

Comparative Effectiveness of Acellular Versus Whole-Cell Pertussis Vaccines in Teenagers



WHAT'S KNOWN ON THIS SUBJECT: The United States switched from whole-cell to acellular pertussis vaccines during the 1990s. Whether pertussis risk during a California outbreak differed between teenagers who previously received whole-cell or acellular pertussis vaccines early in life has not been reported.



WHAT THIS STUDY ADDS: We evaluated pertussis risk in 10 to 17 year olds at Kaiser Permanente Northern California during a recent pertussis outbreak. Those given whole-cell pertussis vaccines in childhood were more protected than those given acellular pertussis vaccines.

abstract

BACKGROUND: During the 1990s, the United States switched from combined diphtheria, tetanus toxoids, whole-cell pertussis (DTwP) vaccines to combined acellular pertussis (DTaP) vaccines because of safety concerns. After a 2010–2011 pertussis outbreak, we sought to evaluate whether disease risk in 10 to 17 year olds differed between those who previously received DTwP from those who received DTaP.

METHODS: A case-control study among individuals born from 1994 to 1999 who received 4 pertussis-containing vaccines during the first 2 years of life at Kaiser Permanente Northern California (KPNC). We separately compared pertussis polymerase chain reaction (PCR)-positive cases with PCR-negative and KPNC-matched controls. We assessed risk of pertussis relative to vaccine type in early childhood (4 DTwPs, mixed DTwP/DTaP, or 4 DTaPs) by using conditional logistic regression stratified for calendar time and adjusted for gender, race, medical clinic, and receipt of reduced antigen content acellular pertussis (Tdap) vaccine.

RESULTS: We compared 138 PCR-positive cases with 899 PCR-negative and 54 339 KPNC-matched controls. Teenagers who had received 4 DTwPs were much less likely to be pertussis PCR-positive than those who had received 4 DTaPs (odds ratio 5.63, 95% confidence interval 2.55–12.46) or mixed DTwP/DTaP vaccines (odds ratio 3.77, 95% confidence interval 1.57–9.07). Decreasing number of DTwP doses was significantly associated with increased pertussis risk ($P < .0001$).

CONCLUSIONS: Teenagers who received DTwP vaccines in childhood were more protected during a pertussis outbreak than were those who received DTaP vaccines. *Pediatrics* 2013;131:e1716–e1722

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KEY WORDS

pertussis infection, whole cell pertussis vaccine, acellular pertussis vaccine, teenagers

ABBREVIATIONS

CI—confidence interval

DTwP—diphtheria, tetanus toxoids, whole-cell pertussis

DTaP—diphtheria, tetanus toxoids, acellular pertussis

KPNC—Kaiser Permanente Northern California

OR—odds ratio

PCR—polymerase chain reaction

PY—person-years

Tdap—reduced antigen content acellular pertussis

Dr Klein led the design of the study, oversaw the data collection, interpreted the data, and was the lead author of the manuscript; Ms Bartlett collected the data, conducted the analyses, and made critical revision of the manuscript for important intellectual content; Mr Fireman contributed to study design, assisted with the analyses, and made critical revision of the manuscript for important intellectual content; Dr Rowhani-Rahbar contributed to study design and critical revision of the manuscript for important intellectual content; and Dr Baxter assisted with the study design, interpreted the data, and made critical revision of the manuscript for important intellectual content.

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Pertussis was widespread in the pre-vaccine era, with annually up to 270 000 cases diagnosed and as many as 10 000 deaths, predominantly among infants, in the United States.¹ Pertussis vaccines derived from whole *Bordetella pertussis* organisms and combined with diphtheria and tetanus toxoid (DTwP) were available from the 1940s to 1990s and were effective,¹ but were also associated with safety concerns,² which ultimately led to the development of acellular pertussis vaccines combined with diphtheria, tetanus toxoid (DTaP).³ By the late 1990s, the United States had switched from DTwP to DTaP vaccines for all 5 recommended infant and childhood doses.⁴

