Tdap Vaccine Effectiveness in Adolescents During the 2012 Washington State Pertussis Epidemic

Anna M. Acosta, MD[a,b], Chas DeBolt, RN, MPH[c], Azadeh Tasslimi, MPH[c], Melissa Lewis, MPH[d], Laurie K. Stewart, MS[c], Lara K. Misegades, PhD, MS[b], Nancy E. Messonnier, MD[b], Thomas A. Clark, MD, MPH[b], Stacey W. Martin, MS[b], Manisha Patel, MD, MS[b]

abstract

BACKGROUND: Acellular pertussis vaccines replaced whole-cell vaccines for the 5-dose childhood vaccination series in 1997. A sixth dose of pertussis-containing vaccine, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap), was recommended in 2005 for adolescents and adults. Studies examining Tdap vaccine effectiveness (VE) among adolescents who have received all acellular vaccines are limited.

METHODS: To assess Tdap VE and duration of protection, we conducted a matched case-control study during the 2012 pertussis epidemic in Washington among adolescents born during 1993–2000. All pertussis cases reported from January 1 through June 30, 2012, in 7 counties were included; 3 controls were matched by primary provider clinic and birth year to each case. Vaccination histories were obtained through medical records, the state immunization registry, and parent interviews. Participants were classified by type of pertussis vaccine received on the basis of birth year: a mix of whole-cell and acellular vaccines (1993–1997) or all acellular vaccines (1998–2000). We used conditional logistic regression to calculate odds ratios comparing Tdap receipt between cases and controls.

RESULTS: Among adolescents who received all acellular vaccines (450 cases, 1246 controls), overall Tdap VE was 63.9% (95% confidence interval [CI]: 50% to 74%). VE within 1 year of vaccination was 73% (95% CI: 60% to 82%). At 2 to 4 years postvaccination, VE declined to 34% (95% CI: −0.03% to 58%).

CONCLUSIONS: Tdap protection wanes within 2 to 4 years. Lack of long-term protection after vaccination is likely contributing to increases in pertussis among adolescents.

[a]*Epidemic Intelligence Service, Scientific Education and Professional Development Program Office,* [b]*Meningitis and Vaccine Preventable Disease Branch, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, and* [d]*Biostatistics Office, Division of Bacterial Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; and* [c]*Communicable Disease Epidemiology, Washington State Department of Health, Shoreline, Washington*

Dr Acosta led the conceptualization and design of the study, oversaw the data collection, performed data analyses, interpreted the data, drafted the initial manuscript, and finalized the final draft; Ms DeBolt assisted with data collection and interpretation and provided critical revision of the manuscript for important intellectual content; Ms Tasslimi assisted with data collection, analyses, and interpretation and provided critical revision of the manuscript for important intellectual content; Ms Lewis assisted with data collection and analyses and provided critical revision of the manuscript for important intellectual content; Ms Stewart assisted with data collection and provided critical revision of the manuscript for important intellectual content; Dr Misegades contributed to the study design and data interpretation and provided critical revision of the manuscript for important intellectual content; Dr. Messonnier contributed to the conceptualization of the study and data interpretation and provided critical revision of the manuscript for important intellectual content; Dr Clark contributed to the conceptualization of the study and data interpretation and provided critical revision of the manuscript for important intellectual content;

WHAT'S KNOWN ON THIS SUBJECT: Although waning immunity with the childhood pertussis vaccination series has been reported, there are limited data on duration of protection of the adolescent pertussis vaccine (Tdap), especially among those who have received only acellular vaccines.

WHAT THIS STUDY ADDS: This study reports that protection from Tdap wanes substantially 2 to 4 years after vaccination among adolescents who received all acellular vaccines during childhood. This waning protection is likely contributing to the increase in adolescent pertussis.

Despite high childhood and adolescent vaccination coverage, >48 000 pertussis cases were reported in the United States in 2012, the greatest number reported since 1955.[1] In addition, there were new and concerning changes in the age distribution of pertussis cases, with increasing incidence among fully vaccinated children and adolescents within a few years of vaccination.[1–3]

Although infants <1 year of age continue to have the highest rates of pertussis, increased rates among 7- to 10-year-olds were recently observed.[3] Notably, this cohort of children was among the first to receive solely acellular pertussis vaccines for the childhood series. Waning immunity after vaccination with diphtheria-tetanus-acellular pertussis (DTaP) vaccines appears to be a major contributing factor for increased disease risk.[4–6]

Because tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap) was recommended for adults and adolescents only in 2006, studies estimating Tdap vaccine effectiveness (VE) and duration of protection are few. Several observational studies noted an overall VE range of 64% to 78% within 2 years of vaccination.[7–10] To our knowledge, only 1 study has measured Tdap duration of protection for >2 years, and it concluded that VE waned over time.[11]

In 2012, Washington State declared a pertussis epidemic with nearly 5000 cases reported. An unexpectedly high disease incidence was seen in adolescents 13 to 14 years of age despite Tdap coverage of 86%.[2,12] The emergence of disease in this age group had not been observed since the introduction of Tdap, raising concerns for waning immunity after the Tdap dose in adolescents who received all acellular pertussis vaccines as children. The epidemic in Washington provided an opportunity to estimate Tdap VE and duration of protection among the first cohort of adolescents who received all acellular vaccines.

