MAJOR ARTICLE

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

Ruth Koepke,[1,2] Jens C. Eickhoff,[3] Roman A. Ayele,[1,2,a] Ashley B. Petit,[1,2,a] Stephanie L. Schauer,[1] Daniel J. Hopfensperger,[1] James H. Conway,[2] and Jeffrey P. Davis[1]

[1]Bureau of Communicable Diseases and Emergency Response, Wisconsin Division of Public Health, and [2]Department of Pediatrics and [3]Department of Biostatistics and Medical Informatics, School of Medicine and Public Health, University of Wisconsin–Madison, Madison

Background. We estimated the vaccine effectiveness (VE) of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis among adolescents during a statewide outbreak of pertussis in Wisconsin during 2012.

Methods. We used the population-based Wisconsin Immunization Registry (WIR) to construct a cohort of Wisconsin residents born during 1998–2000 and collect Tdap vaccination histories. Reports of laboratory-confirmed pertussis with onset during 2012 were matched to WIR clients. Incidence rate ratios (IRRs) of pertussis and Tdap VE estimates [(1 − IRR)*100%], by year of Tdap vaccine receipt and brand (Boostrix/Adacel), were estimated using Poisson regression.

Results. Tdap VE decreased with increasing time since receipt, with VEs of 75.3% (95% confidence interval [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% to 30.1%) for receipt during 2009/2008; point estimates were higher among Boostrix recipients than among Adacel recipients. 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 (adjusted IRR, 0.62 [95% CI, .52–.74]).

Conclusions. Our results demonstrate waning immunity following vaccination with either Tdap brand. Boostrix was more effective than Adacel in preventing pertussis in our cohort, but these findings may not be generalizable to adolescent cohorts that received different diphtheria-tetanus-acellular pertussis vaccines (DTaP) during childhood and should be further examined in studies that include childhood DTaP history.

Keywords. *Bordetella pertussis*; vaccine effectiveness; Tdap (tetanus-diphtheria-acellular pertussis) vaccine; epidemiology; immunization information systems.

Received 24 April 2014; accepted 22 May 2014; electronically published 5 June 2014.

Presented in part: 10th International Symposium on Bordetella, Dublin, Ireland, 8–11 September 2013; IDWeek, San Francisco, California, 4 October 2013.

[a]Present affiliations: School of Public Health and Department of Pediatrics, School of Medicine, University of Colorado–Denver (R. A. A.); Bureau of Communicable Diseases and Emergency Response, Wisconsin Division of Public Health, Madison (A. B. P.).

Correspondence: Ruth Koepke, MPH, Wisconsin Division of Public Health, 1 West Wilson St, Madison, WI 53702 (ruth.koepke@wisconsin.gov).

The Journal of Infectious Diseases 2014;210:942–53

DOI: 10.1093/infdis/jiu322

Pertussis (whooping cough) is a vaccine-preventable disease caused by the bacterium *Bordetella pertussis*. Despite high rates of childhood vaccination with pertussis-containing vaccines [1], reported cases of pertussis in the United States increased during the early 2000s among adolescents and, more recently, among school-aged children [2].The change during 1992–1997 from vaccinating children with diphtheria-tetanus-whole cell pertussis vaccine (DTwP) to vaccinating children with diphtheria-tetanus-acellular pertussis

vaccine (DTaP) [3, 4] has been suggested as a factor contributing to this increased occurrence [5–7]. Results of recent studies suggest that receipt of priming doses using DTwP is more effective in preventing pertussis than receipt of priming doses using DTaP [8–10] and that DTaP-induced immunity wanes during the years following dose 5 [11–13]. Formulation of vaccines that induce long-lasting protection against pertussis has been complicated by an incomplete understanding of the correlates of protection against pertussis [14].

To reduce the burden and reservoir of pertussis among adolescents, during March 2006 the Advisory Committee on Immunization Practices recommended a 1-time booster dose of a new tetanus-diphtheria-acellular pertussis vaccine (Tdap) for routine use among adolescents aged 11–12 years [15]. Two brands of Tdap, Adacel (Sanofi Pasteur, Toronto, Canada) and Boostrix (GlaxoSmithKline Biologicals, Rixensart, Belgium), were licensed for use in the United States during 2005. The Tdap brands differ in the number and concentration of *B. pertussis* antigens and generally contain reduced quantities of these antigens, compared with each company's DTaP formulations. Because of recent introduction, Tdap effectiveness several years after receipt has not been measured in a large population-based study, and the effectiveness of the Tdap products has not been compared.

