ORIGINAL ARTICLE

Waning Protection after Fifth Dose of Acellular Pertussis Vaccine in Children

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ABSTRACT

BACKGROUND

In the United States, children receive five doses of diphtheria, tetanus, and acellular pertussis (DTaP) vaccine before 7 years of age. The duration of protection after five doses of DTaP is unknown.

METHODS

We assessed the risk of pertussis in children in California relative to the time since the fifth dose of DTaP from 2006 to 2011. This period included a large outbreak in 2010. We conducted a case–control study involving members of Kaiser Permanente Northern California who were vaccinated with DTaP at 47 to 84 months of age. We compared children with pertussis confirmed by a positive polymerase-chain-reaction (PCR) assay with two sets of controls: those who were PCR-negative for pertussis and closely matched controls from the general population of health-plan members. We used logistic regression to examine the risk of pertussis in relation to the duration of time since the fifth DTaP dose. Children who received whole-cell pertussis vaccine during infancy or who received any pertussis-containing vaccine after their fifth dose of DTaP were excluded.

RESULTS

We compared 277 children, 4 to 12 years of age, who were PCR-positive for pertussis with 3318 PCR-negative controls and 6086 matched controls. PCR-positive children were more likely to have received the fifth DTaP dose earlier than PCR-negative controls ($P<0.001$) or matched controls ($P=0.005$). Comparison with PCR-negative controls yielded an odds ratio of 1.42 (95% confidence interval, 1.21 to 1.66), indicating that after the fifth dose of DTaP, the odds of acquiring pertussis increased by an average of 42% per year.

CONCLUSIONS

Protection against pertussis waned during the 5 years after the fifth dose of DTaP. (Funded by Kaiser Permanente).

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Pertussis is a worldwide, cyclic infection. Before widespread vaccine coverage, up to 270,000 cases of pertussis were diagnosed in the United States annually, with as many as 10,000 deaths per year, predominantly among infants.[1] Pertussis vaccines prepared from whole *Bordetella pertussis* organisms were available from the 1940s through the 1990s, protecting infants who were 2 months of age or older.[1]

Whole-cell pertussis vaccines, when administered as part of a combined diphtheria, tetanus toxoids, and pertussis vaccine, were effective, but they were associated with adverse effects[2]; this led to the development of the diphtheria–tetanus–acellular pertussis (DTaP) vaccine.[3] Beginning in the early 1990s, the United States started to make the transition from whole-cell pertussis vaccines to DTaP, and by the late 1990s, DTaP was being used for all five recommended doses.[4] DTaP is now used in many countries.

Pertussis vaccination resulted in a marked decrease in the incidence of disease,[1,5] with diagnosed cases of pertussis reaching a nadir in 1976. However, since the 1980s, despite high levels of vaccine coverage in children, outbreaks of *B. pertussis* have occurred every 3 to 5 years, with an increase in the peak incidence with each successive outbreak.[6] The reasons for the ongoing outbreaks are not well understood and are probably multifactorial.[7-9]

Receipt of five doses of DTaP is mandatory for school entry in many states, including California, with the fifth dose usually administered in children between 4 and 6 years of age. Nonetheless, in 2010, California had a large pertussis outbreak,[10] with the highest incidence rates since 1958. After this outbreak, we sought to assess and quantify the waning of DTaP protection against pertussis over time in a highly vaccinated population of school-age children who had received only DTaP rather than whole-cell pertussis vaccines.

METHODS

DATABASES

Kaiser Permanente Northern California is an integrated health care delivery system that provides care to approximately 3.2 million members. It operates 49 medical clinics and 19 hospitals, including pharmacies and laboratories. Databases capture vaccinations and laboratory tests, as well as inpatient, emergency department, and outpatient diagnoses.

Data on race or ethnic group were available in the medical record for approximately 75% of members. For the remainder, we imputed race or ethnic group with the use of the RAND Bayesian Imputed Surname Geocoding algorithm.[11] In members for whom we imputed values for missing data on race or ethnic group (American Indian or Alaska Native, Asian or Pacific Islander, black, Hispanic, or white), the probabilities summed to 1; a single value was not assigned. Microbiologic testing was centralized in a single laboratory that has identified *B. pertussis* and *B. parapertussis* with the use of polymerase-chain-reaction (PCR) assays since 2005. PCR kits were supplied by Roche from December 2005 through May 2009 and by Cepheid beginning in May 2009.

