366	0.08 (0.04-0.13)	92.3 (86.6-95.5)	154	0.11 (0.06-0.14)	89.5 (85.7-93.7)
36-47	108	304	0.13 (0.07-0.24)	87.3 (76.2-93.2)	140	0.16 (0.10-0.20)	84.1 (80.1-90.4)
48-59	141	294	0.17 (0.09-0.31)	82.8 (68.7-90.6)	158	0.18 (0.12-0.24)	82.0 (75.8-88.4)
≥60	231	288	0.29 (0.15-0.54)	71.2 (45.8-84.8)	178	0.27 (0.17-0.35)	73.3 (65.1-83.0)

Abbreviations: IE, interval estimate; OR, odds ratio; VE, vaccine effectiveness.
[a] ORs and estimated VE, accounting for clustering by county and clinic.
[b] Median and 95% IE based on 200 random, iterative samples of n=1029 controls and assuming an even distribution of controls in each age category from 4 to 10 years. When divided into "time since fifth dose" categories, the <12-month category captures a larger number of individuals (n=230) since the fifth dose can be administered at ages 4, 5, or 6 years.

sampling of controls to correct a possible age-associated bias in the selection of controls confirmed results from the primary analysis (overall OR, 0.13; 95% IE, 0.08-0.16 [estimated VE, 87.2%; 95% IE, 83.6%-91.9%; relative decline in VE, 25.4%]) (Table 4).

The ORs did not appreciably change when analyses were restricted to confirmed cases (overall OR, 0.10; 95% CI, 0.06-0.18 [estimated VE, 89.6%; 95% CI, 81.6%-94.1%; relative decline in VE, 24.5%]) or when participants who had received at least 1 DTaP dose off schedule were reintroduced into the analyses (overall OR, 0.11; 95% CI, 0.06-0.20 [estimated VE, 88.9%; 95% CI, 79.8%-93.9%; relative decline in VE, 24.2%]). To evaluate whether geographic clusters of vaccine exempters were influencing estimates, we excluded counties with a high percentage of unvaccinated participants (>5%); the overall OR and estimated VE remained stable, but there was a larger decrease in VE over time (overall OR, 0.12; 95% CI, 0.06-0.23 [estimated VE, 88.1%; 95% CI, 76.8%-93.8%; relative decline in VE, 30.7%]).

To evaluate whether age at administration of fifth DTaP dose modified the associations, we stratified the time since fifth DTaP dose analysis by age at receipt. For participants receiving the fifth dose at age 4 years, the overall OR was 0.11 (95% CI, 0.06-0.20) and estimated VE was 89.2% (95% CI, 80.5%-94.0%). For participants receiving the fifth dose at age 5 years, the OR was 0.13 (95% CI, 0.07-0.24) and estimated VE was 87.3% (95% CI, 76.3%-93.2%). Too few participants received DTaP at 6 years of age to allow for a stratified analysis at this age.

COMMENT

To our knowledge, this is the first large-scale assessment of the US 5-dose DTaP schedule conducted in the setting of a mature vaccination program and allowing for a comparison of fully vaccinated and unvaccinated children. We demonstrated that children with pertussis, compared with controls, had lower odds of having received the 5-dose DTaP series; as time since last DTaP dose increased, the odds increased, which is consistent with a progressive decrease in estimated VE each year after the final dose of pertussis vaccine.

Our estimated VE is within the range of prelicensure vaccine efficacy estimates based on 3 DTaP doses in infants (prelicensure efficacy range, 59%-89%).[5,16] One previous observational study of the US schedule estimated that the short-term effectiveness of 5 pertussis vaccine doses (DTwP and DTaP) among children up to 59 months (5 years) of age was 100%, although the number of 5-dose recipients was small (n=17).[17] Although similar to our estimate within the first year after vaccination (98.1%), the earlier study was initiated shortly after the Advisory Committee on Immunization Practices in 1997 issued the 5-dose DTaP recommendation, and the majority of older participants received DTwP for their first 3 doses.[17] Results from recent studies support our findings of declining estimated VE with time since receipt of the fifth DTaP dose, although none has compared fully vaccinated with unvaccinated children to directly estimate VE or classified pertussis cases based on clinical criteria, as defined by the national notifiable diseases pertussis case definition.[7,8,10]

Although a small proportion of children in California were susceptible to pertussis due to their unvaccinated status,[18] our findings suggest that waning of immunity following DTaP vaccination may have resulted in a much larger pool of susceptible individuals. In periods of increased pertussis transmission, the burden of disease attributable to the vaccinated but susceptible population is high.[19,20]

Other factors, such as changes in the *B pertussis* population leading to a vaccine strain mismatch or improved diagnosis and reporting, were also posited by the popular media and scientific community as factors contributing to the epidemic.[21,22] However, we would not expect increased cases due to these

factors to exhibit the clear age-related trend observed in surveillance data.[2] After a nadir at ages 5 and 6 years, incidence again increases in 7- to 10-year-olds, a likely reflection of waning of vaccine-induced immunity following the 5-dose series and prior to the adolescent Tdap booster at age 11 years.[2] Furthermore, the high estimated short-term VE in our study (estimated $VE_{<12\ \text{months}}$, 98.1%) strongly suggests that acellular vaccines remain effective against circulating *B pertussis* strains.