METHODS

Study Oversight

This evaluation was conducted as part of the public health response to the 2012 Washington pertussis epidemic and was determined to be nonresearch program evaluation by the Centers for Disease Control and Prevention Human Research Protection Office and the Washington State Department of Social and Health Services Institutional Review Board.

Study Design and Population

To estimate Tdap VE and duration of protection, we conducted a matched case-control study. The 7 Washington counties reporting >50 cases among adolescents during the study period of January 1 to June 30, 2012, agreed to participate (Clark, King, Pierce, Skagit, Snohomish, Yakima, and Whatcom).

The study included adolescents 11 to 19 years of age, born from January 1, 1993, through December 31, 2000. We included all suspected, probable, and confirmed pertussis cases reported among residents of the 7 participating counties during the study period. Cases were classified by using the Council of State and Territorial Epidemiologists case definitions for probable and confirmed pertussis cases.[13] A clinical case was defined as cough for ≥14 days with at least 1 of the following symptoms: whoop, posttussive vomiting, or paroxysmal cough. A confirmed case was defined as cough illness of any duration plus isolation of *Bordetella pertussis* from a clinical specimen or a clinical case with either a positive polymerase chain reaction test result or contact with a laboratory-confirmed case (epidemiologic link). Clinical cases that were not laboratory-confirmed or epidemiologically linked to a laboratory-confirmed case were classified as probable cases. The Washington State Department of Health also included a suspected case category defined as a positive polymerase chain reaction test result with illness not meeting the clinical case definition.[14]

We selected 3 controls for each case, matched by birth year and primary provider clinic. Controls were randomly selected from a clinic-generated patient roster that included all adolescents born in the same year as the case and who had at least 1 clinic visit since 2005. Potential controls were excluded and replaced with another randomly selected control if the provider suspected or diagnosed pertussis during the study period, the patient had been discharged from the clinic, the patient had an out-of-state home zip code, or patient medical records were unavailable. The symptom onset date of the case was used as the enrollment date for each case and associated matched controls.

Demographic information (date of birth, gender, home zip code, ethnicity, race) and vaccination histories for cases and controls were collected at provider clinics by using a standardized protocol and medical chart abstraction form. Vaccination date, product, manufacturer, and lot number were recorded for all documented pertussis-, diphtheria-, or tetanus-containing vaccines, including the childhood series and adolescent dose when available. To verify brand, we matched available lot numbers for the childhood series and adolescent dose with known lot numbers provided by the Washington State Department of Health and 2 pertussis vaccine manufacturers (GlaxoSmithKline, Brentford, United Kingdom; Sanofi Pasteur, Swiftwater, PA).

We supplemented provider vaccination histories with information from the Washington State Immunization Information

System.[15] If vaccination history was available in both sources but discrepant, provider records were used as the definitive source. If Tdap vaccination status remained unknown after reviewing these sources, parents or guardians were contacted to verify Tdap vaccine receipt.

The childhood series was considered complete and on schedule if the participant had documentation in the provider records or immunization registry of 5 doses of diphtheria-tetanus toxoids-pertussis (DTP) or DTaP meeting the following criteria: doses 1 through 3 before the first birthday, dose 4 on or after the first birthday and before the second birthday, and dose 5 on or after the fourth birthday and before the seventh birthday.[16]

We classified participants as vaccinated if a Tdap vaccination date was confirmed in the provider records, the immunization registry, or by parent interview. We classified participants as unvaccinated if no record of Tdap vaccination date was found in the provider records or the immunization registry and Tdap nonreceipt was confirmed by a parent. In addition, participants were classified as unvaccinated if Tdap receipt was confirmed but the vaccination occurred after the enrollment date or if Tdap was received within 2 weeks before the enrollment date. We considered a participant's vaccination status to be unknown if a Tdap vaccination date was not documented in the provider records or the immunization registry and the parent interview was inconclusive.

The Washington State Childhood Vaccination Program has been the sole distributor of childhood and adolescent vaccines to public and private health care providers since the early 1990s.[17,18] We reviewed available vaccine distribution data and determined that the transition of whole-cell to acellular pertussis vaccines for the complete childhood series 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.

To evaluate the impact of the whole-cell or acellular pertussis childhood vaccination series on Tdap VE, study participants were stratified on the basis of birth year into 2 groups. The acellular group included adolescents born from 1998 to 2000 and were assumed to have received all acellular pertussis vaccines for the childhood series, whereas the mixed group included those born from 1993 to 1997 and were assumed to have received a mix of whole-cell and acellular pertussis vaccines.

Statistical Analysis

To estimate the association between pertussis and Tdap receipt, we used conditional logistic regression to calculate odds ratios, accounting for matching factors (provider and birth year). VE was calculated as: 1 − odds ratio × 100%. Tdap-unvaccinated participants were the reference group in all models. We estimated duration of protection by measuring the association between pertussis and time since Tdap vaccination (<12 months, 12–23 months, 24–47 months).

We excluded cases and controls if Tdap vaccination status was unknown, or if there was documentation of inadvertent administration of DTaP during adolescence, Tdap before the age of 10 years, or ≥2 Tdap doses. In addition, controls were excluded if they had ever been reported to the Washington State Department of Health as having pertussis.