Kaiser Permanente Northern California first introduced DTaP for the fifth dose of pertussis vaccine in 1991 and completed the transition from whole-cell pertussis vaccines to DTaP for all five doses by 1999.

STUDY OVERSIGHT

The institutional review board of Kaiser Permanente Northern California approved this study and waived the requirement for informed consent.

All authors vouch for the completeness and accuracy of the data and analyses presented.

STUDY DESIGN AND POPULATION

In this case–control study, we selected case patients and controls for the primary analysis from all Kaiser Permanente Northern California members who received a pertussis PCR test result between January 2006 and June 2011. PCR results were positive for *B. pertussis*, positive for *B. parapertussis*, or negative for both.

Potential case patients were all children who were positive for pertussis and negative for parapertussis on PCR testing during the study period and who received a dose of DTaP between the ages of 47 and 84 months (this dose was considered the fifth DTaP dose) before the PCR test was performed. We excluded persons born before 1999 (to limit the analyses to children who exclusively received DTaP vaccines) and persons who received a vaccine with reduced pertussis-antigen content (Tdap) or any pertussis-containing vaccine after the fifth dose but before the PCR test. We also ex-

cluded children in whom a PCR test was performed within 2 weeks after receipt of the fifth DTaP dose and children who were not members of Kaiser Permanente Northern California for more than 3 months between the fifth dose of DTaP and the PCR test.

The study included two control groups. The first group consisted of children who were PCR-negative for both pertussis and parapertussis and who received a fifth dose of DTaP before receiving a negative test result (the PCR-negative controls). The second group consisted of health-plan members who were matched to each PCR-positive child (the matched controls). Matched controls were the same sex and age (year and quarter of birth), of the same race or ethnic group (with seven groups defined: six for available data on race or ethnic group and one for imputed data on race or ethnic group, to account for missing data), and attended the same medical clinic (of 49 clinics) as the PCR-positive children and were members on the date of the PCR test in the PCR-positive children (the anchor date). We retained all matched controls (with no sampling) who received a fifth dose of DTaP before their anchor date. We applied the same exclusion criteria described above to both control groups and excluded children as controls if they had previously tested positive for pertussis.

The final study population consisted of children who were 4 to 12 years of age, 58% of whom were continuously enrolled in the health plan between 1 month of age and either the date on which PCR was performed or the seventh birthday. In this subgroup, the rate of vaccine coverage with five doses of DTaP was 99% and did not differ between PCR-positive case patients and PCR-negative controls.

STATISTICAL ANALYSIS

We assessed the waning of immunity after DTaP vaccination using two analyses. The primary analysis compared PCR-positive case patients with PCR-negative controls, and the secondary analysis compared PCR-positive case patients with matched controls. We considered the comparison with PCR-negative controls to be primary because it minimized the potential biases associated with the general propensity to use health care and the specific propensity of parents and physicians to test for pertussis.

We fit conditional logistic-regression models to estimate the effect of each additional year after receipt of the fifth DTaP dose on the odds of a positive PCR test for pertussis. For the primary analysis, we conditioned the logistic model on blocks of calendar time (yearly from 2006 through 2009 before the epidemic, quarterly for the first quarter of 2010, and then monthly thereafter during the epidemic). We included covariates to adjust for age (4 to <7, 7 to <10, and 10 to 12 years), sex, medical clinic (49 clinics aggregated into 12 service areas), and race or ethnic group (in children for whom data were available or from imputed probabilities). For the secondary analysis, we conditioned the logistic model on all the matching variables (PCR test date, quarter of birth, sex, race or ethnic group, and medical clinic), and we used imputed probabilities of race or ethnic group as covariates for additional adjustment for the strata of children with imputed data. For all analyses, we used SAS software, version 9.2 (SAS Institute).