During 2003–2005, prior to Tdap availability, a large (7525 reported cases) statewide outbreak of pertussis occurred in Wisconsin, with high incidence rates reported among adolescents. During 2008–2010, a requirement was phased in for all Wisconsin adolescents to receive 1 Tdap dose before entry into grades 6–12 [16]. Despite these measures, another statewide outbreak (6462 reported cases) of pertussis occurred in Wisconsin during 2012 [17]; 25% of cases occurred among adolescents aged 11–14 years, 76% of whom previously received Tdap. The objective of this study was to investigate the effectiveness of Tdap, by brand and time since receipt, in preventing pertussis during the 2012 outbreak among age cohorts of adolescents who likely never received DTwP.

METHODS

Study Design

We used the population-based Wisconsin Immunization Registry (WIR) to construct 2 analysis cohorts and collect Tdap vaccination histories. Among the full cohort of Wisconsin residents born during 1998–2000, we estimated Tdap vaccine effectiveness (VE), by brand and year of receipt, for preventing pertussis during 2012. Among the subset of the full cohort that received Tdap before 2012 (the Tdap cohort), we examined the incidence of pertussis during 2012, by Tdap brand and year of receipt.

The WIR

The WIR is a statewide, population-based immunization information system (IIS) that records and tracks immunization histories for Wisconsin residents of all ages [18–20]. Established during 2000 by the Wisconsin Divisions of Public Health (WDPH) and Health Care Access and Accountability, WIR is populated with client demographic information for all Wisconsin births since 1995 by the WDPH Office of Health Informatics. WIR receives new client (for Wisconsin residents born elsewhere or before 1995) and immunization information through direct entry and electronic exchange with public and private healthcare providers, health maintenance organizations, and Medicaid. Providing information to the WIR is voluntary, and some fields, including trade name (TN) and lot number (LN), are not required. Accordingly, TN and LN can be missing and immunization histories incomplete. With quality improvement efforts including meaningful use incentives [21], the number of organizations transmitting information to the WIR and percentage of DTaP and Tdap doses with TN and LN have increased (Figure 1).

Pertussis Case Reporting and Case Definition

Pertussis is a notifiable disease in Wisconsin. We reviewed all reports of pertussis with cough onsets during 2008–2012 among Wisconsin residents born during 1998–2000 that were submitted to WDPH.

We defined a case of pertussis as an acute cough illness with onset during 2012 that met the Council of State and Territorial Epidemiologists (CSTE) definition of confirmed: an illness of any duration in a patient with a clinical specimen culture positive for *B. pertussis* or an illness meeting the CSTE clinical case definition (CCD) of pertussis (cough ≥14 days duration with whoop, paroxysms, or posttussive vomiting) in a patient with a clinical specimen polymerase chain reaction (PCR) positive for *B. pertussis* [22].

We defined a prior incident of pertussis as an acute cough illness with cough onset during 2008–2011 in a patient with symptoms meeting the CCD of pertussis or clinical specimen PCR or culture positive for *B. pertussis*.

Full Cohort

To construct the full cohort of Wisconsin residents born during 1998–2000, we selected all WIR client records with Wisconsin addresses, birth dates during 1998–2000, and no dates of death and matched them to cases and prior incidents of pertussis by name and birth date (and, if necessary, by address or mother's name; Figure 2). Often, the addresses of WIR clients who leave Wisconsin are not updated in WIR. Consequently, as more individuals moved into Wisconsin, the numbers of clients in WIR for these age cohorts became substantially larger (by 21%) than corresponding population estimates [23]. We adjusted the full cohort to equal the population estimate for each age cohort using the following method. All WIR clients with a record of Tdap receipt or with a match to a pertussis case were assumed to be Wisconsin residents during 2012 and were included, along with their demographic and immunization histories, in the full