The primary analysis measured Tdap VE and duration of protection in study participants who received all acellular pertussis vaccines for the childhood series (birth years 1998–2000; ages 11–14 years).

Additional subgroup analyses assessed the stability of the VE estimates by restricting the analysis to those with confirmed and probable case status, those with confirmed case status only, or those with a complete and on-schedule childhood series. We also evaluated Tdap VE among participants who received a mix of whole-cell and acellular vaccines (birth years 1993–1997; ages 15–19 years), as well as differences in VE by Tdap product.

Statistical comparison of demographic characteristics between cases and controls was performed by using conditional logistic regression. We evaluated trends in Tdap vaccine status by birth year using the Cochran-Armitage test. All analyses were conducted in SAS software, version 9.3 (SAS Institute, Cary, NC).

RESULTS

During the study period, 1153 pertussis cases among adolescents were reported in Washington. Of those, 959 were reported in the 7 participating counties, representing 83% of all Washington adolescent cases and 73% of all Washington providers reporting adolescent cases. Pertussis incidence for this age group was 182.3 per 100 000 persons during the study period.

Data were collected for 887 cases and 2599 matched controls. Data were not collected for 72 cases for the following reasons: a provider was not available for the patient (n = 45; 63.4%), the provider refused to participate (n = 14; 19.7%), or the provider was located outside the participating counties (n = 12; 16.9%). An additional 51 cases (5.8%) and 277 controls (10.7%) were excluded from the analysis (Table 1). The final analysis included 836 cases and 2322 controls. Of the 836 cases, 656 (78.5%) were classified as confirmed, 92 (11.0%) as probable, and 88 (10.5%) as suspect.

TABLE 1 Exclusions From Analyses Estimating Tdap VE, Duration of Protection, and Brand Effectiveness Against Pertussis

Reason excluded	Cases (n = 887)	Controls (n = 2599)
Pertussis case in previous years	Not applicable[a]	17 (0.7)
DTaP at adolescence	2 (0.2)	11 (0.4)
Tdap before age 10	5 (0.6)	7 (0.3)
Two or more Tdap doses	15 (1.7)	77 (3.0)
Tdap vaccination status unknown	29 (3.3)	165 (6.3)
Total excluded from the analyses	51 (5.8)	277 (10.7)

Data are presented as n (%).

[a] Only controls were verified as to whether they had been reported as a pertussis case previously.

Table 2 lists demographic and vaccine characteristics of the cases and controls included in the analysis. The median age among study participants was 14 years; 54% were born between 1998 and 2000. Cases were more likely to be white (P = .003) and non-Hispanic (P = .03) than controls; however, a substantial amount of race and ethnicity data was not documented in the medical records and therefore was unknown. Although 74% of cases and 75% of controls had 5 documented doses for the childhood series, only 60% of cases and 58% of controls had a 5-dose series that was on schedule. Brand was identified by lot number for 25% to 29% of the childhood doses administered, depending on the dose number. Although documentation of childhood series lot numbers was limited, all childhood vaccines administered in study participants during 1998 or later with available lot numbers were confirmed to be acellular pertussis vaccines.

TABLE 2 Demographic Characteristics of Participants Included in Analyses Estimating Tdap VE, Duration of Protection, and Brand Effectiveness Against Pertussis

Characteristic	Cases (n = 836)	Controls (n = 2322)	P[c]
Birth year, n (%)			
1993–1997	386 (46.2)	1076 (46.3)	Not applicable[a]
1998–2000	450 (53.8)	1246 (53.7)	
Gender, n (%)			
Male	428 (51.2)	1191 (51.3)	.80
Female	406 (48.6)	1122 (48.3)	
Unknown	2 (0.2)	9 (0.4)	
Race, n (%)			
White	304 (36.3)	570 (24.5)	.003
Other	79 (9.5)	232 (10.0)	
Unknown	453 (54.2)	1520 (65.5)	
Ethnicity, n (%)			
Non-Hispanic	304 (36.4)	625 (26.9)	.03
Hispanic	79 (9.4)	217 (9.4)	
Unknown	453 (54.2)	1480 (63.7)	
Childhood series vaccination, n (%)			
Complete, on-schedule series[b]	506 (60.5)	1357 (58.4)	.29
Tdap vaccination status, n (%)			
No	162 (19.4)	229 (9.9)	<.0001
Yes	674 (80.6)	2093 (90.1)	
Age at Tdap, median (range), y	11 (10–17)	11 (10–18)	.43
Time since Tdap vaccination, median (range), mo			
Overall	33 (1–73)	31 (0–84)	.02
Birth years 1998–2000	22 (1–47)	19 (0–47)	.10
Birth years 1993–1997	44 (2–73)	45 (0–84)	.16
Tdap brand, n (%)			
Adacel	136 (20.2)	342 (16.3)	.05
Boostrix	387 (57.4)	1245 (59.5)	
Unknown brand	151 (22.4)	506 (24.2)	

[a] Cases and controls were matched on birth year, and therefore no P value was calculated.

[b] A complete and on-schedule primary series is considered the following: doses 1 through 3 before the first birthday, dose 4 on or after the first birthday and before the second birthday, and dose 5 on or after the fourth birthday and before the seventh birthday.

[c] P values do not apply to unknown data.