Despite high levels of vaccine coverage, since the 1980s pertussis epidemics have arisen every 3 to 5 years,⁵ with progressively higher incidence rates over time. Early clinical trials comparing DTwP with DTaP reported that both vaccines induced high levels of specific antibody titers and provided good protection against pertussis for several years,^{6–8} yet other studies have suggested that protection after DTaP is less enduring than after DTwP.^{9–11} Although reasons for the recurrent pertussis outbreaks are likely to be complex,^{5,12,13} waning protection after 5 doses of DTaP plays a central role, at least in recent epidemics.^{14,15} Since 2005, the Advisory Committee on Immunization Practices has recommended boosting with reduced antigen content acellular pertussis (Tdap) vaccine for persons 11 years and older.⁵

California, including the Kaiser Permanente Northern California (KPNC) population area, experienced the largest pertussis outbreak in more than 50 years during 2010–2011.¹⁶ The aim of this study was to evaluate risk of pertussis among 10 to 17 year olds in KPNC during this epidemic in relation to the

type of pertussis vaccine (ie, DTwP or DTaP) received in the first 2 years of life. This study also examined whether Tdap vaccination modified the relationship between vaccine type received in early childhood and subsequent pertussis risk in adolescence.

METHODS

Setting

KPNC is an integrated health care delivery system that provides care to ~3.2 million members, and operates 49 medical clinics and 19 hospitals, as well as its own pharmacies and laboratories. KPNC databases capture vaccinations, laboratory tests, and inpatient, emergency department, and outpatient diagnoses. Data on race or ethnic group were available for ~80% of all members, and were imputed for the rest by using the Rand Bayesian Imputed Surname Geocoding algorithm.^{14,17} For members with imputed values, we estimated the probability that of belonging to each of 6 racial and ethnic categories based on address and surname as of 2011.

Since late 2005, nearly all pertussis testing in KPNC was done by real-time polymerase chain reaction (PCR) in a single, centralized laboratory. KPNC has exclusively used pertussis PCR kits from Cepheid (Sunnyvale, CA) since 2009; all pertussis PCR tests used in this study were from Cepheid. PCR results were positive for *B pertussis*, positive for *B paraptussis*, or negative for both as previously described.¹⁴ KPNC introduced DTaP for the fifth dose in 1991, the fourth dose in 1992, the 3-dose primary series in 1997, and completed the transition from DTwP to DTaP for all 5 childhood doses by 1999. Persons born before 1999 either received all DTwP vaccines or a mix of DTwP and DTaP vaccines.

KPNC's Institutional Review Board approved this study.

Study Design and Population

We conducted a case-control study to assess pertussis risk among 10 to 17 year olds during the 2010–2011 outbreak according to pertussis vaccine type received in the first 2 years of life. All subjects received 5 doses of pertussis vaccines during childhood; virtually all subjects received DTaP for the fifth dose. We included individuals if they were born from 1994 to 1999, had received pertussis vaccine doses 1 through 4 at KPNC between ages 1 and 24 months, and had received a fifth pertussis vaccine by age 7.

We selected cases from all KPNC members who tested PCR-positive for pertussis between January 2010 and December 2011. We excluded individuals who had more than a 3-month membership gap between their 11th birthday (the age at which they could have received Tdap) and the PCR test to ensure accurate classification of Tdap vaccination status.

We identified 2 control groups. The first group consisted of members who tested PCR-negative for pertussis and paraptussis between January 2010 and December 2011 (“PCR-negative”). The second group consisted of individuals from the general KPNC population who matched to a PCR-positive case on gender, race or ethnic group, and medical clinic, and who were KPNC members on the day their matched case underwent the PCR test (“KPNC-matched controls”). We used all KPNC-matched controls and anchored the KPNC controls to the date of the PCR test of their matched case.¹⁴

We applied the same exclusion criteria to controls as for cases. We excluded individuals as controls if they had previously tested positive for pertussis.

Statistical Analyses

We used conditional logistic regression to estimate the effect of pertussis vaccine type on the risk of pertussis

after adjustment for calendar time, gender, race, medical clinic, and Tdap vaccination status. We included pertussis vaccine type in the regression models in 2 ways, either categorized as 4 doses of DTwP (reference category), mixed DTwP/DTaP doses, or 4 doses of DTaP, or as a continuous variable (with values 0 to 4 indicating the number of DTaP doses).