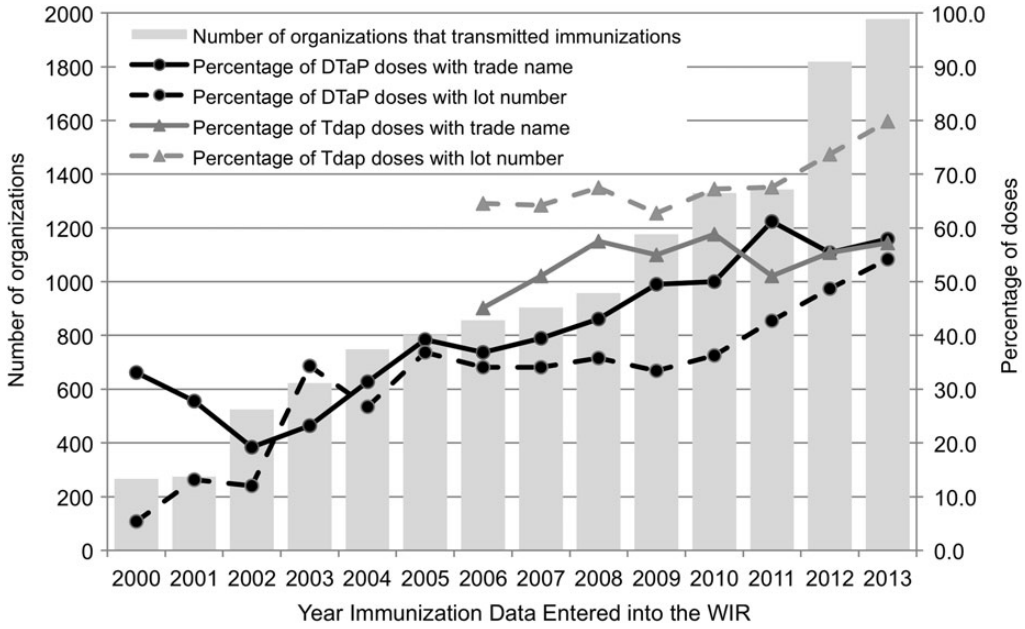

Figure 1. The number of organizations that transmitted immunization information to the Wisconsin Immunization Registry (WIR) and the percentage of diphtheria-tetanus-acellular pertussis vaccine (DTaP) and tetanus-diphtheria-acellular pertussis vaccine (Tdap) doses that included trade name and lot number, by the year of data entry into the WIR. The number of organizations that transmitted immunization data to the WIR, depicted by the gray bars, increased steadily from the inception of the WIR during 2000 through 2013. Of DTaP doses entered into the WIR, inclusion of trade name increased from 33.1% during 2000 to 57.9% during 2013, and inclusion of lot number increased from 5.4% during 2000 to 54.2% during 2013. Of Tdap doses entered into the WIR, inclusion of trade name increased from 45.1% during 2006 to 57.2% during 2013, and inclusion of lot number increased from 64.6% during 2006 to 79.8% during 2013.

cohort. Among WIR clients with no record of Tdap receipt and no match to a pertussis case, we could not specify precisely which were living in Wisconsin but had not received Tdap and which had moved from Wisconsin. Therefore, we included in the full cohort a sample of WIR clients with no record of Tdap receipt and no match to a pertussis case, selected by birth year, so that the sum of all clients in each age cohort was equal to the population estimate. To account for the uncertainty of precisely which clients were included in this sample, for these clients we retained only birth year, Tdap status, and pertussis case status. Demographic information, residence location, and DTaP vaccination history were not retained; consequently, analyses using the full cohort could not be adjusted for these variables.

Tdap Cohort

To further examine the risk of pertussis among a population with demographic, residence location, and DTaP vaccination data available, we constructed the Tdap cohort by selecting WIR clients from the full cohort who received Tdap during 2008–2011 (Figure 2).

Exclusion Criteria

Any clients matched to prior incidents of pertussis were excluded from both cohorts. Cases of pertussis not matched to WIR clients were excluded.

Vaccination Histories

For all clients, history of Tdap receipt was collected from the WIR only and defined as vaccination with Tdap or DTaP on or after the 10th birthday and before cough onset (if a case-client) or before 18 December 2012. Because of delays in developing immunity after Tdap vaccination, all receipt dates were adjusted (14 days were added to the vaccination date). Therefore, among case-clients, doses with vaccination dates <14 days before cough onset were excluded. To limit differential ascertainment of vaccination status, we used WIR as the only source of vaccination information for case- and noncase-clients and, among case-clients, we excluded Tdap doses administered before cough onset but entered into the WIR (per the data entry electronic time stamp) after cough onset.

Tdap brand was obtained from the TN field. During 2008–2012, Boostrix and Adacel had distinctly different LNs (first characters were "A" for Boostrix and "C" or "U" for Adacel); therefore, when LN was available, brand was assigned on the basis of the first character. When TN and LN were both available from WIR, they were compared to detect discordances; when discordancies were detected, brand was assigned on the basis of the LN. DTaP doses received on or after the 10th birthday were categorized as a separate Tdap brand.