RESULTS

INCIDENCE OF PERTUSSIS

From January 2006 through June 2011, a total of 27,912 PCR assays for *B. pertussis* were performed in members of the health plan, regardless of age; of these tests, 1512 (5.4%) had a positive result. During the period from January 2010 through June 2011, when 95% of the cases of pertussis in the study population were diagnosed, the incidence of pertussis was 115 cases per 100,000 person-years among members younger than 1 year of age, decreasing to 29 cases per 100,000 person-years at 5 years of age, sharply increasing to 226 cases per 100,000 person-years at 10 and 11 years of age, sharply decreasing until 15 years of age, and remaining low in persons 15 years of age or older (Fig. 1). Ecologic data showing the percentage of persons who had received DTaP instead of whole-cell pertussis vaccines as infants, according to their current age, are shown in Figure 1.

CHARACTERISTICS OF THE STUDY POPULATION

Our study population included 277 children between the ages of 4 and 12 years who were PCR-positive for pertussis, 3318 PCR-negative controls, and 6086 matched controls. Table 1 lists characteristics of the case patients and controls.

Older age was associated with a higher percentage of positive PCR tests: 4.5% among 6-year-old children, 12.2% among 8-year-old children, and 18.5% among 10-year-old children. Increasing time since the fifth dose of DTaP was associated with an increasing percentage of positive PCR tests (Fig. 2). The time since the fifth dose of DTaP was significantly longer for PCR-positive children (1699 days; 95% confidence interval [CI], 1627 to 1772) than for PCR-negative controls (1028 days; 95% CI, 1003 to 1053) (P<0.001); case children received their fifth dose of DTaP significantly earlier than controls.

WANING OF DTaP EFFECTIVENESS

In the primary analysis comparing PCR-positive children with PCR-negative controls, with adjustment for calendar time, age, sex, race or ethnic group, and medical service area, the odds ratio for pertussis was 1.42 per year (95% CI, 1.21 to 1.66), indicating that each year after the fifth dose of DTaP was associated with a 42% increased odds of acquiring pertussis. A secondary analysis comparing PCR-positive cases with matched controls yielded similar results (Table 2).

SEVERITY OF PERTUSSIS

Cases of pertussis were mild or moderate in severity. Within 5 days before or after the PCR test, 272 of the 277 children had an outpatient encounter (98.2%), and 261 received a prescription for azithromycin (94.2%); 219 children received a diagnosis of whooping cough, cough, or pertussis exposure (79.1%); and 45 children received related diagnoses (respiratory infection, asthma, bronchitis, croup, or unspecified viral infections) (16.2%). Within 100 days before or after the PCR test, 11 of the children (4.0%) had emergency department visits related to pertussis; there were no hospitalizations or deaths related to pertussis.

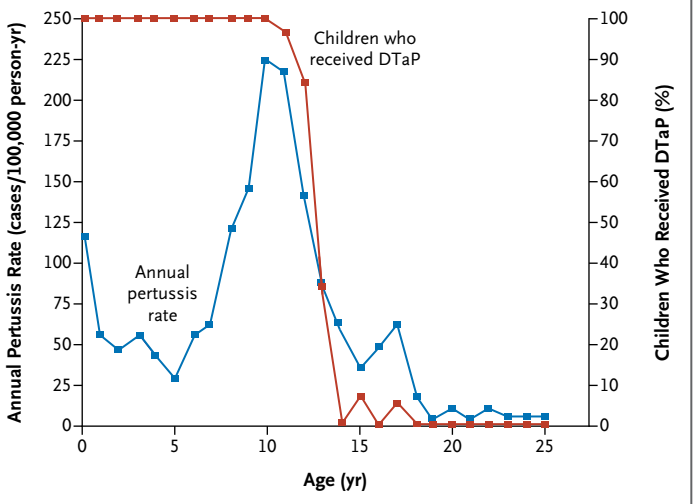

Figure 1. Annual Rate of Pertussis and Vaccination History in the Entire Health-Plan Population, According to Age, during the Pertussis Outbreak from January 2010 through June 2011.