In separate analyses, we compared cases with PCR-negative controls and with KPNC-matched controls. Comparing cases with PCR-negative controls, we conditioned logistic regression models on blocks of calendar time (months during the peak of the epidemic and quarters before and after the peak months), and used covariates to adjust for gender, race, medical clinic, and Tdap vaccination status. Comparing cases with KPNC-matched controls, we conditioned logistic regression models on all the matching variables (PCR test date, gender, race or ethnic group, and medical clinic) and included a covariate to adjust for Tdap vaccination status. We considered subjects to have received Tdap if given 7 or more days before the PCR test (or anchor) date.

We also estimated the association of pertussis vaccine type and pertussis in 2 subgroups defined by Tdap vaccination status. We compared cases to PCR-negative and KPNC controls in adolescents with and without Tdap vaccination by using the same models described for the entire study population. We included an interaction term, Tdap-by vaccine type, in the regression model including all study subjects to test the significance of subgroup differences.

When vaccine type was categorized into 3 groups, we evaluated trend in pertussis risk across the 3 groups by using the Cochran-Armitage test.¹⁸ We used SAS software, version 9.2 (SAS Institute, Inc, Cary, NC) for all analyses.

RESULTS

From January 2010 to December 2011, a total of 22 297 pertussis PCR tests were performed on KPNC members of all ages, of which 1311 (5.9%) were positive. The incidence rate of pertussis varied according to year of birth. Incidence was low for those born before 1992 (5/100 000 person-years [PY]), higher for birth years 1992 to 1996 (34/100 000 PY), much higher for those born after 1996, highest for birth year 2000 (179/100 000 PY), and progressively lower for younger children born after 2000 (blue line, Fig 1). The incidence rate for persons born 1994 to 1999 (those eligible for the case-control analyses) was 78/100 000 PY. The mean number of DTaP vaccines received during the first 2 years of life increased from <1 dose for persons born in 1996 to 4 doses for those born in 1999 (red line, Fig 1).

In the study population (birth cohorts 1994 to 1999), 138 individuals were PCR-positive for pertussis, 899 were PCR-negative, and 54 339 served as KPNC-matched controls (Table 1). Among the 1037 PCR-tested individuals, 234 (22.6%) received all whole-cell doses in the first 2 years of life, 197 (19.0%) received a mix of whole-cell and acellular doses, and 606 (58.4%) received all acellular doses. Among the 197 who received a mix, 157 (79.7%) received 3 DTwP followed by 1 DTaP, 12 (6.1%) had 2 DTwP then 2 DTaP, 17 (8.6%) had 1 DTwP then 3 DTaP, and 11 (5.6%) received some other combination for the first 4 doses (4 had 3 DTwP and 1 DTaP in mixed order; 4 had 2 DTwP and 2 DTaP in mixed order; 3 had 3 DTaP and 1 DTwP in mixed order). Increasing number of DTaP doses from 0 to 4 was significantly associated with an increasing percentage of PCR tests positive for pertussis ($P < .001$ for trend; Fig 2).