Eighty-one percent of cases and 90% of controls were vaccinated with Tdap, and both had similar ages at vaccination and time since vaccination. Overall, >84% of study participants were vaccinated with Tdap at the recommended ages of 11 to 12 years.

For the primary analysis, which included only those who received acellular vaccines for the primary series (450 cases, 1246 controls), the overall Tdap VE estimate against pertussis was 63.9% (95% confidence interval [CI]: 49.7% to 74.1%) (Table 3). When these participants were stratified by time since Tdap vaccination, the VE within 12 months was 73.1% (95% CI: 60.3% to 81.8%). At 12 to 23 months postvaccination, the VE estimate was 54.9% (95% CI: 32.4% to 70.0%), and by 24 to 47 months it was 34.2% (95% CI: −0.03% to 58.0%). Subgroup analyses limited to confirmed cases or those with on-schedule childhood vaccinations were not substantially different from the primary analysis, with overlapping CIs noted (Fig 1, Supplemental Tables 5 and 6). Similarly, a subgroup analysis excluding those with suspect case status was not notably different from the primary analysis (data not shown).

The overall Tdap VE for the mixed-vaccine group (386 cases, 1076 controls) was 51.5% (95% CI: 26.1% to 68.1%). Because the mixed group was heavily weighted toward participants who received Tdap at least 3 years before study enrollment (Fig 2), Tdap duration of protection was stratified by less or more than 4 years since vaccination. The VE estimates for each of these time points were similar to the overall VE

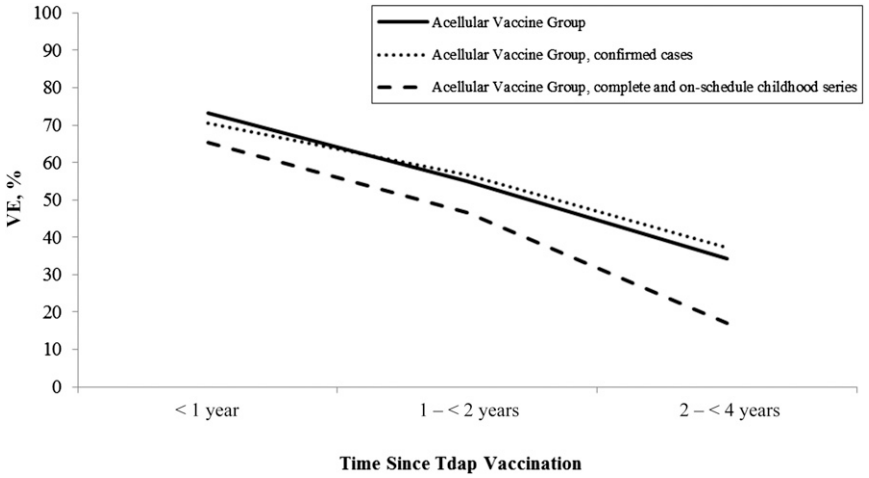

FIGURE 1

Estimated Tdap duration of protection against pertussis among adolescents who received all acellular vaccines (birth years 1998–2000), restricted to confirmed cases or participants with complete and on-schedule childhood series. Acellular vaccine group: adolescents born from 1998 to 2000, assumed to have received all acellular pertussis vaccines for the childhood series (cases = 450, controls = 1256). Acellular vaccine group, confirmed case status: adolescents born from 1998 to 2000, assumed to have received all acellular pertussis vaccines for the childhood series and restricted to confirmed cases and their associated controls (cases = 355, controls = 984). Acellular vaccine group, complete and on-schedule childhood series: adolescents born from 1998 to 2000, assumed to have received all acellular pertussis vaccines for the childhood series and restricted to cases and controls with 5 childhood doses on schedule (cases = 288, controls = 728). A complete and on-schedule primary series is considered the following: doses 1 through 3 before the first birthday, dose 4 on or after the first birthday and before the second birthday, and dose 5 on or after the fourth birthday and before the seventh birthday. Refer to Table 3 and Supplemental Tables 5 and 6 for CIs for each of these time points.

estimate, with overlapping CIs (<48 months: 51.5%; 95% CI: 24.3% to 69%; 48–84 months: 52.2%; 95% CI: 24.6% to 69.6%). Direct comparisons between the mixed group and acellular group could not be made for the following reasons: significant differences in the median age and time since vaccination between the groups ($P < .0001$), a greater proportion of participants with unknown Tdap vaccination status in the mixed group compared with the acellular group (7.2% vs 4.5%, respectively; $P = .0007$), and a significant trend of increasing unknown Tdap vaccination status with increasing age (Cochran-Armitage trend test, $z = -6.04$, $P < .0001$).

The Tdap product (Boostrix; GlaxoSmithKline; Adacel; Sanofi Pasteur) was verified by lot number in 76% of recipients (Table 2). Cases were more likely to have been vaccinated with Adacel compared with controls ($P = .05$), despite Adacel being used less frequently than Boostrix (17% vs 59%, respectively). Analyses of VE estimates by product were stratified by vaccine group. Regardless of group analyzed, Boostrix had slightly higher effectiveness than Adacel, although CIs overlapped (Table 4). Product-specific VE estimates in the mixed group were slightly lower than in the acellular group, but CIs again overlapped.

