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TDAP VACCINE EFFECTIVENESS AND DURATION OF PROTECTION AMONG ADOLESCENTS — CALIFORNIA, 2010

By

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Degree to be awarded: MPH
Executive MPH

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TDAP VACCINE EFFECTIVENESS AND DURATION OF PROTECTION AMONG ADOLESCENTS — CALIFORNIA, 2010

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An abstract of
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Abstract

TDAP VACCINE EFFECTIVENESS AND DURATION OF PROTECTION AMONG ADOLESCENTS — CALIFORNIA, 2010

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Margaret Atito Okomo-Adhiambo

Pertussis (whooping cough) is a highly contagious respiratory infection caused by *Bordetella pertussis.* In 2010, California experienced its largest pertussis epidemic in over 60 years. Despite high coverage with the 5-dose childhood diphtheria, tetanus, and whole cell or acellular pertussis vaccine series (DTP/DTaP) and a recommended tetanus-diphtheria-acellular pertussis (Tdap) booster at age 11-12 years, there were a significant number of cases among adolescents aged 11-18 years. Following this outbreak, an age-matched case-control study was conducted in 9 California counties by the Centers for Disease Control and Prevention (CDC) and the California State Department of Health (CSDH), to evaluate Tdap vaccine effectiveness (VE) and duration of protection among adolescents. Enrolled cases (n=349) were suspected, probable, and confirmed pertussis cases among adolescents aged 11 to 18 years from January through December 2010, identified through 2010 state surveillance data. Three age-matched controls per case (n=963) were selected from the same provider offices reporting the cases. Conditional logistic regression was used to calculate odds ratios (ORs) for the association between pertussis and Tdap receipt; vaccine effectiveness was estimated as (1-OR) x100%. ORs were also calculated for association between pertussis and time since Tdap receipt (<12 months, 12-23 months, 24-35 months, and ≥36 months), the association between pertussis and Tdap brand, and type of childhood pertussis series (whole cell and acellular pertussis vaccines). Among cases and controls, 183 (57.9%) and 321 (38.4%) had not received the Tdap booster, respectively. Adolescents with pertussis, compared with controls, were less likely to have received the Tdap booster (VE, 60.2%; 95% CI, 45.2%-71.2%; p<0.0001), and were also less likely to have received Tdap within the previous 12 months (VE, 73.2%; 95% CI, 57.7%-83.1%; p<0.0001). As time since Tdap vaccination increased, VE progressively declined, consistent with waning immunity from the Tdap booster.

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Introduction

Pertussis (whooping cough) is a highly contagious, vaccine-preventable, respiratory infection caused by *Bordetella pertussis.* The disease can affect all ages but is most severe in infants and young children [1,2]. Prior to the availability of pertussis vaccines in the 1940s, the United States (U.S.) reported >200,000 cases of pertussis annually, but the number of cases decreased dramatically following widespread immunization of infants with whole cell pertussis, tetanus, and diphtheria toxoid (DTP) vaccines [3]. Safety concerns regarding the whole cell component of DTP pertussis vaccines prompted the U.S. to switch to less reactogenic acellular pertussis vaccines (DTaP) in the 1990s [4,5]. In 1992, the U.S. Food and Drug Administration (FDA) licensed DTaP vaccine for use as the fourth and/or fifth doses of the recommended childhood series. In 1997, the Advisory Committee on Immunization Practices (ACIP) recommended that DTaP be used routinely instead of DTP as a 5-dose schedule at ages 2, 4, 6, 15-18 months, and 4-6 years [6]. Despite high DTaP vaccine coverage in infants and children, the U.S. has periodically experienced outbreaks of pertussis. Since the early 1980s, there has been a steady increase in the number of reported cases, especially among adolescents and adults [7-14].

The tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis (Tdap) vaccines were developed to improve protection against pertussis and reduce the burden of disease among adolescents and adults [15,16]. In 2005, two Tdap products, each containing reduced quantities of *B. pertussis* antigens compared to DTaP formulations, were licensed for use in the U.S. – Boostrix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) for use in persons aged 10-18 years, and Adacel™ (Sanofi Pasteur, Toronto, Canada) for those aged 11-64 years [17]. In 2006, ACIP recommended that adolescents aged 11-18 years should receive a single dose of Tdap instead of tetanus and diphtheria toxoids vaccine (Td) if they had completed

the recommended childhood DTP/DTaP childhood vaccination series [15,16]. Studies of Tdap vaccines have demonstrated effectiveness (VE range 64%-78%) [18-20], mostly limited to defined outbreak settings with small numbers of pertussis cases, and in populations who received whole cell pertussis vaccines as children. Recent studies [21,22] have reported effectiveness of the Tdap booster when administered to the emerging cohort of adolescents previously vaccinated entirely with acellular pertussis vaccines instead of whole cell formulations.

In 2010, California experienced the state's largest pertussis epidemic in over 60 years [13,23], with >9,000 reported cases and 10 deaths. An increase in the number of cases (36.4 per 100,000) was noted among adolescents aged 11-18 years [13], despite considerable Tdap coverage (71.2%) among California adolescents aged 13-17 years in 2010 [24]. A case-control assessment was subsequently conducted by the Centers for Disease Control and Prevention (CDC) and the California Department of Public Health (CDPH), in order to determine effectiveness of the Tdap booster and its duration of protection among adolescents aged 11-18 years.

The primary objectives of this study were to: 1) determine overall vaccine effectiveness (VE) and duration of protection of the Tdap booster vaccine among California adolescents; 2) evaluate Tdap VE for cohorts of adolescents who received a mix of whole cell and acellular pertussis vaccines versus those that solely received acellular vaccines for their childhood series; and 3) evaluate the effect of vaccine product on Tdap VE. The results of the Tdap VE evaluation presented in this report are preliminary; additional analyses are ongoing.

Methods

Study Population and Design

A matched case-control study was conducted in 2011 to retrospectively estimate Tdap vaccine effectiveness and duration of protection during the 2010 California pertussis outbreak (Figure 1). The assessment included 9 counties (Alameda, Fresno, Los Angeles, Marin, Orange, San Diego, San Luis Obispo, Santa Clara and Sonoma) that reported pertussis cases (suspected, probable, and confirmed) among 11 to 18 years olds between January 1 and December 31, 2010 and agreed to participate in the evaluation. Three controls per case were selected among active patients of the clinicians reporting pertussis cases. Active patients were defined as those who had received care from the provider in the 5 years preceding the outbreak and who did not have record of a discharge or transfer on file. Controls were age-matched to cases by birth year. Controls were ineligible for inclusion in the study if there was documented suspicion of pertussis in their medical chart or if they were not a California resident in 2010. The enrollment date for cases was their pertussis onset date, while that for age-matched controls was the case's onset date; all enrollment dates were in 2010. Demographic information, including age, sex, race, ethnicity, insurance type, and eligibility for the federally funded Vaccines for Children (VFC) program for underinsured children, were collected using a standardized protocol and abstraction form (Appendix 1). Due to feasibility constraints, data was not collected for all pertussis cases, 11-18 years of age, reported in the participating counties. Characteristics of included and non-included cases were compared to evaluate potential biases from the convenience sample.