Case-control studies can have limitations such as unmeasured confounding, selection bias, and misclassification bias. To minimize the influence of these potential biases, we restricted our participant selection to active patients and accounted for possible correlations between individuals seeking care within the same clinic. In our study, the high vaccine coverage in controls is representative of the high coverage in this age group throughout the state of California, suggesting that we did not select controls with a higher propensity for vaccination than the general population. Additionally, since pertussis illness in vaccinated children is often less severe and the classic signs may not be present, our primary analysis included suspected cases that did not meet the clinical case definition.[23-25] Because a less specific case definition can have the effect of biasing results toward the null and underestimating VE by including noncases, we conducted a secondary analysis using confirmed cases only. The results did not change appreciably, indicating that our primary findings were not negatively influenced by misclassification bias.

The estimated VE can be biased upward when age is not taken into account, as the risk of pertussis generally decreases with age while vaccination coverage increases.[26] However, all vaccinated participants included in our main analyses had completed the 5-dose DTaP series, and our data did not reflect a trend of increasing vaccination coverage with age. Additionally, the majority of children in our study received their fifth DTaP dose at 4 years of age, leading to a strong correlation between age and time since the fifth dose ($r=0.95$; $P<.001$). Adjusting for age resulted in a smaller relative decrease in estimated VE over time, but the parameter estimate for age showed a substantial (22%) increase in the odds of pertussis for each year of age, which, independent of vaccination status, is unlikely. Therefore, our unadjusted results best describe waning immunity following vaccination. Our secondary analysis, assuming an even age distribution of controls, confirmed our primary, unadjusted estimates and provides strong evidence of no age-related selection bias.

The appearance of increasing risk in 7- to 10-year-olds correlates with the US change to acellular pertussis vaccines; the increase in pertussis incidence was initially noted among 7-year-olds in 2005, the first birth cohort to receive acellular vaccine for all 5 childhood doses.[27] Although differences in study methods, populations, case definitions, and vaccination schedules make any direct comparison between DTwP and DTaP difficult, previous observational studies of pertussis risk suggest that adequate levels of protection persist for at least 4 to 12 years following vaccination with whole-cell pertussis vaccines.[28-30] Of note, these evaluations were not specifically designed to assess duration of protection from DTwP, and the overall efficacy of whole-cell vaccines has been reported to vary widely across manufacturers and formulations.[16,28,31] Although the lower bound of this range (4 years) is similar to the timing of the largest decreases in estimated VE observed in this study, the shift in incidence to younger ages, as observed in recent national and state surveillance trends, suggests that vaccination with DTwP may have provided longer-lasting protection. The magnitude of the difference in duration of protection between DTwP and DTaP and the immunologic factors underlying the difference are unclear and need further study.

The increase in reported cases among children 7 to 10 years old is not unique to California. In 2010, a total of 34 states reported their second highest incidence among the 7- to 10-year-old age group (age groups: <1, 1-6, 7-10, 11-19, and ≥20 years).[2] Other states also experienced elevated overall rates of pertussis during 2010, supporting the premise that factors not specific to California were responsible for the increases. Both Minnesota and Iowa have DTaP coverage levels comparable with California but reported a higher incidence of pertussis in 2010; California's large population translated to significantly larger case counts than states with a smaller population size.[2,18] Continued monitoring of national surveillance data will help illuminate whether a cohort effect resulting from the DTwP to DTaP change adequately explains these recent age-related trends in pertussis.

The increasing incidence of pertussis, changing epidemiology, and demonstrated decline in the estimated DTaP VE over time have raised concerns about the current US pertussis vaccine program and may prompt consideration of alternative schedules. Options include delaying administration of the fifth DTaP dose or administering the Tdap booster at earlier than 11 years of age. However, a recommendation to delay the fifth DTaP dose until 6 years of age or later may unintentionally increase the burden of disease between the fourth and fifth doses of the childhood series, and implementation would likely be programmatically challenging because many states' school entry immunization requirements for pertussis are built around the current DTaP schedule. Alternatively, shifting the Tdap booster to 10 years of age or earlier may have the unwanted effect of reducing coverage, as there is no established routine health care visit for children before the adolescent vaccine platform visit at 11 to 12 years of age.[32]

Given the options for adjustments to the pertussis vaccine schedule, these issues will require careful and ongoing

review of the epidemiology and vaccine program nationwide. Ultimately, improved control of pertussis may require a vaccine that provides longer duration of protection or differently affects transmission in the community.

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