TABLE 3 Estimated Tdap VE and Duration of Protection Against Pertussis Among Adolescents Who Received All Acellular Vaccines (Birth Years 1998–2000)

	Cases (n = 450)	Controls (n = 1246)	Odds Ratio (95% CI)	Estimated VE (95% CI), %
No Tdap	109	154	Reference	Reference
Tdap	341	1092	0.36 (0.26 to 0.50)	63.9 (49.7 to 74.1)
Time since Tdap dose				
No Tdap	109	154	Reference	Reference
<12 months	69	332	0.27 (0.18 to 0.40)	73.1 (60.3 to 81.8)
12–23 months	124	389	0.45 (0.30 to 0.68)	54.9 (32.4 to 70.0)
24–47 months	148	371	0.66 (0.42 to 1.03)	34.2 (−0.03 to 58.0)

DISCUSSION

Tdap was recommended in the early 2000s to address the burden of pertussis among adolescents and adults.[19] The preferred administration age of 11 to 12 years targeted the peak of disease in adolescence and supported the established adolescent vaccination platform. Among adolescents, national Tdap vaccine uptake has increased steadily after its introduction, and early evaluations indicated it was effective in reducing the adolescent disease burden.[20–22] However, it is notable that the group of adolescents who initially received Tdap also received whole-cell vaccines during childhood. Despite promising indicators, the number of pertussis cases among adolescents has climbed during 2012, mainly in 13- to 14-year-olds who received solely acellular vaccines.[1] We have found that among adolescent recipients of all acellular vaccines, overall Tdap VE is 64%, with substantial waning of protection after 2 years. Although the study methodology differed substantially, our results were consistent with a recent Tdap VE study in Wisconsin.[11] The waning protection revealed in both studies indicates that it likely is a major contributor to the increasing pertussis incidence in this age group.

Although an initial study aim was to compare Tdap VE between adolescents who received a mix of whole-cell and acellular vaccines with those who received all acellular

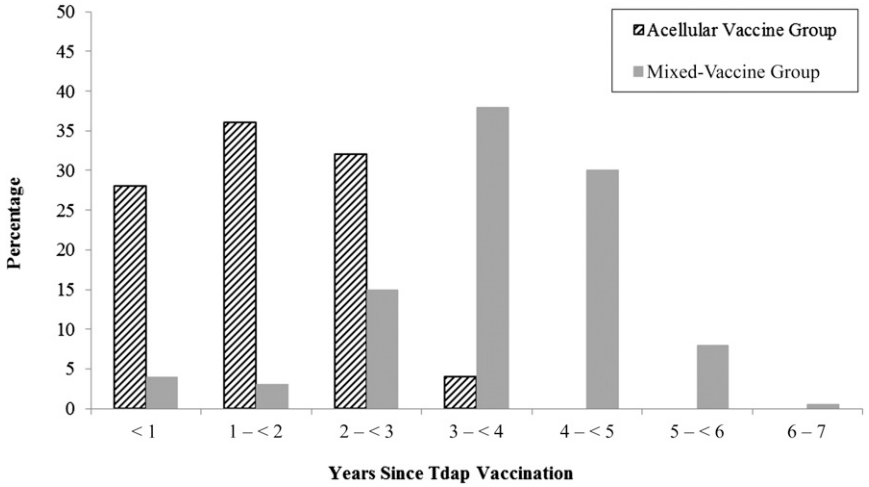

FIGURE 2

Time since Tdap vaccination, by vaccine group. Acellular vaccine group: adolescents born from 1998 to 2000, assumed to have received all acellular pertussis vaccines for the childhood series (cases = 450, controls = 1256). Mixed-vaccine group: adolescents born from 1993 to 1997, assumed to have received a mix of whole-cell and acellular pertussis vaccines (cases = 386, controls = 1076).

vaccines, this was not possible due to the difference in time since vaccination between the groups. Seventy-seven percent of adolescents in the mixed-vaccine group received Tdap at least 3 years before study enrollment in comparison with only 4% in the acellular vaccine group. Of note, however, was the finding that VE estimates in the mixed-vaccine group at less or more than 4 years since Tdap vaccination were similar (51.5% vs 52.2%). This finding suggests that durability of protection after Tdap is limited regardless of type of vaccines received during childhood, but that the rate of waning may be higher in those vaccinated solely with acellular vaccines.

Reasons for more rapid waning of Tdap-induced protection in persons vaccinated with acellular pertussis vaccines may be related to the immunologic response to acellular vaccines and a potential limitation of acellular vaccines to prevent transmission. Both whole-cell and acellular vaccines elicit pertussis-specific antibodies, which decrease after immunization.[23,24] However, other immunologic mechanisms, such as cell-mediated immunity, have also been associated with protection against pertussis disease and may be suboptimal after vaccination with acellular vaccines.[25–28] In addition, recent data from a novel nonhuman primate model showed that although acellular vaccines prevented symptomatic disease, they failed to prevent infection and transmission.[29]

Recently observed genetic variation in pertussis strains may also be playing a role in VE. In particular, the rapid emergence of pertactin-deficient pertussis strains is concerning, because pertactin is one of the major antigenic components of acellular pertussis vaccines.[30,31] A recent evaluation of available isolates obtained during the Washington 2012 outbreak revealed that over half carried a particular mutation resulting in pertactin deficiency.[30] Because our study was not designed to measure VE against these emerging strains, further evaluation is needed.