Among the Tdap cohort, the number of DTaP doses received before the 10th birthday and date of last DTaP dose were collected from WIR only.

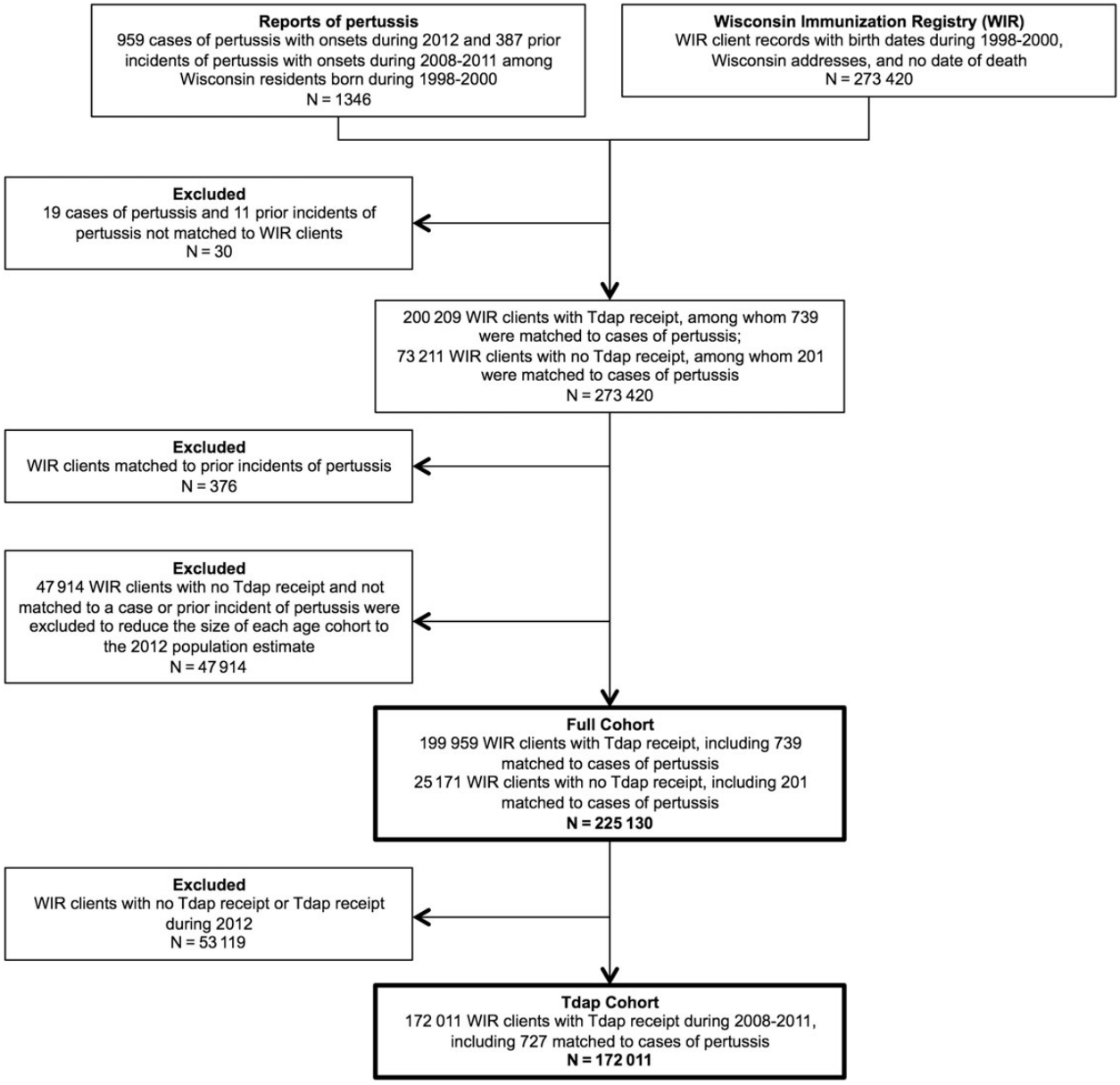

Figure 2. The inclusion of Wisconsin Immunization Registry (WIR) clients into the 2 analysis cohorts: the full cohort and the tetanus-diphtheria-acellular pertussis vaccine (Tdap) cohort. For the full cohort, 273 420 client records with Wisconsin addresses, birth dates during 1998–2000, and no date of death were selected from the WIR. Prior incidents of pertussis with onsets during 2008–2011 (n = 387) and cases of pertussis with onsets during 2012 (n = 959) were identified, and the related records were matched to WIR client records. Nineteen of 959 cases of pertussis and 11 of 387 prior incidents of pertussis were not matched to WIR client records and were excluded. Among the 273 420 selected WIR client records, 200 209 had a record of Tdap receipt (including 739 matched to a case of pertussis), and 73 211 had no record of Tdap receipt (including 201 matched to a case of pertussis). A total of 376 WIR clients were matched to prior incidents of pertussis and were excluded. Among the WIR clients who had no record of Tdap receipt and were not matched to a case or prior incident of pertussis, 47 914 were excluded to reduce the size of each age cohort to the 2012 population estimate for each age cohort [23]. This was necessary because it could not be determined whether WIR clients who had no record of Tdap receipt and were not matched to a case of pertussis had not received Tdap or were no longer Wisconsin residents. The final full cohort (n = 225 130) included 199 959 clients with a record of Tdap receipt (including 739 with cases of pertussis) and 25 171 clients with no record of Tdap receipt (including 201 with cases of pertussis). The Tdap cohort was constructed by selecting from the full cohort clients who had received Tdap during 2008–2011. The final Tdap cohort of 172 011 WIR clients included 727 with a case of pertussis with onsets during 2012.

Statistical Analyses

Data analyses were conducted using SAS, version 9.3 (Cary, NC). Incidence rates of pertussis during 2012 per 100 000 person-years at risk were calculated. Noncase-clients contributed to person-time at risk during all of 2012. Case-clients stopped contributing to person-time at risk on the cough onset date.

Among the full cohort, we estimated incidence rate ratios (IRRs) of pertussis by Tdap receipt year and brand, using Poisson regression with data for unvaccinated individuals as the reference group. Birth year was evaluated as a potential confounder and tested for collinearity with Tdap receipt year. Separate models were fit for clients with Tdap receipt dates during 2008–2011 and during 2012. In the latter model, Tdap receipt was treated as a time-varying covariate with vaccinated clients contributing to person-time at risk in both the vaccinated and unvaccinated groups to account for change in Tdap receipt status. VE estimates were calculated as $[1.0 - \text{IRR}] \times 100\%$ and reported with corresponding 95% confidence intervals (CIs).

