Pertussis Vaccine Effectiveness in the Setting of Pertactin-Deficient Pertussis

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abstract

BACKGROUND: In the United States, the proportion of *Bordetella pertussis* isolates lacking pertactin, a component of acellular pertussis vaccines, increased from 14% in 2010 to 85% in 2012. The impact on vaccine effectiveness (VE) is unknown.

METHODS: We conducted 2 matched case-control evaluations in Vermont to assess VE of the 5-dose diphtheria, tetanus, and acellular pertussis vaccine (DTaP) series among 4- to 10-year-olds, and tetanus, diphtheria, and acellular pertussis vaccine (Tdap) among 11- to 19-year-olds. Cases reported during 2011 to 2013 were included. Three controls were matched to each case by medical home, and additionally by birth year for the Tdap evaluation. Vaccination history was obtained from medical records and parent interviews. Odds ratios (OR) were calculated by using conditional logistic regression; VE was estimated as (1-OR) × 100%. Pertactin status was determined for cases with available isolates.

RESULTS: Overall DTaP VE was 84% (95% confidence interval [CI] 58%–94%). VE within 12 months of dose 5 was 90% (95% CI 71%–97%), declining to 68% (95% CI 10%–88%) by 5–7 years post-vaccination. Overall Tdap VE was 70% (95% CI 54%–81%). Within 12 months of Tdap vaccination, VE was 76% (95% CI 60%–85%), declining to 56% (95% CI 16%–77%) by 2–4 years post-vaccination. Of cases with available isolates, >90% were pertactin-deficient.

CONCLUSIONS: Our DTaP and Tdap VE estimates remain similar to those found in other settings, despite high prevalence of pertactin deficiency in Vermont, suggesting these vaccines continue to be protective against reported pertussis disease.

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WHAT'S KNOWN ON THIS SUBJECT: The recent resurgence in pertussis disease may be associated with the previously demonstrated waning immunity from acellular vaccines. However, little is known about the impact of genetic changes in the bacteria, such as the loss of pertactin, on vaccine effectiveness.

WHAT THIS STUDY ADDS: This is the first evaluation of pertussis vaccine effectiveness in the setting of pertactin deficiency. Our vaccine effectiveness estimates remain similar to those from other settings, despite the high prevalence of pertactin-deficient strains, suggesting pertussis vaccines continue to be protective.

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The US pertussis vaccine program began in the 1940s, with widespread use of diphtheria, tetanus, and whole-cell pertussis vaccine for the 5-dose childhood series. Safety concerns prompted whole-cell vaccine to be replaced with diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine (DTaP) in 1992 for the fourth and fifth doses given at 15 to 18 months and 4 to 6 years of age, and ultimately for the complete childhood series in 1997, including the primary doses at 2, 4, and 6 months of age.[1–3] Due to an increase of disease among adolescents and adults, a single adolescent booster dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) was recommended in 2006, with preferred administration at 11 to 12 years of age.[4] Although coverage for both vaccines is high, pertussis incidence is increasing, with 48 000 cases reported in 2012.[5–7] Of concern, the number of cases has increased among fully vaccinated children and adolescents, particularly among those who received only acellular vaccines as children.[8–10] Possible explanations for this include waning immunity, less protective immune responses induced by acellular pertussis vaccines, increased provider awareness and reporting, and more sensitive diagnostic techniques.[11–15] Additionally, genetic changes in the bacteria could have a role in the resurgence of disease. The proportion of pertussis strains in the United States lacking pertactin sharply increased from 14% in 2010 to 85% in 2012.[16–18] Pertactin is an autotransporter potentially involved in bacterial adhesion to the respiratory tract and resistance to neutrophil-induced bacterial clearance.[19,20] It is also a component of all acellular pertussis vaccines currently administered in the United States.[21] Pertactin deficiency may have evolved in response to acellular vaccine–induced selection pressure, providing an advantage to the bacteria.[18,22]

In 2012, an epidemic year for pertussis in the United States, Vermont reported the second highest pertussis incidence rate (103/100 000 population) in the country.[7] During this period, Vermont Department of Health Laboratory was one of a few laboratories in the nation that routinely cultured all specimens from suspected pertussis cases. This provided a unique opportunity to determine pertactin status for many pertussis cases in Vermont. An initial analysis demonstrated that of those cases with isolates available, >90% were pertactin-deficient.[18] It was in this setting of high pertactin deficiency that we sought to assess vaccine effectiveness (VE) and duration of protection of the 5-dose DTaP childhood series and the adolescent Tdap dose.