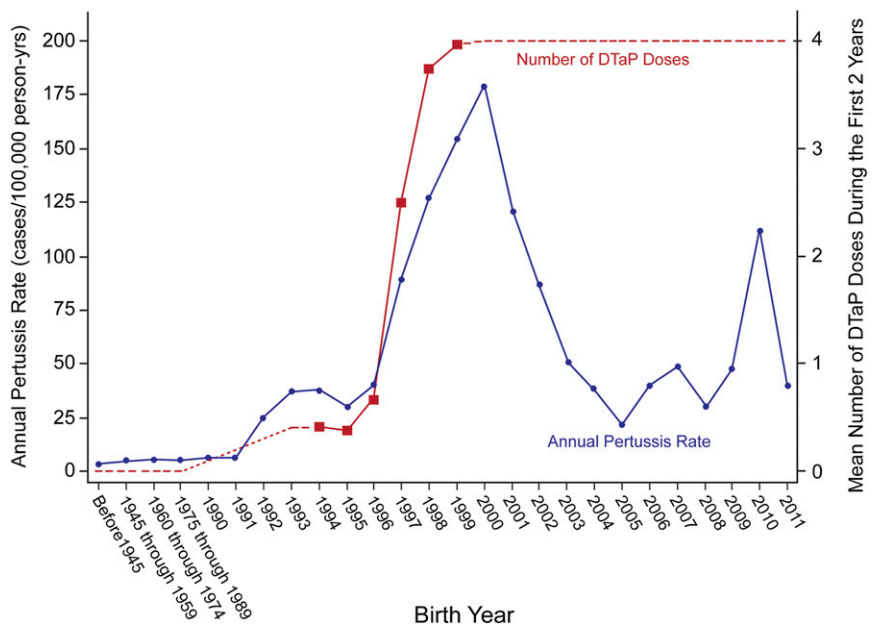


FIGURE 1

Annual rate of pertussis and pertussis vaccine type received during the first 2 years of life in the entire KPNC population from January 2010 to December 2011, by birth year. Blue line represents annual rate of pertussis per 100 000 PY calculated for each birth year cohort as follows: the sum of all PCR-confirmed pertussis cases in 2010 and 2011 was divided by all PY at risk and then multiplied by 100 000. Red line represents the mean number of DTaP doses received during the first 2 years of life for persons enrolled in the health plan as of August 2010. It was calculated based on the 25% to 40% of members in each birth year cohort who had received pertussis vaccine doses 1 through 4 at KPNC between 1 and 24 months of age. August 2010 was the median month of pertussis cases during the 2-year period.

TABLE 1 Characteristics of PCR-Positive Cases and PCR-Negative and KPNC Controls, January 2010 to December 2011

	PCR-Positive Cases, <i>n</i> = 138 (%)	PCR-Negative Controls, <i>n</i> = 899 (%)	KPNC-Matched Controls, <i>n</i> = 54 339 (%)
Male gender	72 (52.2)	429 (47.7)	28 351 (52.2)
Mean age ± SD (range)	12.0 ± 1.4 (10–17)	12.7 ± 1.8 (10–17)	13.0 ± 1.8 (10–17)
Birth year			
1994	5 (3.6)	93 (10.3)	7472 (13.8)
1995	3 (2.2)	99 (11.0)	8006 (14.7)
1996	12 (8.7)	123 (13.7)	8293 (15.3)
1997	23 (16.7)	140 (15.6)	9531 (17.5)
1998	49 (35.5)	197 (21.9)	10 538 (19.4)
1999	46 (33.3)	247 (27.5)	10 498 (19.3)
Age at anchored PCR test, y			
10	12 (8.7)	69 (7.7)	3147 (5.8)
11	52 (37.7)	235 (26.1)	9627 (17.7)
12	33 (23.9)	157 (17.5)	10 254 (18.9)
13	22 (15.9)	136 (15.1)	9492 (17.5)
14	12 (8.7)	134 (14.9)	8655 (15.9)
15	3 (2.2)	89 (9.9)	7306 (13.4)
16	3 (2.2)	72 (8.0)	5224 (9.6)
17	1 (0.7)	7 (0.8)	634 (1.2)
Year of PCR test			
2010	102 (73.9)	639 (71.1)	40 164 (73.9)
2011	36 (26.1)	260 (28.9)	14 175 (26.1)
Race			
American Indian/Alaska Native	5 (3.6)	11 (1.2)	1969 (3.6)
Asian or Pacific Islander	10 (7.2)	132 (14.7)	3938 (7.2)
Black	6 (4.3)	72 (8)	2363 (4.3)
Hispanic (regardless of race)	39 (28.3)	182 (20.2)	15 357 (28.3)
Imputed	1 (0.7)	21 (2.3)	394 (0.7)
White	77 (55.8)	481 (53.5)	30 320 (55.8)
First 4 doses received			
All whole cell	8 (5.8)	226 (25.1)	16 483 (30.3)
Mix	19 (13.8)	178 (19.8)	12 670 (23.3)
All acellular	111 (80.4)	495 (55.1)	25 185 (46.3)
No. of whole cell doses among those receiving mixed vaccine types			
1	4 (21.1)	16 (9.0)	999 (7.9)
2	1 (5.3)	15 (8.4)	980 (7.7)
3	14 (73.7)	147 (82.6)	10 692 (84.4)
Tdap vaccination status			
No	92 (66.7)	414 (46.1)	18 534 (34.1)
Yes	46 (33.3)	485 (53.9)	35 805 (65.9)