Among the Tdap cohort, we estimated IRRs of pertussis by Tdap brand and year of receipt using Poisson regression. Sex, age on 1 January 2012, Wisconsin region of residence [24], number of DTaP doses received before the 10th birthday, years since last DTaP dose, and age at Tdap receipt were evaluated as potential confounders, and relationships were evaluated for effect modification. The most parsimonious model excluding collinear covariates was selected.

To examine the impact of missing Tdap brand on our IRR estimates by brand among the full cohort and Tdap cohort, we conducted sensitivity analyses using multiple imputation under the missing-at-random assumption [25]. Missing brand names were imputed (given a value of Adacel or Boostrix) using the logistic regression multiple imputation method, with provider, Tdap receipt date, and age at receipt as predictors of brand. The SAS procedure MI was used to generate 5 imputed data sets (relative efficiency rate, 96%) [26]. IRRs for each imputed data set and corresponding variances and covariances were calculated using Poisson regression. Using the SAS procedure MIANALYZE, the results from the 5 data sets were combined for overall inferences, accounting for variability between imputations.

RESULTS

Figure 2 depicts inclusion of WIR clients into the full cohort (N = 225 130) and Tdap cohort (N = 172 011). Among 959 pertussis cases with onsets during 2012 (all PCR positive, 3 also culture positive) reported to WDPH, 940 (98%) were matched to WIR clients. Specimens from 494 case-clients (53%) were tested using PCR assays that detect both *B. pertussis* (IS*481*) and *Bordetella parapertussis* (IS*1001*); 1 (0.2%) was positive for both species. No specimens were tested for pertactin expression.

Among WIR records of Tdap recipients, 53% included both TN and LN (0.17% records [185 of 106 305] were discordant), 17% included LN only, 10% included TN only, and 20% included neither TN nor LN.

Full Cohort: Estimation of VE

Among the full cohort, reported cases of pertussis increased with age (Table 1); pertussis incidence was 334.7, 379.1, and 543.5 cases per 100 000 person-years among WIR clients born during 2000, 1999, and 1998, respectively. Tdap receipt increased with increasing age. Receipt of Adacel and Boostrix varied by birth year. Although birth year and Tdap receipt year were correlated (Pearson correlation coefficient, 0.73; $P < .001$), sufficient variability remained for birth year to be included in the adjusted model. Because few clients received Tdap during 2008, receipt years 2008 and 2009 were combined.