The annual rate of pertussis (the number of cases per 100,000 person-years) for each age was calculated as follows: all cases of pertussis confirmed by a positive polymerase-chain-reaction (PCR) assay were divided by all person-years at risk and then multiplied by 100,000. Age was calculated on the date of the PCR test (for persons counted in the numerator) and on the last date of each month (for persons counted in the denominator). The percentage of members as of August 14, 2010, who were likely to have received diphtheria, tetanus, and acellular pertussis (DTaP) vaccine for all five doses (i.e., none of the doses were whole-cell pertussis vaccines) was calculated from population-based data on the timing of the transition in the health plan from diphtheria, tetanus, and whole-cell pertussis vaccines to DTaP vaccine. August 14, 2010, was the midpoint of cases (the median diagnosis date) during the 18-month period.

DISCUSSION

In the 2010 pertussis outbreak in California, a longer time since receipt of a fifth dose of DTaP was associated with an elevated risk of acquiring pertussis among children who had received all recommended acellular pertussis vaccines. In this study, the risk of pertussis increased by 42% each year after the fifth DTaP dose. If DTaP effectiveness is initially 95%, so that the risk of pertussis in vaccinated children is only 5% that of unvaccinated children, then the risk would increase after 5 years by a factor of 1.42^5 to 29% that of unvaccinated children. The corresponding decrease in DTaP effectiveness would be from 95% to 71%. The amount of protection remaining after 5 years depends heavily on the initial effectiveness. If the initial effectiveness of DTaP was 90%, it would decrease to 42% after 5 years. Regardless of the initial effectiveness, the protection from disease afforded by the fifth dose of DTaP among fully vaccinated children who had exclusively received DTaP vaccines waned substantially during the 5 years after vaccination.

The results of clinical trials evaluating the duration of protection conferred by DTaP vaccines after three or four doses suggested that protection against pertussis was sustained 5 to 6 years after

Table 1. Characteristics of PCR-Positive Children and Controls, January 2006–June 2011.*

Variable	PCR-Positive Children (N=277)	PCR-Negative Controls (N=3318)	P Value†	Matched Controls (N=6086)‡	P Value†
Male sex — no. (%)	121 (43.7)	1684 (50.8)	0.02	2659 (43.7)	1.00
Age — yr			<0.001		0.78
Mean	8.8±1.7	6.9±2.1		8.8±1.7	
Range	4–12	4–12		4–12	
Age distribution — no. (%)			<0.001		0.60
4 to <7 yr	36 (13.0)	1629 (49.1)		765 (12.6)	
7 to <10 yr	121 (43.7)	1164 (35.1)		2844 (46.7)	
10 to 12 yr	120 (43.3)	525 (15.8)		2477 (40.7)	
Year of PCR test — no. (%)			0.003		1.00
2006	2 (0.7)	97 (2.9)		44 (0.7)	
2007	1 (0.4)	102 (3.1)		22 (0.4)	
2008	6 (2.2)	107 (3.2)		132 (2.2)	
2009	6 (2.2)	155 (4.7)		132 (2.2)	
2010	201 (72.6)	2150 (64.8)		4416 (72.6)	
2011	61 (22.0)	707 (21.3)		1340 (22.0)	
Race or ethnic group — no. (%)§			<0.001		1.00
American Indian or Alaska Native	2 (0.7)	14 (0.4)		44 (0.7)	
Asian or Pacific Islander	23 (8.3)	547 (16.5)		505 (8.3)	
Black	9 (3.2)	216 (6.5)		198 (3.2)	
Hispanic	83 (30.0)	790 (23.8)		1824 (30.0)	
White	133 (48.0)	1328 (40.0)		2922 (48.0)	
Unknown and imputed	27 (9.7)	423 (12.7)		593 (9.7)	

* Plus–minus values are means ±SD. PCR denotes polymerase chain reaction.
† P values, which are based on comparisons between PCR-positive children and either PCR-negative controls or matched controls, were calculated with the use of the t-test for the continuous variable of age and with the use of the chi-square test for the rest of the variables.
‡ The controls were matched according to all the characteristics shown. The numbers and percentages in this column are weighted to indicate that the comparison of PCR-positive children with the matched controls was balanced in the analysis.
§ Race or ethnic group was determined from the medical record or was imputed in the case of missing data. The Hispanic ethnic group includes children of all races.

vaccination.[12-14] Other studies showed some waning of protection,[15-17] and several showed that increasing time since DTaP vaccination was a risk factor for vaccine failure, observations that are consistent with our findings.[17-19] Disease-free intervals after pertussis vaccination have decreased over the past two decades in Massachusetts.[20] A study in Canada showed that the transition from whole-cell pertussis vaccines to DTaP was associated with an increased incidence of pertussis among children who received only DTaP.[21] Taken together, these studies indicate that protection is less enduring with DTaP than with whole-cell pertussis vaccines.[22] The recent California epidemic provides data from a large population of children who only received acellular vaccines and for whom enough time had passed that we could quantify the extent to which DTaP protection waned.