Analysis of Tdap product revealed a trend toward slightly higher VE estimates with Boostrix as opposed to Adacel, regardless of vaccine group analyzed. However, CIs overlapped between Tdap product and between vaccine group. On the basis of this analysis, definitive conclusions cannot be drawn regarding specific Tdap product effectiveness; nevertheless, these trends mirror findings of the Wisconsin study, which showed higher VE with Boostrix.[11]

As with all case-control studies, unaddressed biases could influence our findings. The likelihood and timing of Tdap receipt are strongly correlated with age; to control for this potential bias, we matched on birth year. We also matched on primary provider clinic in an attempt to control for differences in provider

TABLE 4 Estimated Tdap VE Against Pertussis, by Brand and Vaccine Group

	Cases	Controls	Odds Ratio (95% CI)	Estimated VE (95% CI), %
All birth years				
n	836	2322		
Tdap-unvaccinated	162	229	Reference	Reference
Boostrix	387	1245	0.40 (0.30 to 0.52)	60.1 (47.7 to 69.6)
Adacel	136	342	0.51 (0.37 to 0.71)	48.8 (28.8 to 63.2)
Unknown brand	151	506	0.37 (0.27 to 0.50)	63.2 (49.9 to 73.0)
Acellular vaccine group (birth years 1998–2000)				
n	450	1256		
Tdap-unvaccinated	109	154	Reference	Reference
Boostrix	231	725	0.37 (0.27 to 0.53)	62.6 (47.4 to 73.4)
Adacel	50	129	0.44 (0.28 to 0.71)	55.7 (29.3 to 72.2)
Unknown brand	60	238	0.27 (0.17 to 0.42)	73.3 (58.5 to 82.8)
Mixed-vaccine group (birth years 1993–1997)				
n	386	1076		
Tdap-unvaccinated	53	75	Reference	Reference
Boostrix	156	520	0.44 (0.28 to 0.68)	56.5 (31.7 to 72.3)
Adacel	86	213	0.61 (0.37 to 0.99)	39.2 (0.04 to 62.8)
Unknown brand	91	268	0.49 (0.31 to 0.78)	50.6 (22.2 to 68.7)

reporting and diagnostic testing practices and patient access to medical care. Cases were more likely to be white and non-Hispanic, but the large proportion of missing data limited our ability to evaluate the relevance of these potential demographic differences. To minimize misclassification of controls, all were checked against surveillance records and excluded if they had ever been reported as a pertussis case. Secondary analyses were also performed to confirm that inclusion of suspect or probable cases in the analysis, which use a less specific case definition, did not affect the VE estimates.

Expanding the vaccination program to include additional Tdap booster doses is unlikely to result in significant disease reduction given its short duration of protection and the assumed lower burden of disease in adults.[1] A cost-effectiveness analysis of a second dose of Tdap, modeling a best-case scenario of VE and duration of protection, revealed only a small reduction in the number of cases while incurring very high costs.[32] For these reasons, in addition to the challenges of improving adult vaccination coverage, the Advisory Committee on Immunization Practices has not supported a recommendation for additional Tdap doses for the general population.[33,34] In the interim, efforts to protect infants, who are at highest risk of critical disease and death, should be prioritized by reinforcing the recent recommendation for Tdap use during each pregnancy.[35]

CONCLUSIONS

We showed that Tdap protection substantially wanes within 2 to 4 years; this waning is likely contributing to the increase in pertussis among adolescents. Advances in our understanding of the immunology and bacteriology of *B pertussis* are essential to optimize future prevention and control measures. However, novel pertussis vaccines that effectively limit infection and transmission are also likely needed to reduce the burden of pertussis disease in the United States.

ACKNOWLEDGMENTS

We acknowledge the Washington State Department of Health and the local health jurisdictions of Clark, King, Pierce, Skagit, Snohomish, Yakima, and Whatcom counties for their leadership and strong support of this study. We also thank the members of the Epi-Aid team for successfully completing the important task of data collection in a very short time period. Participating county health departments included the following: Clark County Public Health; Public Health Seattle and King County, Communicable Diseases and Epidemiology; Tacoma Pierce County Health Department; Skagit County Public Health; Snohomish Health District; Yakima Health District; and Whatcom County Health Department.

We thank the following individuals for contributions to data collection: Bayo Arthur, Albert E. Barskey, Celia Bird, Amy Blain, Kate Rose Bobseine, Elizabeth Briere, Kimberly Brinker, Claire Brostrom-Smith, Jean Cadet, Tegan Callahan, Abbey Canon, Emma Carroll, Julia Chang, Tabitha Cheng, Natasha Close, Kpandja Djawe, Stephanie Dunkel, Sarah Ekerholm, David Fitter, Leah Gilbert, Dan Gingold, Wendy Hancock, Geoffrey Hart-Cooper, Joni Hensley, Kristen N. Hosey, Hajime Kamiya, Emmaculate Lebo, Adria Lee, Kara Levri, Jessica MacNeil, Sarah Meyer, Rebekah Miner, Janee Moore, Angela M. Orozco, Carolyn Othieno, Megan Popielarczyk, Anna T. Rapp, Charleen Ross, Stephanie J. Salyer, Kerry Schnell, Miriam Shiferaw, Reed Sorensen, Mandy Stahre, Jamille Taylor, Tracy Thomas, Rebecca Tsai, Joshua Van Otterloo, Tristan Victoroff, Joanna Watson, Emily Weston, Melissa Whaley, Misha Williams, and Jonathan M. Wortham.