METHODS

Study Design and Population

To assess VE and duration of protection of DTaP and Tdap, we conducted 2 matched case-control studies. We included persons aged 4 to 10 years (born 2000–2009) and 11 to 19 years (born 1991–2002) for the DTaP and Tdap evaluations, respectively. All probable and confirmed pertussis cases reported to the Vermont Department of Health with cough onset from January 1, 2011, to December 31, 2013 were included, unless a medical home could not be identified for a case or it was based outside of Vermont. Cases were classified according to Vermont Department of Health definitions, a modified version of the Council of State and Territorial Epidemiologists definitions.[23,24] A clinical case was considered any person with cough illness lasting ≥2 weeks with paroxysms of coughing, inspiratory "whoop," or posttussive vomiting. A confirmed case was defined as any person with cough plus *Bordetella pertussis* isolation from a clinical specimen, or a clinical case with either a positive polymerase chain reaction (PCR) result or contact with a laboratory-confirmed case (epidemiologic link). A probable case was defined as a clinical case (ie, not laboratory-confirmed or epidemiologically linked to a laboratory-confirmed case).

Three controls were selected for each case, matched on medical home for the DTaP evaluation, and medical home and birth year for the Tdap evaluation. Controls were not matched on birth year for the DTaP evaluation due to the expected high correlation of age with vaccination status. Controls were randomly selected from patient rosters that included patients in the target age range with at least 1 clinic visit since January 1, 2006. Controls who had an out-of-state home zip code, only had an emergency or specialist visit at the medical home, or were suspected of having had pertussis in the previous 12 months were ineligible. The cough-onset date of the case was used as the enrollment date for each case and its matched controls.

Demographic information (age, gender, ethnicity, race, insurance, and Vaccines for Children program eligibility), and pertussis vaccination history were collected for all participants at their medical home by using a standardized abstraction form. Vaccine administration date, type, brand, manufacturer, and lot number were recorded for all pertussis-containing vaccines. If a participant's pertussis vaccination history was incomplete, pertussis-containing vaccine receipt was verified by interviewing parents. Of history provided by parents, only vaccinations with exact dates (day, month, year) were considered verified. Access to the Vermont Immunization Registry was limited by state law, and could not be used to verify vaccination history.[25]

Vaccination Definitions

The number of pertussis-containing vaccines received at least 14 days before the enrollment date was determined for each participant, based on vaccination dates documented in the medical chart or provided by parents. For the 5-dose DTaP series, participants were considered vaccinated on-schedule if they had received doses 1 to 3 at age <1 year, dose 4 at age 1 to <2 years, and dose 5 at age 4 to <7 years.[3] Participants who received 5 DTaP doses but did not meet this schedule were considered to be vaccinated off-schedule. Participants who received only 4 DTaP doses were considered vaccinated on a catch-up schedule if they had received doses 1 to 3 at age <4 years and dose 4 at age 4 to <7 years. Participants were considered unvaccinated with DTaP if no pertussis-containing vaccine was documented in their chart and nonreceipt was confirmed by a parent. If receipt of vaccination could not be confirmed for any of the DTaP doses by chart or parent interview, participants were classified with unknown vaccination status. Participants were considered vaccinated with Tdap if they had received 1 Tdap dose at age ≥11 years. They were considered unvaccinated if they had no Tdap documented in their chart and a parent confirmed nonreceipt. Participants without documentation of Tdap vaccination in their chart and for whom the parent interview was inconclusive were classified with unknown vaccination status.