Comparing cases with PCR-negative controls, after adjusting for calendar time, gender, race, medical clinic, and Tdap vaccination status, the odds ratio (OR) of having a positive pertussis PCR test was 5.63 (95% confidence interval [CI] 2.55–12.46) among those who received 4 DTaP versus 4 DTwP, and 3.77 (95% CI 1.57–9.07) among those who received mixed DTwP/DTaP versus 4 DTwP. Comparing cases with KPNC-matched controls yielded similar results (Table 2). When compared with 4 doses of DTwP, the OR of a positive

pertussis PCR test according to the number of DTaP doses received was 1.40 (95% CI 1.20–1.62, $P < .001$), indicating that individuals had, on average, a 40% increased risk of pertussis for each additional acellular dose received (ie, each additional dose of DTwP foregone) between ages 1 and 24 months.

In subgroup analyses, among those who had not received a Tdap booster, the adjusted OR for 4 DTaP versus 4 DTwP was 9.92 (95% CI 1.31–75.31). Among the subgroup that had received the Tdap

booster, the adjusted OR was 4.85 (95% CI 1.92–12.21). The OR estimates from the 2 subgroups were not significantly different ($P = .54$ for the interaction term in the model comparing cases with PCR-negative controls). Results comparing cases with KPNC-matched controls were consistent, although not identical (Table 3).

Within 5 days before or after the PCR test, 137 (99.3%) of 138 cases had an outpatient visit; 113 (81.9%) received a whooping cough, cough, or pertussis contact or exposure diagnosis; another 22 (15.9%) received a related diagnosis (upper respiratory infection, asthma/wheezing, bronchitis, allergic rhinitis, atypical pneumonia, and sinusitis); and 128 (92.8%) received a prescription for azithromycin. Within 100 days before or after the PCR test, 4 children (2.9%) had an emergency department visit related to pertussis; of these, 1 child received 4 DTwP and 3 children received 4 DTaP. There were no hospitalizations or deaths related to pertussis.

DISCUSSION

The results of this study demonstrate that among teenagers, increased protection against pertussis correlated with previous receipt of whole-cell pertussis vaccines during the first 2 years of life. Teenagers who were vaccinated with 4 doses of DTaP vaccines were at almost 6 times higher risk of pertussis than were those who had received 4 doses of DTwP vaccines. Protection from pertussis appeared to be dose related, as persons who received mixed DTwP and DTaP vaccines had an intermediate level of risk between those who received all DTwP or all DTaP vaccines; those who received mixed vaccines were at nearly 4 times higher risk of pertussis than were those who received all DTwP vaccines. Further, when evaluating the number of acellular doses as a continuous variable, the risk of pertussis increased by an