Pertussis Case Classification

The Council of State and Territorial Epidemiologists (CTSE) case definition [25] was used to classify cases as follows: 1) Clinical cases – cough for ≥14 days and at least 1 of the following symptoms: whoop, posttussive vomiting, and paroxysmal cough; 2) Confirmed cases – cough plus isolation of *B. 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; 3) Probable cases – clinical cases not laboratory-confirmed or epidemiologically linked. The CDPH case definition also included a suspected case category [26], defined as cough with positive PCR result or cough with at least 1 other sign and an epidemiologic link to a confirmed case.

Pertussis Vaccine Histories

The Tdap vaccination status at the time of study enrollment was determined for both cases and controls by reviewing provider records, supplemented with information from state and local immunization registries. Medical records were the gold standard for reconciling discrepancies between clinician vaccine history information and immunization registries. If Tdap vaccination status remained unknown after reviewing both information sources, parents and guardians were contacted by telephone to verify the receipt or non-receipt of Tdap vaccine.

To account for the time needed to elicit an immune response following vaccination, participants with Tdap doses received <2 weeks prior to the case illness onset or control enrollment were classified as unvaccinated. Participants who received Tdap after their enrollment date were also classified as unvaccinated. Participants were excluded from the VE analysis if Tdap vaccination status remained unknown after attempted confirmation by parent phone calls, Tdap was administered at <10 years of age, or ≥2 Tdap doses were received. The

DTP/DTaP childhood series was considered up-to-date if the minimum number of doses by age were received as recommended by ACIP (doses 1 through 3 received at <1 year, dose 4 between 1-2 years, and dose 5 between 4-6 years) [6].

Statistical Analyses

Statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC). Demographic characteristics between cases and controls were compared using Wald X^2 (α=0.05) tests from conditional logistic regression. Conditional logistic regression was used to estimate the association of pertussis and Tdap receipt among adolescents aged 11-18 years old and calculate ORs. Adolescents unvaccinated with Tdap were the reference group in all models. Tdap VE was calculated as $(1-\text{OR}) \times 100\%$ [27]. Sex and age at Tdap were evaluated as potential confounders and effect modifiers of the overall OR. Time since Tdap vaccination was calculated as number of months between the date of the Tdap booster receipt and the date of illness onset for cases, or date enrollment for controls. Duration of protection was estimated by determining the association between pertussis and time since Tdap vaccination - ORs were determined for each year after receipt of the booster: <12 months, 12-23 months, 24-35 months, and ≥36 months.

Tdap VE was also estimated among subgroups with different pertussis vaccination histories including: 1) those who presumably received "mixed" (whole cell and acellular) childhood DTP/DTaP vaccine (birth years 1991-1996), those who received the "acellular" type (birth years 1998-1999) and the "transition" type (birth year 1997 – the year pediatric DTaP replaced pediatric DTP); 2) those who received a complete and on-schedule DTaP childhood series; 3) those who received Adacel™ or Boostrix™ brand of Tdap booster.

This assessment was conducted as part of the public health response to the 2010 California pertussis epidemic and was designated a non-research 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.

Results

The median 2010 pertussis incidence among the 9 participating California counties was 29.3 (range 13.8 to 140.7) per 100,000 [28]. Three-hundred and forty-nine (26%) of the total 1325 cases, ages 11-18 years, reported in the 9 counties were enrolled in the study. Data were collected for the 349 cases and 963 age-matched controls. A total of 33 cases (9.5%) and 126 controls (12.0%) were excluded from the Tdap VE analysis (Table 1). The proportions of excluded cases and controls were similar for all criteria. The majority of exclusions among cases (9.2%), and (11.1%) were due to unverified Tdap status. Due to these exclusions, some cases in the final VE analysis had <3 age-matched controls.

The demographic and vaccination characteristics of participants included in the analysis of Tdap VE and duration of protection are shown in Table 2. Cases and controls were similar by sex, ethnicity, age at enrollment, age at Tdap booster, insurance status, VFC eligibility, Tdap brand, birth year and assumed type of DTP/DTaP childhood series, as well as complete and on-schedule childhood pertussis vaccine series. However, cases were significantly more likely than the controls to be unvaccinated with Tdap (57.9% vs 38.4%). The majority of cases (84.2%) and controls (78.7%) had received the recommended 5 doses of the childhood DTP/DTaP childhood series; of those 85.7% of cases and 84.3% of controls had received the 5 doses on schedule. The median age at Tdap receipt was 12 years for both cases and controls.

Overall and time since Tdap OR estimates are shown in Table 3. Compared with controls (n=837), adolescents with pertussis (n=316) had a lower odds of having received the Tdap booster (VE, 60.2%; 95% CI, 45.2%-71.2%). Adjusting for sex did not change the overall OR and VE estimates (VE 60.0%; 95% CI, 45.0%-71.0%). However, adjusting for age at Tdap changed the overall ORs (by >10%) and the VE estimates (VE, 82.0%; 95% CI, 71.1%-88.8%).

When participants were categorized by time since Tdap receipt in months, using the unvaccinated group as reference, adolescents with pertussis compared to controls were less likely to have received their booster within the prior 12 months (VE, 73.2%; 95% CI, 57.7%-83.1%). The association was also evident with longer time since vaccination, with ORs increasing with time since Tdap. There was a relative VE decline of 14.2% between <12 months and 12-23 months since Tdap receipt (VE 62.8%; 95% CI, 39.8%-77.0%), and a decline of 51.9% between <12 months and 24-35 months (VE 35.2%; 95% CI, -9.5%-61.6%). There was a relative decline of 54.9% between <12 months and ≥ 36 months (VE, 33.1%; 95% CI, -19.1%-62.4%).

When participants were categorized by brand of Tdap booster, adolescents with pertussis compared to controls were less likely to have received Boostrix™ (VE, 70.3%; 95% CI, 28.8%-87.6%). This association was also evident with the Adacel™ brand (VE, 60.1%; 95% CI, 38.6%-74.0%]). To estimate Tdap effectiveness among adolescents who received a mix of whole cell and acellular, and those who received acellular, participants were categorized by their presumed type of DTP/DTaP vaccine received at childhood, based on birth year. Adolescents with pertussis compared to controls were less likely have received acellular DTaP (1998-1999 cohort) (VE, 73.7%; 95% CI, 52.7%-85.4%). This association was also evident for the mixed group (VE, 53.2%; 95% CI, 26.1%-72.1%) as well as the transition group (VE, 47.3%; 95% CI, 2.6%-71.5%). The Tdap VE for those with complete (5 doses) and on-schedule DTP/DTaP childhood series was 68.7% (95% CI, 39.0%-83.9%).