B pertussis Pertactin Deficiency Determination

During the epidemic period, 66% of reported pertussis cases were confirmed by laboratory testing, and, of these, 80% were tested by the state laboratory, representing ~50% of all reported pertussis cases. All specimens sent to the state laboratory underwent both culture and PCR testing; other laboratories conducted only PCR testing. Specimens were cultured per standard procedure, and pertussis-positive cultures (73% of cultured specimens) were tested for pertactin deficiency at the Centers for Disease Control and Prevention (CDC) as described previously.[17,18]

Statistical Analyses

Participants were excluded from the analysis if their vaccination history was unknown, or if they had ever been reported to Vermont Department of Health as a previous pertussis case. Specific DTaP analysis exclusion criteria included the following: mis-administration of Tdap, Tdap receipt >14 days before enrollment to exclude individuals that had received both DTaP and Tdap vaccines, receipt of >5 DTaP doses, receipt of 5 DTaP doses off-schedule, or receipt of <5 DTaP doses. Tdap analysis exclusion criteria included the following: mis-administration of DTaP, receipt of >1 Tdap dose, receipt of Tdap before age 11 years, or receipt of Tdap before 2006. Individuals who had received a Tdap dose before 2006 were excluded as the record was likely to be erroneous because Vermont only introduced Tdap in 2006.

Demographics of cases and controls were compared by using matched odds ratios (ORs) from conditional logistic regression analyses; where cells had <5 observations, exact analyses were conducted. The 2-sided Wilcoxon rank-sum test assessed for differences in age-related characteristics.

For the primary analyses, conditional logistic regression was used to determine ORs for the association of pertussis with receipt of (1) 5-dose DTaP series on-schedule or (2) Tdap on-schedule. VE was calculated as $(1 - OR) \times 100\%$. Unvaccinated participants were used as the referent for all models. To evaluate duration of protection, ORs were calculated for time since receipt of fifth DTaP dose (classified as follows: <12, 12–23, 24–35, 36–47, 48–59, or >59 months) or Tdap (classified as follows: <12, 12–23, or >23 months).

To assess stability of the DTaP VE estimates, a number of sensitivity analyses were conducted by restricting the analytic population to the following: a combined group including 5 DTaP doses on-schedule and 4 doses on catch-up schedule; 5 DTaP doses regardless of schedule; 5 DTaP doses on-schedule, excluding public health districts with higher percentages of unvaccinated participants; and confirmed cases only and their matched controls.

Since 1993, the Vermont Immunization Program has purchased all recommended pertussis vaccines for children.[26] We reviewed Immunization Program–provided vaccine distribution data, and determined the transition to acellular pertussis vaccines occurred during 1997, after which we assumed that whole-cell vaccines were no longer available. We verified this assumption by cross-checking study-obtained lot numbers against manufacturer data. The primary analysis for Tdap VE was restricted to participants who had received only acellular vaccines for all childhood series and adolescent doses (born after 1997), although we attempted to evaluate Tdap VE among participants who received a mix of whole-cell and acellular vaccines (born 1997 or earlier). The stability of the Tdap VE estimates was assessed by conducting sensitivity analyses restricting the analytic populations to the following: 5 DTaP doses on-schedule, 5 DTaP doses regardless of schedule, and confirmed cases only and their matched controls.

All analyses were conducted in SAS 9.3 (SAS Institute, Inc, Cary, NC).

TABLE 1 Number and Percentage of Participants Who Met the 5-Dose DTaP Series VE Analysis Exclusion Criteria

Evaluation Type	DTaP				
	Case, n = 382		Control, n = 1113		P
	n	%	n	%	
Reasons for exclusion					
Vaccine history unknown	20	5.2	45	4.0	.32
Identified as pertussis case in surveillance data	—	—	3	0.3	—
Mis-administered Tdap[a]	1	0.3	4	0.4	.99
Received Tdap as part of catch-up schedule	3	0.8	7	0.6	.75
Received ≤4 of DTaP	50	13.1	203	18.2	.02
Received >5 of DTaP	6	1.6	20	1.8	.77
Received 5 doses of DTaP off-schedule[b]	44	11.5	136	12.2	.72
No. of excluded participants	119	31.2	387	34.8	.20
No. of participants included in overall VE evaluation	263	68.1	726	64.4	—

P values are derived from χ^2 test unless cell numbers are <5, then Fisher's exact test was used. If no participants matched the exclusion criteria or the P value was not determined the cell is blank.

[a] Tdap given outside of approved age range.

[b] DTaP on-schedule was defined as doses 1 to 3 before 12 months of age, dose 4 at 1 to <2 years, and dose 5 at 4 to <7 years.

Ethical Review

This evaluation was determined to be a public health evaluation and designated as nonresearch by CDC Human Research Protection Office and the Vermont Agency of Human Services.