Ms Martin supervised the conceptualization and design of the study, contributed to data interpretation, and provided critical revision of the manuscript for important intellectual content; Dr Patel supervised the conceptualization and design of the study, assisted with data collection, contributed to data interpretation, and provided critical revision of the manuscript for important intellectual content; and all authors approved the final manuscript as submitted.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-3358

DOI: 10.1542/peds.2014-3358

Accepted for publication Mar 16, 2015

Address correspondence to Anna M. Acosta, MD, 1600 Clifton Rd, NE, Mailstop C-25, Atlanta, GA 30329. E-mail: amacosta@cdc.gov

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found on page 1130, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2014-4118.

REFERENCES

1. Division of Integrated Surveillance Systems and Services, National Center for Public Health Informatics, Coordinating Center for Health Information and Service, Centers for Disease Control and Prevention, US Department of Health and Human Services. National Notifiable Disease Surveillance System. Available at: www.cdc.gov/pertussis/surv-reporting.html. Accessed August 12, 2013
2. Centers for Disease Control and Prevention. Pertussis epidemic—Washington, 2012. *MMWR Morb Mortal Wkly Rep*. 2012;61(28):517–522
3. Winter K, Harriman K, Zipprich J, et al. California pertussis epidemic, 2010. *J Pediatr*. 2012;161(6):1091–1096
4. Misegades LK, Winter K, Harriman K, et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. *JAMA*. 2012;308(20):2126–2132
5. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. *N Engl J Med*. 2012;367(11):1012–1019
6. Tartof SY, Lewis M, Kenyon C, et al. Waning immunity to pertussis following 5 doses of DTaP. *Pediatrics*. 2013;131(4):e1047–e1052
7. Baxter R, Bartlett J, Rowhani-Rahbar A, Fireman B, Klein NP. Effectiveness of pertussis vaccines for adolescents and adults: case-control study. *BMJ*. 2013;347:f4249
8. Rank C, Quinn HE, McIntyre PB. Pertussis vaccine effectiveness after mass immunization of high school students in Australia. *Pediatr Infect Dis J*. 2009;28(2):152–153
9. Skoff TH, Martin K, Cohn A, et al. Tdap vaccine effectiveness among adolescents: a case-control study in Minnesota. Talk presented at: 9th International Bordetella Symposium; September 30, 2010; Baltimore, MD.
10. Wei SC, Tatti K, Cushing K, et al. Effectiveness of adolescent and adult tetanus, reduced-dose diphtheria, and acellular pertussis vaccine against pertussis. *Clin Infect Dis*. 2010;51(3):315–321
11. Koepke R, Eickhoff JC, Ayele RA, et al. Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis: evidence of rapidly waning immunity and difference in effectiveness by Tdap brand. *J Infect Dis*. 2014;210(6):942–953
12. Centers for Disease Control and Prevention. National and state vaccination coverage among adolescents aged 13-17 years—United States, 2012. *MMWR Morb Mortal Wkly Rep*. 2013;62(34):685–693
13. Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. *MMWR Recomm Rep*. 1997;46(RR-10):25
14. Washington State Department of Health. Pertussis: reporting and surveillance guidelines. Available at: www.doh.wa.gov/Portals/1/Documents/5100/420-066-Guideline-Pertussis.pdf#nameddest=casedef. Accessed August 12, 2013
15. Washington State Department of Health. About the Washington State Immunization Information System. Available at: www.doh.wa.gov/ForPublicHealthandHealthcareProviders/HealthcareProfessionsandFacilities/DataReportingandRetrieval/ImmunizationInformationSystem/Aboutus.aspx. Accessed February 14, 2014
16. Centers for Disease Control and Prevention. Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1997;46(RR-7):1–25
17. Guyer B, Smith DR, Chalk R. Calling the shots: immunization finance policies and practices. Executive summary of the report of the Institute of Medicine. *Am J Prev Med*. 2000;19(3 suppl):4–12
18. Howell-White SR, Rosato NS. Examination of universal vaccine purchasing states and New Jersey. New Brunswick, NJ: Rutgers Center for State Health Policy; 2005
19. Broder KR, Cortese MM, Iskander JK, et al; Advisory Committee on Immunization Practices. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-3):1–34
20. Centers for Disease Control and Prevention. National and state vaccination coverage among adolescents aged 13-17 years—United States, 2011. *MMWR Morb Mortal Wkly Rep*. 2012;61(34):671–677
21. Ward JI, Cherry JD, Chang SJ, et al; APERT Study Group. Efficacy of an acellular pertussis vaccine among adolescents and adults. *N Engl J Med*. 2005;353(15):1555–1563
22. Skoff TH, Cohn AC, Clark TA, Messonnier NE, Martin SW. Early impact of the US Tdap vaccination program on pertussis trends. *Arch Pediatr Adolesc Med*. 2012;166(4):344–349
23. Hendrikx LH, Berbers GA, Veenhoven RH, Sanders EA, Buisman AM. IgG responses after booster vaccination with different pertussis vaccines in Dutch children 4 years of age: effect of vaccine antigen content. *Vaccine*. 2009;27(47):6530–6536
24. Vermeulen F, Dirix V, Verscheure V, et al. Persistence at one year of age of antigen-induced cellular immune responses in preterm infants vaccinated against whooping cough: comparison of three different vaccines and effect of a booster dose. *Vaccine*. 2013;31(15):1981–1986
25. Ausiello CM, Urbani F, la Sala A, Lande R, Cassone A. Vaccine- and antigen-dependent type 1 and type 2 cytokine induction after primary vaccination of infants with whole-cell or acellular pertussis vaccines. *Infect Immun*. 1997;65(6):2168–2174