Subgroup analyses of time since Tdap (Table 4) restricted to participants who had 5 doses of DTP/DTaP on-schedule, those in the acellular (1998-1999) cohort, those in the mixed (1991-1996) cohort, and those who received Boostrix™ or Adacel™, respectively, were also performed. Overall, the subgroup VE estimates at <12 months since Tdap (Table 4) were consistent with the primary unrestricted estimates (Table 3), with evidence of decreasing duration of protection between <12 months and ≥36 months in most of the subgroups. When the duration of protection analysis was restricted to participants who had received a complete and on-schedule childhood pertussis vaccine series, the VE estimates were not appreciably different from the unrestricted analysis. Duration of protection analyses restricted to those with confirmed Adacel™ receipt were not appreciably different from the unrestricted results. However, the Boostrix™ numbers were too small to evaluate duration of protection following receipt of the brand.

To evaluate the potential bias from incomplete data collection, limited characteristics of pertussis cases enrolled in the study were compared to those not enrolled (Table 5). Enrolled and unenrolled cases were similar by sex and age at pertussis onset, but differed significantly by time of pertussis onset in months (p=0.001). Further analyses are ongoing, including an evaluation of the impact of pertussis case classification on the overall and duration of protection Tdap VE estimates.

Discussion

During the 2010 California outbreak, adolescents with pertussis, compared to controls, had lower odds of having received the Tdap booster, and as time since receipt of Tdap increased, the odds increased and VE decreased. Overall, Tdap VE among California adolescents aged 11-18 years was 60.2%. This VE was comparable to previously reported post-licensure VE

estimates for Tdap. One study investigating a pertussis outbreak in the U.S. Virgin Islands [19] reported Tdap VE of 66%, while one another showed Tdap VE of 92% in preventing clinical pertussis [18].

The findings of this study were consistent with a progressive decrease in estimated VE each year after the receipt of Tdap; VEs of 73.2%, 62.8%, 35.2%, and 33.1% were observed at <12, 12-23, 24-35 and ≥36 months since Tdap receipt, respectively. The estimates within three years since Tdap receipt (73.2%, 62.8% and 35.2%) were similar to those reported following a 2012 Wisconsin statewide pertussis outbreak among a cohort of adolescents born during 1998–2000, where Tdap VE was 75.3%, 68.2%, and 34.5% within three years since Tdap receipt, respectively [20]. In the present study, like the Wisconsin study above [20], estimated Tdap VE within 2 years of receipt were similar to those previously reported among adolescents (57.6%–74.4%) within 2 years since Tdap [19,21]. The decreasing effectiveness with increasing time since Tdap receipt were also similar to estimates from a case-control study conducted during the 2012 pertussis outbreak in Washington state among adolescents aged 11–14 years where estimated Tdap VE among adolescents who received acellular DTaP declined from 73.1% to 34.2%, respectively, <1 and ≥2 years after Tdap receipt [22].

The results of this study suggested differences in overall Tdap VE by brand (Boostrix™ VE=73.2%; Adacel VE=59.1%). These finding were consistent with those of a case-control study [22] conducted during the 2012 pertussis outbreak in Washington which reported overall Tdap VE of 60.1% for Boostrix™ and 48.8% for Adacel™ among adolescents aged 11–14 years. In the present study, when VE analysis for time since Tdap was restricted to Boostrix™ and Adacel™, respectively, the Tdap VE for Adacel™ was 69.3%, however, the Boostrix™ numbers were not sufficient for evaluating duration of protection following receipt of the brand. A previous study [20] reported differences in Tdap effectiveness by brand, with apparent waning of

immunity among recipients of both brands, although Boostrix™ appeared to be more effective in preventing pertussis than Adacel™ (VE, 90.6% vs 61.3% in 2012; 78.9% vs 58.1% in 2011; 59.5% vs 26.8% in 2010; and 40.1% vs 12% in 2008/2009).

In the present study, there were apparent differences in overall Tdap VE by type of DTP/DTaP childhood series, based on birth cohorts (73.7% for the acellular [1998-1999] cohort, 53.2% for the mixed [1991-1996] cohort, and 47.3% for the transition [1997] cohort). Although these results initially seem in contrast with studies that suggest children who received only acellular pertussis vaccines have increased pertussis risk compared with those who received whole-cell vaccines [29-31], when VE analyses for time since Tdap were restricted to the respective mixed and acellular cohorts, the Tdap VE for the mixed cohort was 79.7% at <12 months since Tdap receipt, compared to 66.3% for the acellular group. The VE among the mixed group decreased with time since Tdap. Vaccine effectiveness for the acellular group could not be calculated beyond 12-23 months since receipt of Tdap due to small or zero cell counts, limiting the duration of protection comparison between the mixed and acellular cohorts.

Case-control studies can be impacted by unmeasured confounding, selection bias, and misclassification bias. Since pertussis is a rare disease in the U.S., affecting ~0.02% of overall California population in 2010 [28], the ORs are assumed to be a good estimate of the risk ratio. Approximately 70% of race and ethnicity data were missing for both cases and controls, precluding an in-depth analyses of these data. Information on race is typically captured during pertussis case investigations. However, we restricted data on race to those captured from participant medical records in order to maintain comparable data sources between cases and controls. To reduce misclassification bias of the main outcome variable, Tdap vaccine status was verified using three different sources – records, vaccine registries and parental interviews. Potential bias from incomplete data collection was evaluated by comparing cases enrolled in the

study versus those not enrolled; there were no significant differences between the two groups, except for the month of disease onset; however, this observation was unlikely to impact VE estimates.

The national resurgence in reported pertussis cases, especially the increase among adolescents, is likely driven by factors such as increased recognition and reporting by physicians, improved laboratory diagnostics, and waning of immunity following vaccination with the childhood pertussis vaccine series and the Tdap booster. It is also thought that changes in the organism may be contributing to the resurgence [32]. Sustained monitoring of disease burden and vaccine effectiveness in fully vaccinated children will be important to assess ongoing risk. Additionally, as options are explored regarding improved vaccine formulations for the future, it will be important to generate further immunologic and epidemiologic data to investigate determinants of waning immunity with Tdap, as well as acellular DTaP vaccines. Maintaining strong DTaP and Tdap immunization programs is critical to control of pertussis in this era of increased disease circulation.

Conclusion

The results of this study provide additional evidence of waning protection from Tdap vaccination. Tdap vaccination was moderately protective against pertussis during the 2010 outbreak in California. These findings emphasize the need for novel pertussis vaccines that can induce durable, highly effective immunity to prevent pertussis outbreaks. However, reinforcing current best practices such as vaccination education and achieving high coverage are still the best options against pertussis.

TABLES

Table 1. Exclusions from Estimation of Odds Ratio and Overall Vaccine Effectiveness

Reason excluded	No. (%)	
	Cases (n=349)	**Controls (n=963)**
Unverified Tdap status	32 (9.2)	116 (11.1)
≥2 Tdaps doses recorded	1 (0.3)	9 (0.9)
Other	0 (0.00)	1 (0.1)
Total excluded	**33** (9.5)	**126** (12.1)

Abbreviations: DTaP, diphtheria, tetanus and acellular pertussis vaccine; DTP, diphtheria, tetanus, and whole cell pertussis vaccine; Tdap, adolescent booster dose.