RESULTS

From January 1, 2011, to December 31, 2013, 1252 pertussis cases were reported to Vermont Department of Health. Sixty-eight percent of patients were aged 4 to 19 years (n = 848) and, of these, 73% (n = 624) were reported during 2012. Twenty-eight patients (3%) were ineligible because their medical home was located outside of Vermont (n = 20), could not be determined (n = 7), or declined to participate (n = 1). Data were collected on 820 patients aged 4 to 19 years and 2369 controls from 91 medical homes. For 2673 participants (83.8%), vaccine history was confirmed by medical chart review, for 160 participants (5.0%), nonreceipt or incomplete pertussis vaccine history was verified by parental recall.

Five-Dose DTaP Series VE and Duration of Protection

Data were collected on 382 cases and 1113 controls aged 4 to 10 years to evaluate DTaP VE. Overall, 119 cases (31%) and 387 controls (35%) were excluded from analyses (Table 1). The proportion of cases and controls excluded was similar for nearly all exclusion criteria, except excluded controls were more likely than excluded cases to have received <5 DTaP doses.

Of the 263 cases included in the analysis, 71% (n = 186) were classified as confirmed and 29% (n = 77) as probable. Of confirmed cases, 83% (n = 154) were laboratory-confirmed and 17% (n = 32) were epidemiologically linked. Eighty-five specimens (representing 32% of all cases included in the DTaP analysis) were tested for pertactin deficiency; 83 (98%) of these were pertactin-deficient. Cases and controls had similar demographics, but cases were more likely to be older (P < .01) and unvaccinated (P < .01; Table 2). Age at receipt of fifth DTaP dose was similar for cases and controls (P = .32); however, the median time since receipt of the fifth DTaP dose was longer for cases (P < .01; Table 2).

For the primary analysis, the estimated overall VE of the 5-dose DTaP series on-schedule was 84% (95% confidence interval [CI] 58%–94%; Table 3). When participants were stratified by time since fifth DTaP dose receipt, the estimated VE within 12 months was 90% (95% CI 71%–97%). By 60 to 83 months, VE declined to 68% (95% CI 10%–88%; Table 3). Sensitivity analyses, including VE among confirmed cases only, were not substantially different from the primary analysis, with overlapping confidence intervals noted (Supplemental Table 6).

Tdap VE and Duration of Protection

Data were collected on 438 cases and 1256 controls aged 11 to 19 years to evaluate Tdap VE. Overall, 66 cases (15%) and 166 controls (13%) were excluded from analyses (Table 4). The proportion of cases and controls excluded was similar for all reasons.

Of the remaining 372 cases, 80% (n = 297) were classified as confirmed and 20% (n = 70) as probable. Of confirmed cases, 90% (n = 266) were laboratory confirmed and 10% (n = 31) epidemiologically linked. A total of 110 specimens (representing 30% of all cases included in the Tdap analysis) were tested for pertactin deficiency and 104 (95%) of these were pertactin-deficient. Cases and controls had similar demographics, but cases were more likely to be unvaccinated (P < .01; Table 5). Age at receipt of Tdap was similar for cases and controls (P = .13); however, median time since Tdap receipt was slightly longer for cases (30 months vs 26 months, P < .01; Table 5).

For the primary analysis of Tdap VE, which comprised participants who received only acellular vaccines, 244 cases (66% of all eligible cases) and 714 controls (66% of all eligible controls) were included. The estimated overall VE of the Tdap was 70% (95% CI 54%–81%; Table 3). When participants were stratified by time since Tdap vaccination, VE within 12 months was 76% (95% CI 60%–85%). By 24 to 46 months, VE declined to 56% (95% CI 16%–77%; Table 3). The Tdap VE estimates remained stable for all sensitivity analyses, including VE among

confirmed cases only, with CIs that overlapped those of the primary analysis (Supplemental Table 6). VE among participants who received a mix of whole-cell and acellular vaccines for the childhood series (born in 1997 or earlier) could not be estimated because of insufficient number in the referent group (n = 24).

Discussion

Our results provide the first estimates of VE against reported pertussis predominately caused by pertactin-deficient *B pertussis*. Remarkably, our findings are consistent with earlier published VE studies, even though >90% of tested isolates included in our evaluation were pertactin deficient.[11,12,27–31] For example, pertussis VE was assessed during the 2010 California outbreak (DTaP; VE 89%, 95% CI 79%–94%) and the 2012 Washington State outbreak (Tdap; VE 64%, 95% CI 50%–74%); the proportions of pertactin-deficient strains during these outbreaks were estimated to be 14% and 76%, respectively.[11,12,17,18] Our findings suggest that both acellular pertussis vaccines remain protective against reported pertussis disease in the setting of high pertactin deficiency.