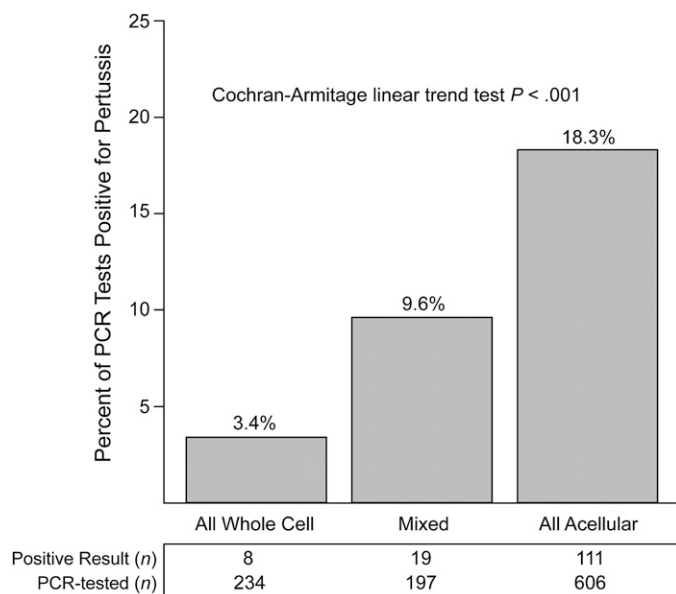


FIGURE 2

Percentage of pertussis PCR tests with a positive result in the study population by pertussis vaccine type for the first 4 doses received between 1 and 24 months of age, January 2010 to December 2011.

average of 40% for each additional dose when compared with 4 doses of whole-cell vaccine. These findings indicate that in the setting of a large pertussis outbreak, teenagers who received DTWP instead of DTaP during the first 2 years of life were substantially more protected against disease.

We previously showed that protection from the fifth dose of DTaP wanes substantially during the 5 years after vaccination in our study of children 4 to 12 years of age who had received only DTaP vaccine.¹⁴ Figure 1 depicts the effect of DTaP waning on pertussis incidence rates for persons born from 2000 onward. Our current study included only individuals born in 1999 or

earlier; thus, at least 5 years had passed (and usually more) since receipt of the fifth pertussis dose. This is an important consideration because the results presented here depend in part on the extent of fifth dose waning among DTaP recipients. For example, if individuals born in 2000 and 2001 had been included, we would predict some attenuation in the difference in risk of pertussis between all DTWP and all DTaP recipients because the youngest individuals would have had less fifth DTaP waning because of having received their fifth dose more recently.

The increased risk of pertussis associated with having received 4 doses of DTaP versus 4 doses of DTWP was seen in

both subgroups defined by Tdap vaccination status. Those who had not received a Tdap booster had a nearly 10-fold higher risk associated with having received 4 DTaP versus 4 DTWP doses, whereas the corresponding OR for those who had received the Tdap booster was nearly 5. The difference between these ORs was not statistically significant; this study had limited power to detect a meaningful difference in ORs between Tdap subgroups. These results indicate that a booster dose of Tdap does not overcome the advantage in protection from pertussis afforded to those who previously received 4 doses of DTWP. Despite this, boosting the newly emerging cohort of DTaP-only teenagers with Tdap remains the best means currently available to help protect this group against disease.

Notably, as a consequence of the birth cohorts range used in this study, virtually everyone included received DTaP for their fifth pertussis vaccine dose. Fig 1 illustrates that persons born 1991 and earlier had low incidence rates of pertussis. Although the dramatic rise in pertussis incidence began with the 1996 birth cohort, there was a slight rise in pertussis incidence among those born from 1992 to 1995, which may have been associated with the gradual transition to DTaP for the fourth dose.

The findings of this study are consistent with a previous Canadian study that observed that the transition from DTWP to DTaP was associated with increased pertussis incidence for children who received only DTaP.⁹ Another recent study in Australia also noted that children who had received 3 doses of DTaP had higher rates of pertussis in an outbreak than did children who had received 3 doses of DTWP.¹¹

It is well recognized that whole-cell and acellular pertussis vaccines trigger different immune responses in infants.^{19,20} Both vaccines yield high specific

TABLE 2 Risk of Pertussis Among Adolescents and Teenagers According to Vaccines Received During the First 2 y of Life, January 2010 to December 2011

Vaccine Type	PCR-Positive Cases Compared With	OR	95% CI	P Value
4 DTaP versus 4 DTWP	PCR-negative controls ^a	5.63	2.55–12.46	<.001
	KPNC-matched controls ^b	6.27	2.97–13.21	<.001
Mixed DTWP/DTaP versus 4 DTWP	PCR-negative controls ^a	3.77	1.57–9.07	.003
	KPNC-matched controls ^b	3.12	1.35–7.20	.008

^a Conditional logistic regression stratified by calendar time, and including covariates to adjust for gender, race or ethnic group, medical clinic, and Tdap vaccination status. This model deleted 2 observations for PCR-negative controls because of missing covariate data.