Unverified Tdap status - Tdap vaccination status unknown.

Other – Non-resident of CA in 2010.

Table 2. Characteristics of Participants Included in the Analysis for Evaluation of Tdap Vaccine Effectiveness and Duration of Protection (n=1153), California, 2010

Characteristics	No. (%)		*p*-value[a]
	Cases (n=316)	Controls (n=837)	
Sex			
Female	150 (47.5)	398 (47.6)	0.774
Male	166 (52.5)	424 (50.7)	
Missing	0 (0.0)	15 (1.8)	
Race			
Black	2 (0.6)	16 (1.9)	
White	69 (21.8)	163 (19.5)	0.021
Other (>1 Race)	21 (6.7)	56 (6.7)	
Missing	221 (69.9)	586 (70.0)	
Ethnicity			
Hispanic	71 (22.5)	146 (17.4)	0.328
Non-Hispanic	41 (36.61)	106 (42.06)	
Missing	204 (64.6)	585 (69.9)	
Birth Year (DTP/DTaP)[b]			
1991-1996 (Mixed)	117 (37.0)	331 (39.6)	0.213
1997 (Transition)	60 (19.0)	184 (22.0)	
1998-1999 (Acellular)	139 (44.0)	322 (38.5)	
Age at Tdap, years – median (range)	12 (11-18)	12 (11-18)	0.849
Insurance Type			
Private	224 (70.9)	573 (68.5)	0.656
Medi-Cal	73 (23.1)	179 (21.4)	
Missing	3 (1.0)	27 (3.2)	
Vaccines for Children (VFC) Eligibility			
Yes	80 (25.3)	181 (21.6)	0.143
Missing	10 (3.2)	48 (5.7)	
Vaccinated with Tdap booster			
Yes	131 (41.5)	501 (59.9)	<0.0001
No	183 (57.9)	321 (38.4)	
Missing	2 (0.6)	15 (1.8)	
Tdap Brand[c]			
Boostrix™	9 (6.9)	43 (8.6)	0.518
Adacel™	66 (50.4)	245 (48.9)	
Unknown	56 (42.8)	213 (42.5)	
Complete and on-schedule DTP/DTaP childhood series[c]			
Yes	228 (72.15)	555 (66.31)	0.122
No	38 (12.0)	108 (21.15)	
Missing	50 (15.8)	174 (20.8)	

Abbreviations: DTaP, diphtheria, tetanus and acellular pertussis vaccine; DTP, diphtheria, tetanus, and whole cell pertussis vaccine; Tdap, adolescent booster dose.

[a] X^2 p-value.

[b] Presumed DTP/DTaP type based on birth year

[c] 5-doses of DTP/DTaP received on-schedule.

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Table 3. Matched Odds Ratios for Pertussis Disease with Receipt of Tdap Booster and Estimated Vaccine Effectiveness, California, 2010

Estimated VE Model	Cases (n=314)[a]	Controls (n=822)[a]	Matched OR (95% CI)	Estimated VE, % (95% CI)	*p*-value[b]
Tdap booster received					
No	183	321	1 (Reference)	--	
Yes	131	501	0.40 (0.29,0.55)	60.2 (45.2,71.2)	<0.0001
Time since Tdap booster, months					
No Tdap	183	321	1 (Reference)	--	
<12	30	194	0.27 (0.17,0.42)	73.2 (57.7,83.1)	<0.0001
12-23	34	134	0.37 (0.23,0.60)	62.8 (39.8,77.0)	<0.0001
24-35	35	88	0.65 (0.38,1.10)	35.2 (-9.5,61.6)	0.101
≥36[c]	32	85	0.67 (0.38,1.19)	33.1 (-19.1,62.4)	0.178
Brand of Tdap Brand					
No Tdap	183	321	1 (Reference)	--	
Boostrix™	9	43	0.28 (0.12,0.66)	72.3 (34.5,88.3)	0.004
Adacel™	66	245	0.41 (0.28,0.60)	59.1 (40.0,72.1)	<0.0001
Unknown	56	213	0.41 (0.28, 0.62)	58.8 (38.2,72.5)	<0.0001
Complete and on-schedule DTP/DTaP childhood series[d]					
No Tdap	183	321	1 (Reference)	--	
Yes	104	356	0.31 (0.16, 0.61)	68.7 (39.0,83.9)	0.0006
No	14	67	0.45 (0.32, 0.63)	55.4 (36.8,68.5)	<0.0001

Abbreviations: DTaP, diphtheria, tetanus and acellular pertussis vaccine; DTP, diphtheria, tetanus, and whole cell pertussis vaccine; Tdap, adolescent booster dose.

[a] Missing values excluded.

[b] Wald X^2 p-value.

[c] Months since Tdap: median=50; range 36-64 months.

[d] 5-doses of DTP/DTaP received on-schedule; among those who received Tdap.

Table 4. Tdap Vaccine Effectiveness and Duration of Protection among Selected Subgroups, California, 2010

Subgroup	Time since Tdap booster, months	Cases (n=314)	Controls (n=822)	Matched ORs (95% CI)	Estimated VE, % (95% CI)	*p*-value[a]
5 doses of DTP/DTaP, On-schedule	No Tdap	124	195	1 (Reference)	--	
	<12	23	128	0.30 (0.17,0.54)	70.1 (46.4,83.3)	<0.0001
	12-23	30	100	0.46 (0.25,0.87)	53.7 (12.8,75.4)	0.017
	24-35	25	64	0.84 (0.41,1.73)	16.2 (-72.6,59.3)	0.632
	≥36[b]	26	64	0.45 (0.20,0.97)	55.4 (2.7,79.6)	0.043
Acellular cohort (1998-1999)[c]	No Tdap	86	122	1 (Reference)	--	
	<12	15	8	0.34 (0.16,0.71)	66.3 (29.5,83.9)	0.004
	12-23	5	26	0.23 (0.06,0.81)	77.5 (18.7,93.8)	0.023
	24-35	0	3	N/A	N/A	--
	≥36	0	0	N/A	N/A	--
Mixed cohort (1991-1996)	No Tdap	39	76	1 (Reference)	--	
	<12	6	48	0.20 (0.08,0.53)	79.70 (47.0,92.2)	0.001
	12-23	12	45	0.37 (0.16,0.86)	62.60 (14.5,83.6)	0.019
	24-35	26	70	0.54 (0.27,1.05)	46.50 (-5.2,72.8)	0.070
	≥36	33	85	0.63 (0.34,1.19)	36.60 (-18.8,66.1)	0.155
Adacel™ Brand	No Tdap[d]	183	321	1 (Reference)	--	
	<12	16	90	0.31 (0.17,0.56)	69.30 (43.8,83.3)	0.0001
	12-23	20	86	0.43 (0.23,0.81)	57.40 (19.4,77.5)	0.009
	24-35	18	39	0.79 (0.36,1.75)	20.80 (-74.8,64.1)	0.564
	≥36	12	30	0.82 (0.31,2.14)	18.10 (-113.8,68.6)	0.684

Abbreviations: DTaP, diphtheria, tetanus and acellular pertussis vaccine; DTP, diphtheria, tetanus, and whole cell pertussis vaccine; Tdap, adolescent booster dose.