The role of pertactin in pathogenesis is unclear, with potential roles in adhesion of the bacterium to respiratory tract epithelium and resistance to neutrophil-mediated clearance.[20,32] However, pertactin-deficient strains show no deficiency in growth or infection, suggesting a high level of redundancy in the genes responsible for these functions.[33,34] Pertactin deficiency thus far has not been associated with any detectable changes in the clinical disease process or disease severity.[18,35] In animal models, infection of a baboon with a pertactin-deficient strain showed no defect in colonization or leukocytosis compared with a pertactin-expressing strain, and infection of mice resulted in only minor deficiencies in lung colonization.[36,37] In humans, a higher proportion of patients infected with pertactin-expressing strains of *B pertussis* reported apnea, but otherwise there was no difference.[18,35]

The rapid increase in pertactin-deficient *B pertussis* in multiple countries, combined with evidence that several mutations can result in lack of pertactin, suggest pertactin deficiency may confer a selective advantage to the bacteria.[22,38–41] More specifically, several recent studies indicate pertactin deficiency may especially benefit the bacteria among a highly immunized population. For instance, pertactin-deficient strains were found to colonize mice primed with acellular pertussis vaccine more effectively than pertactin-expressing strains; a separate study found that acellular vaccinated individuals had two- to fourfold greater odds of being infected with a pertactin-deficient

TABLE 2 Demographic Characteristics of Cases and Controls Included in the Overall Estimation of 5-Dose DTaP Series VE

Characteristic	DTaP, n = 989				
	Case, n = 263		Control, n = 726		P
	n	%	n	%	
Gender					.88
Female	126	47.9	341	47.0	
Male	136	51.7	383	52.8	
Unknown	1	0.4	2	0.2	
Ethnicity					.99
Hispanic	1	0.4	5	0.7	
Non-Hispanic	207	78.7	521	71.8	
Unknown	55	20.9	200	27.5	
Race					.07
White	216	82.1	549	75.6	
Other	6	2.3	28	3.9	
Unknown	41	15.6	149	20.5	
Age at enrollment, y					<.01[a]
4–6	54	20.5	244	33.6	
7–8	62	23.6	254	35.0	
9–10	147	55.9	228	31.4	
Eligible for Vaccines for Children Program					
Yes	119	45.3	301	41.5	.23
No	104	39.5	312	43.0	
Unknown	40	15.2	113	15.6	
Insurance status					
Private	126	47.9	365	50.3	.54
Medicaid	119	45.2	314	43.2	
No coverage	1	0.4	8	1.1	
Unknown	17	6.5	39	5.4	
Vaccine status[b]					<.01
Unvaccinated	19	7.2	11	1.5	
Vaccinated	244	92.8	715	98.5	
Median age at vaccination, y (range)					
Vaccinated	5 (4–5)		5 (4–5)		.32[a]
Median time since fifth-DTaP dose, mo (range)					
Vaccinated	52 (33–64)		35 (18–53)		<.01[a]

P values presented are from matched ORs.

[a] Calculated using Wilcoxon rank-sum test.

[b] Participants classified as unvaccinated had no recorded pertussis-containing vaccines in their chart and had parental confirmation of nonreceipt; vaccinated participants had received 5 doses of DTaP on-schedule, defined as doses 1–3 at age <12 months, dose 4 at age 1 to <2 years, dose 5 at age 4 to <7 years.

TABLE 3 Estimates of the 5-Dose DTaP Series and Tdap Pertussis VE and Duration of Protection