^b Conditional logistic regression stratified by calendar time, gender, race or ethnic group, and medical clinic, and including a covariate to adjust for Tdap vaccination status.

TABLE 3 Risk of Pertussis Among Adolescents and Teenagers According to Tdap Receipt and Vaccines Received During the First 2 y of Life, January 2010 to December 2011

Vaccine Type During First 2 Years of Life	Received Tdap	PCR-Positive Cases Compared With	OR	95% CI	P Value
4 DTaP versus 4 DTwP	No	PCR-negative controls ^a	9.92	1.31–75.31	.027
		KPNC-matched controls ^b	16.28	2.26–117.49	.006
	Yes	PCR-negative controls ^a	4.85	1.92–12.21	<.001
		KPNC-matched controls ^b	4.74	1.99–11.32	<.001

^a Conditional logistic regression stratified by calendar time, and including covariates to adjust for gender, race or ethnic group, and medical clinic. The model for each Tdap subgroup deleted 1 observation for PCR-negative controls because of missing covariate data.

^b Conditional logistic regression stratified by calendar time, gender, race or ethnic group, and medical clinic.

antibody titers after immunization, although whole-cell vaccines and natural infection produce Th1 cytokine responses, whereas acellular vaccines elicit mixed Th1/Th2 immune responses, which skew toward Th2 responses.^{21,22} Although it is not clear whether skewed Th2 cytokine responses fully persist throughout childhood,^{23–25} 1 study noted that 4-year-olds who received 5 doses of acellular vaccines had a pronounced immunoglobulin G4 subclasses response when compared with either DTwP-primed or naturally infected children, implying a Th2 skewed immune response,²⁶ whereas others have detected at least some Th2 cytokine response bias at 10 to 14 years of age.^{21,22,26,27} Similarly, adolescents primed with either whole-cell or acellular vaccines demonstrated strong humoral and cellular immune response after Tdap vaccination. However, those with a whole-cell history had higher titers to pertussis toxin, indicating that DTwP induced better B-cell memory priming.^{25,28} Taken together, these studies demonstrate that DTwP or DTaP vaccines administered to infants elicit fundamentally different immune

responses that at least partially persist through the teenage years, yet long-term clinical consequences of such differences have been unknown. The results presented here suggest that variations in immune responses induced by primary immunization during infancy with the 2 different vaccines play a central role in protection from disease years later.

An important strength of this study was complete capture of precise vaccine data, including vaccine type for every dose, for all cases and controls. We also had near complete demographic data on all subjects. Finally, our findings were strengthened by obtaining similar results using comparisons from 2 different control groups. The PCR-negative controls were probably more similar to the PCR-positive cases on unmeasured potential confounders, such as the likelihood to have been tested for pertussis, whereas the KPNC-matched controls were more similar to PCR-positive cases on all measured potential confounders.

A limitation in this study was that our analyses were not age adjusted because age was highly collinear with the

type of vaccine received and we were unable to statistically separate these 2 factors in the analyses. However, because we restricted the study population to persons born between 1994 and 1999, the age range was narrow and age differences were too small to plausibly explain the difference in risk observed between DTwP and DTaP. Yet, adolescents who received all whole-cell vaccines were older and farther away in time from their fifth dose than were those who received only acellular vaccines. If waning also occurs after whole-cell vaccine, then not adjusting for age may underestimate the increase in pertussis risk associated with DTaP compared with DTwP vaccines.

CONCLUSIONS

Adolescents who received 4 doses of whole-cell pertussis vaccines during the first 2 years of life were substantially more protected against pertussis during a large outbreak than were adolescents who had received 4 doses of acellular pertussis vaccines. Protection against disease further correlated with the number of whole-cell vaccines received. The benefits of whole-cell pertussis vaccines in terms of its more enduring protection from disease must be weighed against its safety concerns. Designing an optimal strategy to protect against pertussis will likely be complex. Future strategies could involve whole-cell vaccines, additional doses of acellular vaccines, and developing new vaccines. This study supports and highlights the need for new pertussis vaccines that provide both an improved safety profile and long-lasting immunity.

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