[a] Wald X^2 p-value.

[b] Months since Tdap: 36-64 months; median=50.

[c] Restricted to those with complete (5 doses) and on-schedule childhood series.

[d] OR and VE estimates for Tdap brands are relative to Tdap unvaccinated in entire study.

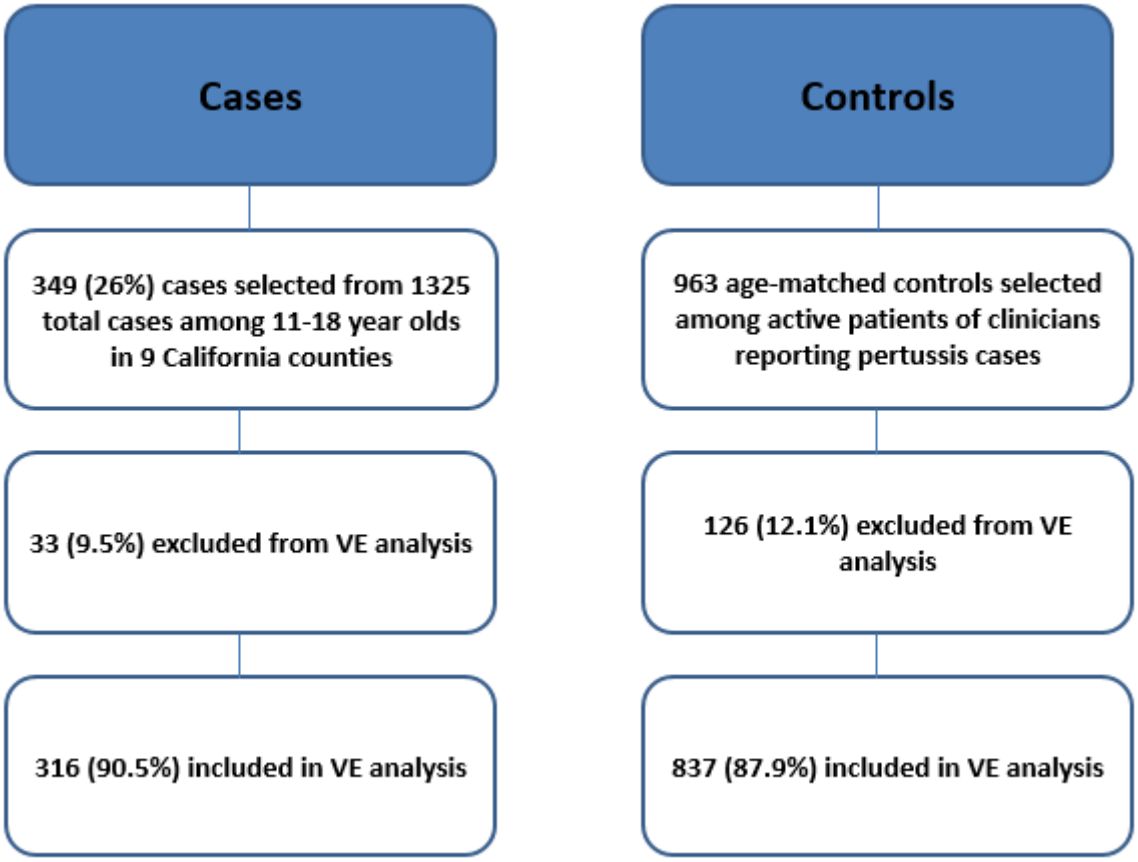
Table 5. Characteristics of Pertussis Cases Aged 11-18 Years Enrolled in the Study Compared to Those Not Enrolled, California, 2010

Characteristics	No. of Cases (%)		*p*-value[a]
	Enrolled (n=349)	Not Enrolled (n=976)	
Sex			
Female	169 (48.4)	350 (46.0)	0.282
Male	180 (51.6)	411 (54.0)	
Onset Age			
11	105 (30.1)	223 (29.3)	
12	73 (20.9)	140 (18.4)	
13	59 (16.9)	128 (16.8)	
14	32 (9.2)	61 (8.0)	0.292[b]
15	28 (8.0)	53 (7.0)	
16	21 (6.0)	54 (7.1)	
17	20 (5.7)	78 (10.2)	
18	11 (3.2)	25 (3.3)	
Onset Month			
Jan	3 (0.9)	7 (0.9)	
Feb	2 (0.6)	10 (1.3)	
Mar	10 (3.06)	23 (3.0)	
Apr	21 (6.4)	43 (5.6)	
May	82 (25.1)	93 (12.2)	
Jun	56 (17.1)	129 (16.9)	0.0001
Jul	33 (10.1)	119 (15.6)	
Aug	34 (10.4)	75 (9.8)	
Sept	22 (6.7)	91 (11.9)	
Oct	31 (9.5)	82 (10.8)	
Nov	21 (6.4)	58 (7.6)	
Dec	12 (3.7)	32 (4.2)	

[a] Pearson X^2 p-value.
[b] Calculated using the Wilcoxon rank-sum test.

FIGURES

Figure 1. Age–matched case-control study design



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Appendix A

California Tdap VE Assessment: Data Collection Tool

IDENTIFICATION | **Abstractor Initials:** __ __ | **Today's Date:** MM/DD/2013

☐ Case | **Case Onset Date:** MM/DD/2010 | **Case in patient roster:** ☐ Yes (1) ☐ No (0)

☐ Control

Patient Name: _____ (Last) _____ (First)

DOB: MM/DD/YYYY

Subject ID: __ __ __ __ __ -- __ (CDPH Case ID → Case/Control ID)

City: _____ **Zip code** __ __ __ __ __

Telephone Number 1: (__ __ __) __ __ __ -- __ __ __ __ **Telephone Number 1 Type:** ☐ Home ☐ Cell ☐ Work ☐ Other _____

Telephone Number 2: (__ __ __) __ __ __ -- __ __ __ __ **Telephone Number 2 Type:** ☐ Home ☐ Cell ☐ Work ☐ Other _____

Telephone Number 3: (__ __ __) __ __ __ -- __ __ __ __ **Telephone Number 3 Type:** ☐ Home ☐ Cell ☐ Work ☐ Other _____

DEMOGRAPHICS

Sex: ☐ Female (1) ☐ Male (2) ☐ N/A (9)

Ethnicity: ☐ Hispanic (1) ☐ Not Hispanic (0) ☐ N/A (9)