Evaluation Type	Vaccine Status	Case	Control	OR (95% CI)	VE %	95% CI
DTaP		*n* = 263	*n* = 726			
Overall VE	Unvaccinated[a]	19	11	Ref	Ref	Ref
	5 doses DTaP on-schedule[b]	244	715	0.16 (0.06–0.42)	84	58–94
Time since fifth-DTaP dose, mo	Unvaccinated[a]	19	11	Ref	Ref	Ref
	<12	19	95	0.10 (0.03–0.29)	90	71–97
	12–23	21	144	0.07 (0.02–0.21)	93	79–98
	24–35	28	119	0.11 (0.04–0.31)	89	69–96
	36–47	33	120	0.13 (0.05–0.37)	87	63–95
	48–59	60	113	0.24 (0.09–0.67)	76	33–91
	60–83	83	124	0.33 (0.12–0.90)	68	10–88
Tdap		*n* = 244	*n* = 714			
Overall VE	Unvaccinated[c]	103	163	Ref	Ref	Ref
	1 Tdap dose on-schedule[d]	141	551	0.30 (0.20–0.46)	70	54–81
Time since Tdap dose, mo	Unvaccinated[c]	103	163	Ref	Ref	Ref
	<12	35	202	0.24 (0.15–0.40)	76	60–85
	12–23	51	180	0.37 (0.22–0.64)	63	37–78
	24–46	55	169	0.44 (0.23–0.84)	56	16–77

ORs were adjusted for medical home and age range for the DTaP VE analyses and for medical home and birth year for the Tdap analyses. The Tdap analyses focused on participants who had received acellular vaccines only for the childhood pertussis vaccine series.

[a] Unvaccinated DTaP participants had no recorded pertussis-containing vaccines in their chart and had parental confirmation of nonreceipt.

[b] Vaccinated DTaP participants had received 5 doses of DTaP on-schedule, defined as doses 1 to 3 at age <12 months, dose 4 at age 1 to <2 years, dose 5 at age 4 to <7 years.

[c] Unvaccinated Tdap participants had no recorded Tdap vaccine in their chart and had parental confirmation of nonreceipt.

[d] Vaccinated Tdap participants had received 1 dose of Tdap at or after age 11 years.

rather than a pertactin-expressing *B pertussis* strain.[18,22] Pertactin deficiency may also facilitate transmission by supporting longer infections: acellular-vaccinated mice infected with pertactin-deficient pertussis sustained longer infections than those infected with pertactin-expressing strains.[34] In addition, pertactin deficiency may result in improved transmission by avoidance of pertactin-specific vaccine-induced host immune responses. This would be especially relevant to acellular vaccine–primed individuals, in whom it has been demonstrated that antibodies to pertactin correlated with protection.[42] Through these mechanisms, pertactin deficiency may be amplifying the pertussis disease resurgence, especially in the setting of exclusive use of acellular vaccines that are associated with waning immunity and that fail to prevent *B pertussis* colonization and transmission.[43–45]

Because our findings suggest pertussis vaccines remain protective in the setting of high prevalence of pertactin deficiency, other vaccine components (pertussis toxin, filamentous hemagglutinin, or fimbriae) are likely preventing symptomatic pertussis. Antibodies against pertussis toxin were shown to correlate modestly with protection in 2 trials, and Denmark has used a mono-component pertussis toxin vaccine for >15 years with an estimated VE of 78%, although this efficacy is now being questioned.[42,46–48] However, data regarding protection elicited by filamentous hemagglutinin or fimbriae-specific immune responses are limited. Because correlates of protection are not well defined for pertussis, it is difficult to determine which vaccine components may be eliciting the necessary immune response.

TABLE 4 Number and Percentage of Participants Who Met the Tdap Dose VE Analysis Exclusion Criteria

Evaluation Type	Tdap				
	Case, *n* = 438		Control, *n* = 1256		*P*
	n	%	*n*	%	
Reasons for exclusion					
Vaccine history unknown	20	4.5	61	4.9	.82
Identified as pertussis case in surveillance data	—	—	10	0.8	—
Mis-administered DTaP[a]	0	0.0	2	0.2	.99
Received >1 Tdap dose	2	0.5	6	0.5	.99
Tdap given before 11 y of age	45	10.3	93	7.4	.06
Tdap given before 2006[b]	2	0.5	2	0.2	.27
No. of excluded participants	66	15.1	166	13.2	.33
No. of participants included in overall VE evaluation	372	84.9	1090	86.8	—

P values are derived from χ^2 test unless cell numbers are <5 then Fisher's exact test was used. If no participants matched the exclusion criteria or the P value was not determined the cell is blank.

[a] DTaP given outside of approved age range.

[b] Tdap was introduced in Vermont in 2006.