The incidence of pertussis was highest among the population of children who were 8 to 11 years of age and who had received the full five-dose series of DTaP in childhood, suggesting that the waning efficacy of the fifth dose among school-age children played a key role in both allowing

and sustaining the recent pertussis outbreak. This observation was surprising because it is not until children reach their teenage years that they are usually considered to be a reservoir for pertussis,[23] and teenagers have been disproportionately affected in previous pertussis outbreaks.[20] Figure 1 shows that on a population basis, the incidence of pertussis decreased very sharply at 12 to 15 years of age, precisely the same ages of children who were likely to have received whole-cell pertussis vaccines as infants. These ecologic data show that the risk of pertussis was lower among older adolescents, who were likely to have previously received at least one dose of the whole-cell pertussis vaccine than among younger adolescents, who had exclusively received DTaP.

Most children in this study received their fifth dose of DTaP between 4 and 6 years of age. Thus, age and time since vaccination were highly collinear (r=0.97), and we were unable to fully separate out these two variables in the primary analysis involving PCR-negative controls. We could not entirely rule out the possibility that the incidence of pertussis among older children was higher because they were older rather than because of waning protection. The sharp increase in the incidence of pertussis among children 8 to 11 years of age, followed by a sharp decrease at 12 to 15 years (Fig. 1), is not characteristic of the epidemiology of pertussis in unvaccinated persons or in previous outbreaks. Furthermore, the secondary analyses involving controls who were closely matched for age showed that the association between the time since vaccination and the risk of pertussis was similar to that in the primary analysis. Therefore, it is more plausible to attribute the increased incidence of pertussis in children between 8 and 11 years of age to the waning effectiveness of DTaP rather than to aging.

The Centers for Disease Control and Prevention recommends routine administration of Tdap beginning at 11 years of age, with vaccination of children as young as 7 years of age in certain circumstances.[24] The limited duration of DTaP protection raises the question of whether routine administration of Tdap in younger children (e.g., 8-year-old children) is warranted. However, several issues must be clarified, including the effectiveness and duration of protection of Tdap, the possibility of increased local reactions with more frequent administration of Tdap, the increased cost and burden associated with earlier Tdap boosting (particularly since no other vaccines are routinely given at this age), and the risk of transmission to infants posed by mild-to-moderate pertussis infections that could be prevented with earlier Tdap boosting. Prevention of future outbreaks will be best achieved by developing new pertussis-containing vaccines that provide long-lasting immunity.

The large population in the health plan allowed controls to be matched to PCR-positive children on many potential confounders, and matched con-