Insurance Status:
☐ Private (1) ☐ Medi-Cal (2)
☐ No coverage (3) ☐ N/A (9) ☐ Other (0): _____

Race: ☐ American Indian/Alaskan Native (1) ☐ Asian (2) ☐ Black (3)
☐ Native Hawaiian/Pacific Islander (4) ☐ White (5) ☐ N/A (9)
☐ Other or more than one race (0): _____

VFC Beneficiary: ☐ Yes (1) ☐ No (0) ☐ N/A (9)

PRACTICE INFORMATION

Practice Name: _____ **Practice County Location:** _____

Date of first visit with Practice: MM/DD/YYYY

Date of last visit with Practice on or prior to 12/31/10: MM/DD/YYYY (If case, date of visit prior to pertussis diagnosis visit) ☐ No visit prior to pertussis visit (If case)

CONTROL EXCLUSION CRITERIA ☐ *Check box if case, and proceed to vaccination exemption*

1. **Date of last visit prior to Jan 1, 2005**[1]: ☐ Yes (1) ☐ No (0)
2. **Pertussis diagnosis/suspicion noted between 1/1/10 – 12/31/10**[2]: ☐ Yes (1) ☐ No (0)
3. **Patient noted as 'active discharge' from clinic between 1/1/2005-12/31/10**[3]: ☐ Yes (1) ☐ No (0)
4. **Medical record unavailable**[4]: ☐ Yes (1) ☐ No (0)
5. **Patient on roster but no visits documented**[5]: ☐ Yes (1) ☐ No (0)

Exclusion Criteria Met: ☐ Yes (1) ☐ No (0)
If yes, please select new control.
If no, please continue abstraction below.

VACCINATION EXEMPTION

Vaccine exemption noted in chart: ☐ Yes (1) ☐ No (0) | **If yes, why:** ☐ Medical (1) ☐ PBE (2) ☐ Not listed (9) ☐ Other (0) _____

VACCINATION INFORMATION *For vaccine type, manufacturer, and brand, please see codes in 'Key Points and References' document*

DTaP/DTP ☐ No doses recorded	Vaccine			NOTES
Dose # Vaccination Date	Type	Manuf.	Brand	
1 MM/DD/YYYY ☐ n/a				
2 MM/DD/YYYY ☐ n/a				
3 MM/DD/YYYY ☐ n/a				
4 MM/DD/YYYY ☐ n/a				
5 MM/DD/YYYY ☐ n/a				
6 MM/DD/YYYY ☐ n/a				

Tdap/Td ☐ No doses recorded	Vaccine			
Dose # Vaccination Date	Type	Manuf.	Brand	Lot Number
1 MM/DD/YYYY ☐ n/a				☐ n/a
2 MM/DD/YYYY ☐ n/a				☐ n/a

Case OR Control with transfer in 2010 from another clinic AND missing doses/lot number for DTaP and/or Tdap: ☐ Yes (1) ☐ No (0)

If yes, previous clinic name: _____ **Date of last visit at previous clinic:** MM/DD/YYYY (To be completed at previous clinic)

Appendix B

Literature Review

1. General Introduction

Pertussis, commonly known as whooping cough, is an acute, infectious respiratory illness caused by the gram-negative bacterium *Bordetella pertussis*. The disease is endemic in the United States (U.S.) despite routine childhood pertussis vaccination for more than half a century and high coverage levels in children [1-3]. The introduction of whole cell pertussis, tetanus, and diphtheria toxoid (DTP) vaccines for childhood vaccination in the 1940s resulted in a dramatic decline in the number of reported pertussis cases in the U.S., from >200,000 to a historic low of 1,010 in 1976 [1].

Pertussis is the least controlled reportable bacterial vaccine-preventable disease in the U.S. compared to diseases for which universal childhood vaccination is recommended [4,5]. Since the 1980s, the number of reported pertussis cases has risen steadily, especially among adolescents and adults [3,6,7], despite widespread childhood immunization with pertussis vaccines, suggesting early waning of immunity [8,9]. Increased reports of pertussis may also be attributed to improvements in surveillance and diagnostics [10], the evolution of the etiological agent *B. pertussis* [11], the switch from whole-cell to acellular vaccines [12], and the invasion and spread of *Bordetella* congeners [13].

Pertussis is endemic in the U.S., with peaks in disease every 3 to 5 years and frequent outbreaks [14]. In 2010, California experienced the state's largest pertussis epidemic in over 60 years [15], with >9,000 reported cases and 10 deaths. During this outbreak, an increase in the number of cases was noted among adolescents aged 11-18 years [15], despite considerable Tdap coverage (71.2%) in that age-group in 2010 [16]. In 2012, the state of Washington reported nearly 5,000 cases [17], with an unexpectedly high disease incidence among in adolescents aged

13-14 years, despite Tdap coverage of 86% [18]. The emergence of pertussis among adolescents had not been observed since the introduction of Tdap in 2005, eliciting concerns for waning immunity following the Tdap dose in adolescents who received all acellular pertussis vaccines as children. The epidemics in California and Washington provided opportunities to assess Tdap vaccine effectiveness (VE) and to estimate duration of protection among the first cohort of adolescents who received all acellular vaccines.

2. Clinical Characteristics of Pertussis

B. pertussis is primarily transmitted from person to person through large respiratory droplets generated by coughing or sneezing [19]. The pathogen, a fastidious gram-negative coccobacillus, elaborates toxins that damage respiratory epithelial tissue and have systemic effects. The incubation period for pertussis is 7-10 days (range: 5-21 days) [20,21]. Classic pertussis is characterized by three phases of illness - catarrhal, paroxysmal, and convalescent [19]. During the catarrhal phase, which lasts 1-2 weeks, infected persons experience coryza and an intermittent cough; high fever is uncommon. The paroxysmal phase usually lasts 4-6 weeks and is characterized by spasmodic cough, posttussive vomiting, and inspiratory whoop. Persons with pertussis are most infectious during the catarrhal and early paroxysmal phases of illness [19]. Complications can occur during the course of illness, including hypoxia, pneumonia, weight loss, seizures, encephalopathy, and death [22].

The clinical presentation of pertussis is affected by age, the level of immunity, and use of antimicrobials early in the course of the illness [23]. Infants aged <12 months with pertussis are more likely than older age groups to have complications or be hospitalized during their illness [24]. Among adolescents, the spectrum of disease caused by *B. pertussis* ranges from mild cough illness to classic pertussis; infection also can be asymptomatic [25]. A prolonged cough is a

common feature of pertussis in adolescents. Complications and pertussis-related deaths are rarely reported among adolescents [25,26].