Case-control study designs are susceptible to a number of limitations, including information, selection, and misclassification biases. To mitigate these, controls were selected from the same

TABLE 5 Demographic Characteristics of Cases and Controls Included in the Overall Estimation of Tdap VE

Characteristic	Tdap, n = 1462				
	Case, n = 372		Control, n = 1090		P
	n	%	n	%	
Gender					.22
Female	197	53.0	527	48.3	
Male	172	46.2	558	51.2	
Unknown	3	0.8	5	0.5	
Ethnicity					.99
Hispanic	2	0.5	6	0.6	
Non-Hispanic	290	78.0	810	74.3	
Unknown	80	21.5	274	25.1	
Race					.06
White	313	84.1	844	77.5	
Other	10	2.7	57	5.2	
Unknown	49	13.2	189	17.3	
Age at enrollment, y					.45[a]
11–12	142	38.2	377	34.6	
13–14	132	35.5	430	39.5	
15–19	98	26.3	283	26.0	
Eligible for Vaccines for Children Program					.06
Yes	147	39.5	346	31.7	
No	150	40.3	461	42.3	
Unknown	75	20.2	283	26.0	
Insurance status					.22
Private	188	50.5	633	58.0	
Medicaid	148	39.8	366	33.6	
No coverage	6	1.6	16	1.5	
Unknown	30	8.1	75	6.9	
Vaccine status[b]					<.01
Unvaccinated	110	29.6	180	16.5	
Vaccinated	262	70.4	910	83.5	
Birth year					.99
Birth year <1998	128	34.4	376	34.5	
Birth year >1997	244	65.6	714	65.5	
Median age at vaccination, y (range)					
Vaccinated	11 (11–12)		12 (11–13)		.13[a]
Median time since Tdap, mo (range)					
Overall	30 (18–42)		26 (12–39)		<.01[a]
Birth year <1998	42 (34–54)		42 (33–52)		.54[a]
Birth year >1997	19 (12–28)		15 (7–26)		<.01[a]

P values presented are from matched odds ratios.

[a] Calculated using Wilcoxon rank-sum test.

[b] Participants classified as unvaccinated had no recorded Tdap in their chart and had parental confirmation of nonreceipt or had received a Tdap dose after or during the 14 days before enrollment; vaccinated participants had received 1 dose of Tdap at or after age 11 years.

medical home as the cases to ensure exposure to similar circulating *B pertussis* strains and to limit provider-associated diagnostic and reporting biases. To control for information bias, we collected vaccination history in a standardized manner. Although the evaluation was limited to 1 state where pertactin deficiency was extremely high, recent analyses of specimens from around the country showed similar high levels of pertactin deficiency associated with the same insertion sequence, extending the applicability of these findings to across the United States.[17,18] A further limitation was the low proportion of participants with confirmed pertactin status. All available culture isolates were tested for pertactin, but these represented only 40% of all cases included in the analyses: those that were Vermont state laboratory confirmed and *B pertussis* culture positive. Due to the low proportion of cases with confirmed pertactin status, the tested isolates may not be representative of all circulating pertussis strains. In addition, if there is a selective advantage to pertactin deficiency among vaccinated individuals, as suggested by Martin et al[18] and Safarchi et al,[22] we may expect more pertactin-expressing strains among unvaccinated cases. By including these cases, VE could be overestimated. Although a third of participants were excluded from the DTaP evaluation, the proportion of cases and controls excluded was similar for nearly all criteria, and is therefore unlikely to have biased our results. The one exception to this was the criteria for receipt of ≤4 doses DTaP: controls were more likely than cases to be excluded. This may be because controls were younger than cases, and therefore had less opportunity to complete their DTaP series before enrollment. Finally, our VE estimates are also unlikely to account for mild disease, which may be more prominent among vaccinated individuals and less likely to be reported.[49,50]

CONCLUSIONS

In summary, genetic changes in *B pertussis* may be one of the factors contributing to the recent resurgence in pertussis. We have shown that the current acellular vaccines continue to be effective in the setting of high pertactin-deficient *B pertussis* prevalence, and therefore remain the best way to protect against severe disease. However, further investigation is needed to better understand the implications of pertactin deficiency on pertussis pathogenesis and host immunologic response, which could provide

insight into the development of novel pertussis vaccines.

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ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
CI: confidence interval
DTaP: diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine
OR: odds ratio
PCR: polymerase chain reaction
Tdap: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
VE: vaccine effectiveness

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