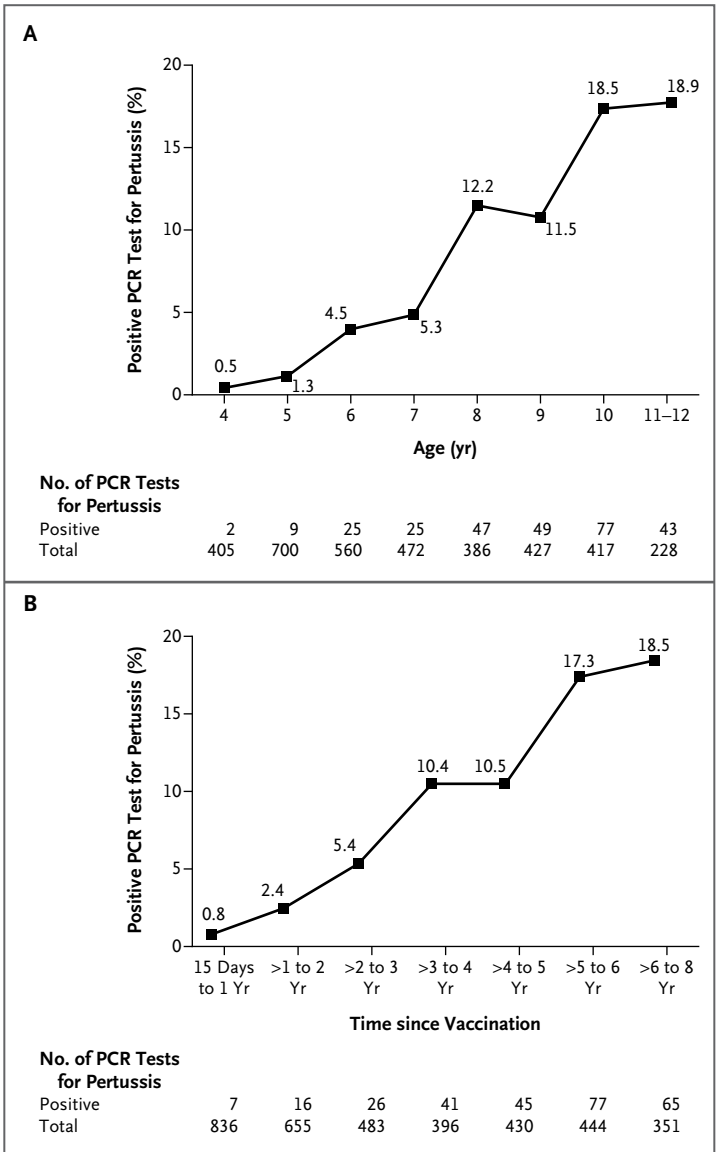

Figure 2. Percentage of PCR Tests That Were Positive for Pertussis from January 2006 through June 2011, According to Age and Time since Vaccination.

Table 2. Waning of Effectiveness per Year after Fifth Dose of DTaP Vaccine.

Group Compared with PCR-Positive Children	Odds Ratio for Pertussis (95% CI)	P Value
PCR-negative controls	1.42 (1.21–1.66)*	<0.001
Matched controls	1.50 (1.13–2.00)†	0.005

* The odds ratio was estimated on the basis of a conditional logistic-regression analysis that was stratified according to calendar time and included covariates to adjust for age, sex, race or ethnic group, and medical service area. This model deleted 10 observations for PCR-negative controls because of missing covariate data.

† The odds ratio was estimated on the basis of a conditional logistic-regression analysis that was stratified according to calendar time, age, sex, race or ethnic group, and medical clinic and included imputed probabilities of race or ethnic group as covariates to provide additional adjustment within the strata of children with imputed data.

trols were more similar to PCR-positive children than were PCR-negative controls on all measured potential confounders. However, matched controls were probably not as similar to PCR-positive children as PCR-negative controls were with respect to unmeasured potential confounders, such as the propensity to have undergone a PCR test to detect pertussis. Because we believe that such unmeasured confounders were probably a greater source of bias than the ones we were able to measure, we considered the analysis involving PCR-negative controls to be more informative.

Our study has several important strengths. One was that we compared PCR-positive children with two sets of controls and obtained similar results with each comparison. Another was that we had precise histories regarding the number of doses of vaccine received and the timing of vaccination and nearly complete demographic data for PCR-positive children and controls. Finally, we observed that older age was associated with an increasing proportion of positive PCR tests (Fig. 2); this supports our inference that the increase in the incidence of pertussis reflected a true increase in the incidence of disease rather than increased testing for pertussis.

Our study has limitations. First, although we estimated that the fifth dose of DTaP became 42% less effective each year, we could not anchor this estimate to the initial effectiveness of the vaccine because of the absence of an unvaccinated population. Second, it is possible that PCR testing misclassified a small fraction of persons (i.e., false positive and false negative tests). Since it was highly unlikely that such potential misclassification depended on the time since immunization, misclassification would imply that DTaP effectiveness may have waned even more than we estimated.

In conclusion, our evaluation of data from a large pertussis outbreak in California showed that protection from disease after a fifth dose of DTaP among children who had received only DTaP vaccines was relatively short-lived and waned substantially each year. Our findings highlight the need to develop new pertussis-containing vaccines that will provide long-lasting immunity.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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