26. Leef M, Elkins KL, Barbic J, Shahin RD. Protective immunity to Bordetella pertussis requires both B cells and CD4 (+) T cells for key functions other than specific antibody production. *J Exp Med*. 2000;191(11):1841–1852

27. Rieber N, Graf A, Hartl D, Urschel S, Belohradsky BH, Liese J. Acellular pertussis booster in adolescents induces Th1 and memory CD8+ T cell immune response. *PLoS ONE*. 2011;6(3): e17271

28. Hendrikx LH, Schure RM, Oztürk K, et al. Different IgG-subclass distributions after whole-cell and acellular pertussis infant primary vaccinations in healthy and pertussis infected children. *Vaccine*. 2011;29(40):6874–6880

29. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proc Natl Acad Sci USA*. 2014;111(2):787–792

30. Pawloski LC, Queenan AM, Cassiday PK, et al. Prevalence and molecular characterization of pertactin-deficient Bordetella pertussis in the United States. *Clin Vaccine Immunol*. 2014;21(2): 119–125

31. Queenan AM, Cassiday PK, Evangelista A. Pertactin-negative variants of Bordetella pertussis in the United States. *N Engl J Med*. 2013;368(6):583–584

32. Kamiya H. Decision and cost effectiveness analysis: a second dose of Tdap. Talk presented at: Meeting of the Advisory Council on Immunization Practices; June 19, 2013; Atlanta, GA. Available at: www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun13.pdf. Accessed August 1, 2013

33. Miller BL, Kretsinger K, Euler GL, Lu PJ, Ahmed F. Barriers to early uptake of tetanus, diphtheria and acellular pertussis vaccine (Tdap) among adults-United States, 2005-2007. *Vaccine*. 2011; 29(22):3850–3856

34. Advisory Committee on Immunization Practices. Pertussis vaccines: working group conclusions on a second dose of Tdap. Talk presented at: Meeting of the Advisory Committee on Immunization Practices; June 19, 2013; Atlanta, GA. Available at: www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-jun13.pdf. Accessed August 1, 2013

35. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR Morb Mortal Wkly Rep*. 2013; 62(7):131–135

TIMING IS KEY: *During the college football season, some games begin at noon while others begin late in the evening. I have always wondered if the start time for the game could affect athletic performance. I have noticed that when I exercise I seem slower first thing in the morning. As it turns out, athletes have a natural circadian rhythm and performance depends on whether the event is in sync with the athlete's circadian rhythm.*

As reported in The New York Times *(Well: January 29, 2015), researchers evaluated the athletic performance of 20 competitive field hockey players and 22 competitive squash players six times a day. When the results were assessed in aggregate, the researchers found that overall, athletic performance peaked in the evening. This was consistent with previous findings by other researchers. However, when they looked at peak performance based on time of day and whether the athlete was an early morning, mid-morning, or late morning riser, they found that athletic performance peaked 4 to 6 hours after waking. Early morning risers did their best at noon, while late risers did their best in the evening. Nobody did well early in the morning. In fact, performance diminished by as much as 26% if not in sync with the natural circadian rhythm. While the study involved a limited number of adults, and the exercise measured was not related to the sporting event, the data suggest that to maximize performance athletes should consider the time of the event. If necessary, they should stagger their sleep time to help ensure their circadian rhythm is in sync with the timing of the event.*

As for me, I do not think it matters too much what time of day I exercise. After all, I am not in a competition. Still, it is nice to know there is a reason why I seem so sluggish while exercising early in the morning.

Noted by WVR, MD

Tdap Vaccine Effectiveness in Adolescents During the 2012 Washington State Pertussis Epidemic

Anna M. Acosta, Chas DeBolt, Azadeh Tasslimi, Melissa Lewis, Laurie K. Stewart, Lara K. Misegades, Nancy E. Messonnier, Thomas A. Clark, Stacey W. Martin and Manisha Patel

Pediatrics 2015;135;981
DOI: 10.1542/peds.2014-3358 originally published online May 4, 2015;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Tdap Vaccine Effectiveness in Adolescents During the 2012 Washington State Pertussis Epidemic

Anna M. Acosta, Chas DeBolt, Azadeh Tasslimi, Melissa Lewis, Laurie K. Stewart, Lara K. Misegades, Nancy E. Messonnier, Thomas A. Clark, Stacey W. Martin and Manisha Patel

Pediatrics 2015;135;981
DOI: 10.1542/peds.2014-3358 originally published online May 4, 2015;