3. Diagnosis of Pertussis

Pathogen culture is currently the gold standard for a pertussis diagnosis, and is essential for antimicrobial susceptibility testing and molecular subtyping of strains [27]. Although the isolation of *B. pertussis by* culture is 100% specific, the sensitivity is quite low due to special growth requirements of the organism [28]. Polymerase chain reaction (PCR) is increasingly used in pertussis diagnosis due to its higher sensitivity and faster result reporting [29]. To reduce false-positive and false-negative rates, PCR testing is recommended only in case pertussis is highly suspected. It is common practice to use PCR as an alternative test to culture, but obtaining culture confirmation is recommended when an outbreak is suspected [27]. Several serological tests, using enzyme immunoassay, are available, but most are not validated. A serological correlate of immunity and the cut-off levels for the IgG diagnostic value to pertussis toxin (PT) has not been clearly established, and IgM assays lack sensitivity and specificity [30].

4. Pertussis Case Definition

Pertussis is reportable in all 50 states and the District of Columbia. State health departments report confirmed and probable cases of pertussis to CDC through the passive National Notifiable Diseases Surveillance System (NNDSS); additional information for pertussis cases is collected through the Supplemental Pertussis Surveillance System (SPSS) [31].

The CDC and Council of State and Territorial Epidemiologists (CSTE) [32] pertussis case definition includes the following information:

a) Clinical Case Definition: In the absence of a more likely diagnosis a cough illness lasting ≥2 weeks with one of the following symptoms - paroxysms of coughing, or Inspiratory "whoop," or posttussive vomiting, or apnea, with or without cyanosis (for infants aged <1 year only).

b) Laboratory Criteria for Diagnosis: Isolation of *B. pertussis* from a clinical specimen, or positive PCR assay for *B. pertussis*.

c) Epidemiologic Linkage: Contact with a laboratory-confirmed case of pertussis. Note: An illness meeting the clinical case definition should be classified as "probable" rather than "confirmed" if it occurs in a patient who has contact with an infant aged <1year who is PCR positive for pertussis and has ≥1 sign or symptom and cough duration <14 days (classified as "probable" case).

d) Case Classification: A confirmed case is defined as an acute cough illness of any duration associated with *B. pertussis* isolation, or a case that meets the clinical case definition and is confirmed by PCR, or a case that meets the clinical definition and is epidemiologically linked directly to a case confirmed by either culture or PCR. A probable case is one that meets the clinical case definition, is not laboratory confirmed by culture or PCR, and is not epidemiologically linked directly to a laboratory-confirmed case.

5. Pertussis Prevention and Control

Vaccination of children, adolescent and adults remains the most important preventive strategy against pertussis. Despite continuous high immunization coverage rates in the U.S., pertussis has remained endemic, and the incidence of reported pertussis disease has gradually increased. Waning of vaccine-acquired immunity and decreased opportunities for boosting of immunity are cited as some of the possible reasons for the reemergence of pertussis [33-35].

5.1. Whole cell pertussis vaccines

Whole-cell pertussis vaccine, composed of a suspension of formalin-inactivated *B. pertussis* cells, was developed in the 1930s and used widely in clinical practice by the mid-1940s. The combination of diphtheria and tetanus toxoids and whole cell pertussis vaccine (DTP) was not routinely recommended for children until the 1940s and 1950s [36,37]. Based on controlled efficacy trials conducted in the 1940s and on subsequent observational efficacy studies, a primary series of 4 doses of whole-cell DTP vaccine was 70%-90% effective in preventing serious pertussis disease [38]. Protection decreased with time, resulting in little or no protection 5-10 years following the last dose. Local reactions such as redness, swelling, and pain at the injection site occurred following up to half of doses of whole-cell DTP vaccines. Fever and other mild systemic events were also common. Concerns about safety led to the development of more purified (acellular) pertussis vaccines that are associated with a lower frequency of adverse reactions. Whole-cell pertussis vaccines are no longer available in the U.S. but are still used in many other countries.

5.2. Acellular pertussis vaccines

Acellular pertussis vaccines contain purified, inactivated components of *B. pertussis* cells. Several acellular pertussis vaccines have been developed for different age groups; these contain different pertussis components in varying concentrations. Acellular pertussis vaccines are available only as combinations with tetanus and diphtheria toxoids. In 1991, diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) was first licensed for use in children for the fourth and fifth doses of the 5-dose childhood vaccination series in the U.S. [39,40], and in 1996, pediatric DTaP was licensed for the first three infant doses [41]. In 1997, the Advisory

Committee on Immunization Practices (ACIP) recommended that pediatric DTaP be used routinely instead of pediatric DTP as a 5-dose DTaP schedule at ages 2, 4, 6, 15-18 months and 4-6 years [41,42].

Tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis (Tdap) vaccines were developed to improve protection against pertussis among adolescents and adults. The pertussis antigen composition of the adolescent and adult Tdap formulations is similar to pediatric DTaP, but some of the pertussis antigens are reduced in quantity. The tetanus and diphtheria toxoid composition of Tdap is similar to licensed adult formulations of Td. In 2005, two Tdap products, Boostrix™ (GlaxoSmithKline) and Adacel™ (Sanofi Pasteur), were licensed in the U.S. for use in adolescents and adults [43,44]. That same year, the ACIP recommended a single dose of Tdap to replace the next scheduled tetanus diphtheria (Td) booster for all people aged 11-64 [45], and in 2012 the committee extended its recommendation for routine Tdap vaccination to all people aged 65 and older [46].

5.3. Pertussis vaccination recommendations in the United States

The ACIP recommends a 4-dose primary series of DTaP, administered at 2, 4, 6 and 15-18 months of age, followed by a fifth booster dose given at 4-6 years [47]. In 2005 and 2006, the ACIP recommended the replacement of a single Td booster with a dose of Tdap for adolescents (ages 11-18) and adults (ages 19-64) who have not previously received Tdap [48,49]. On October 27, 2010, ACIP expanded Tdap recommendations to include both under-vaccinated children and senior adults. The new recommendations state that children aged 7-10 years who are not up-to-date with their childhood pertussis vaccinations should receive a single dose of Tdap. Additionally, Tdap is recommended for adults aged 65 years and older who anticipate close contact with an infant and who have not previously received the vaccine. ACIP further

recommended that Tdap be administered regardless of time since last tetanus and diphtheria-containing booster [50]. On February 23, 2011, ACIP recommended that all healthcare personnel who have not yet received a dose of Tdap, regardless of age, should be vaccinated.

5.4. Evaluation of Tdap Vaccine Effectiveness

Post-licensure VE studies are a critical component of vaccine program evaluation. Studies of Tdap vaccines have demonstrated effectiveness of 64%-78% [51-55]. In a study that used a screening approach to evaluate a mass vaccination program for high school students [51] the estimated VE of the Boostrix™ Tdap booster was 78% (95% CI, 60.7%–87.6%), for all study cases (n=167), increasing to 85.4% (95% CI: 83.0–87.5%) for laboratory-confirmed cases (n=155). These VEs were comparable in settings with similar programs, such as the U.S. and Canada. A case-control investigating a pertussis outbreak in the U.S. Virgin Islands [52] reported Tdap VE of 65.6% (95% CI, -35.8%-91.3%) among adolescents, while another study reported Tdap VE of 92% (95% CI; 32%-99%) in preventing clinical pertussis [53], although only 10 people met the definition of a primary case. These studies were mostly limited to adolescents who received whole cell pertussis vaccines as children, and were also limited by low numbers of cases.

Recent studies [54-56] have reported effectiveness of the Tdap booster when administered to the emerging cohort of adolescents previously vaccinated entirely with acellular pertussis vaccines instead of whole cell formulations. In a cohort study [54] of Wisconsin adolescents born during 1998-2000, Tdap VE decreased with increasing time since receipt, with VEs of 75.3% (95% CI, 55.2%-86.5%) for receipt during 2012, 68.2% (95% CI, 60.9%-74.1%) for receipt during 2011, 34.5% (95% CI, 19.9%-46.4%) for receipt during 2010, and 11.9% (95% CI, -11.1%-30.1%) for receipt during 2009/2008; point estimates were higher among

Boostrix recipients than among Adacel recipients. In this study, among Tdap recipients, increasing time since receipt was associated with increased risk, and receipt of Boostrix™ (vs Adacel™) was associated with decreased risk of pertussis (VE, 90.6% vs 61.3% in 2012; 78.9% vs 58.1% in 2011; 59.5% vs 26.8% in 2010; and 40.1% vs 12% in 2008/2009).

A case-control study [55] conducted to assess the effectiveness of Tdap vaccines in adolescents and adults during the California pertussis outbreak in 2010 and 2011 reported that Tdap vaccination was estimated to reduce the risk of PCR confirmed pertussis by 53% (95% CI, 42% to 62%) in the comparison with PCR negative controls and by 64% (56% to 71%) in comparison with other controls. A matched case control study [56] conducted during the 2012 pertussis epidemic in Washington state among adolescents born between 1993-2000 reported Tdap VE of 63.9% (95% CI, 50%-74%) among adolescents who received all acellular vaccines In this study, the overall VE within one year of Tdap vaccination was 73% (95% CI, 60%-82%). At 2-4 years post-vaccination, VE declined to 34% (95% CI, -0.03-58%).

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Appendix C

SAS Code for Backward Elimination

```
libname ca '\\cdc.gov\private\M119\gfv3\My Documents\cMPH\THESIS
Project\Thesis_SAS_Analysis';
run;
proc contents data=ca.cavefinal;
run;
proc format;
value Casef  1="Case"
             0="Control";
value Vaccinatedf 2="Unvaccinated"
                  1="Vaccinated";
value Sex2f 1="Female"
            2="Male";
value Tdapbrandf 1="Unvaccinated"
                 2="Boostrix"
                 3="Adacel"
                 4="Unknown";
value DTAP_Seriesf 1="Unvaccinated"
                   2="Mixed"
                   3="Transition"
                   4="Acellular";
Value TimeSinceTdapf 1="0 months"
                     2="<12 months"
                     3="12-23 months"
                     4="24-35 months"
                     5="36-47 months"
                     6=">=48 months";
Value TimeSinceTdap2f 1="0 months"
                      2="<12 months"
                      3="12-23 months"
                      4="24-35 months"
                      5=">=36 months";
value Tdapage2f 1="11 years"
                2="12 years"
                3="13 years"
                4="14 years"
                5="15 years"
                6="16 years"
                7="17 years"
                8="18 years";
value Sex2f 1="Female"
            2="Male";
value Racef 3="Black"
            5="White"
            0="Other";
value Ethnicityf 1="Hispanic"
                 0="Not Hispanic";
value Ageatenrollment2f 1="11 years"
                        2="12 years"
                        3="13 years"
                        4="14 years"
                        5="15 years"
                        6="16 years"
                        7="17 years"
                        8="18 years";
run;
```

```
*BACKWARD ELIMINATION (to assess INTERACTION and CONFOUNDING)*
*Include all variables of interest and interactions in model*;
proc logistic data=ca.cavefinal descending;
format case casef.;
strata id;
where excluded=0;
class vaccinated (param=ref ref='2')
      sex2 (param=ref ref='1')
      tdapage2 (param=ref ref='1');
model case (event = 'case') = vaccinated sex2 tdapage2 vaccinated*sex2
vaccinated*tdapage2 / SELECTION=backward SLSTAY=0.05 INCLUDE=5;
run;

*Remove interactions that are not significant (None of the interactions are
significant - remove all)*;
proc logistic data=ca.cavefinal descending;
format case casef.;
strata id;
where excluded=0;
class vaccinated (param=ref ref='2')
      sex2 (param=ref ref='1')
      tdapage2 (param=ref ref='1');
model case (event = 'case') = vaccinated sex2 tdapage2 /SELECTION=backward
SLSTAY=0.05 INCLUDE=5;
run;
*Odds Ratio for Vaccinated=0.19 - this is the Gold Standard OR*'

*Remove Sex2;
proc logistic data=ca.cavefinal descending;
format case casef.;
strata id;
where excluded=0;
class vaccinated (param=ref ref='2')
      tdapage2 (param=ref ref='1');
model case (event = 'case') = vaccinated tdapage2 /SELECTION=backward
SLSTAY=0.05 INCLUDE=5;
run;
*Vaccinated OR=0.18 is <10% change in OR, leave sex2 out of model*;

*Remove Tdapage2;
proc logistic data=ca.cavefinal descending;
format case casef.;
strata id;
where excluded=0;
class vaccinated (param=ref ref='2');
model case (event = 'case') = vaccinated / SELECTION=backward SLSTAY=0.05
INCLUDE=5;
run;
*Vaccinated OR=0.40 is >10% change in OR, return Tdapage2 to model*;

*Final model*;
proc logistic data=ca.cavefinal descending;
format case casef.;
strata id;
where excluded=0;
class vaccinated (param=ref ref='2')
      tdapage2 (param=ref ref='1');
model case (event = 'case') = vaccinated tdapage2;
```

```
run;

*OR and VE estimates for various outcome variables*;
*Conditional logistic regression - Tdap Vaccination Status*;
proc logistic data=ca.cavefinal;
format case casef.;
strata id;
where excluded=0;
class vaccinated (param=ref ref='2');
model case (event = 'case') = vaccinated;
run;

*Conditional logistic regression - Time Since Tdap2;
proc logistic data=ca.cavefinal;
format case casef.;
strata id;
where excluded=0;
class timesincetdap2 (param=ref ref='1');
model case (event = 'case') = timesincetdap2;
run;

*Conditional logistic regression - Tdap Brand*;
proc logistic data=ca.cavefinal;
format case casef.;
strata id;
where excluded=0;
class tdapbrand (param=ref ref='1');
model case (event = 'case') = tdapbrand;
run;

*Conditional logistic regression - presumed DTAP Childhood Series, based on
birthyear;
proc logistic data=ca.cavefinal;
format case casef.;
strata id;
where excluded=0;
class dtap_series(param=ref ref='1');
model case (event = 'case') = dtap_series;
run;
```