The unadjusted and birth-year-adjusted estimates of Tdap VE decreased with increasing time since Tdap receipt, with (adjusted) values of 75.3% (95% CI, 55.2%–86.5%), 68.2% (95% CI, 60.9%–74.1%), 34.5% (95% CI, 19.9%–46.4%), and 11.9% (95% CI, −11.1% to 30.1%) associated with receipt during 2012, 2011, 2010, and 2009/2008, respectively ($P < .0001$, by the test for linear trend; Table 2). Additionally, unadjusted and birth-year-adjusted point estimates of VE were greater among Boostrix recipients than among Adacel recipients during each year of Tdap receipt (Table 2).

When clients with imputed brand names were included (Supplementary Table 1) and a more inclusive case definition was used (Supplementary Table 2), the results were similar: point estimates of VE were greater among Boostrix recipients than among Adacel recipients during each year of Tdap receipt.

Tdap Cohort

Characteristics of the Tdap cohort, by brand received, are presented in Table 3. Adacel recipients were slightly older on 1 January 2012 than Boostrix recipients. Receipt of Adacel and Boostrix varied by region of residence. Receipt of Tdap at age 10 years was more common among Boostrix recipients, consistent with the approved earliest ages of use (Boostrix, 10 years; Adacel, 11 years). Median time from Tdap receipt to 1 January 2012 was 1.2 years among Adacel and Boostrix recipients. Among Adacel and Boostrix recipients, differences in percentages who received ≥4 DTaP doses and times from last DTaP dose were small. Data regarding formulation of DTaP doses received were missing for 78% of all doses and 86% of first doses documented in WIR.

In unadjusted analyses, the incidence of pertussis increased with increasing age, increasing time since Tdap receipt, and increasing time since the last DTaP dose (Table 4). Pertussis incidence varied significantly by region of residence and age at Tdap receipt and was higher among Adacel recipients than among Boostrix recipients.

After adjustment for region of residence, receipt of Boostrix, compared with Adacel, was associated with a 38% decreased incidence of pertussis (IRR, 0.62 [95% CI, .52–.74]), and compared with receipt during 2011, increasing time since Tdap receipt was associated with an increasing incidence of pertussis (Table 5). The effect of time since receipt did not vary significantly by brand ($P = .89$). Results were similar in sensitivity analyses when all who received Tdap at age 10 years were

Table 1. Characteristics of the Full Cohort by Birth Year

Characteristic	Birth Year, No. (%)			*P* Value[a]
	1998	1999	2000	
Pertussis case during 2012				
No	74 168 (99.5)	74 252 (99.6)	75 770 (99.7)	<.001
Yes	404 (0.5)	282 (0.4)	254 (0.3)	
Total	74 572 (100.0)	74 534 (100.0)	76 024 (100.0)	
Tdap receipt				
No	6253 (8.4)	7111 (9.5)	11 807 (15.5)	<.001
Yes	68 319 (91.6)	67 423 (90.5)	64 217 (84.5)	
Total	74 572 (100.0)	74 534 (100.0)	76 024 (100.0)	
Tdap brand[b]				
Adacel	26 805 (39.2)	25 423 (37.7)	25 999 (40.5)	<.001
Boostrix	25 839 (37.8)	28 051 (41.6)	28 016 (43.6)	
DTaP	490 (0.7)	433 (0.6)	335 (0.5)	
Unspecified	15 185 (22.2)	13 516 (20.0)	9867 (15.4)	
Total	68 319 (100.0)	67 423 (100.0)	64 217 (100.0)	
Tdap receipt year[b]				
2012	1930 (2.8)	3721 (5.5)	22 297 (34.7)	<.001
2011	4133 (6.0)	23 158 (34.3)	38 618 (60.1)	
2010	23 061 (33.8)	37 650 (55.8)	3302 (5.1)	
2009	36 679 (53.7)	2894 (4.3)	0 (0.0)	
2008	2516 (3.7)	0 (0.0)	0 (0.0)	
Total	68 319 (100.0)	67 423 (100.0)	64 217 (100.0)	

Abbreviations: DTaP, diphtheria-tetanus-acellular pertussis vaccine; Tdap, tetanus-diphtheria-acellular pertussis vaccine.

[a] By the χ^2 test.

[b] Among Tdap recipients only.

excluded and when unspecified Tdap brand names were imputed to have a value of Adacel or Boostrix.

DISCUSSION

Among our cohort of Wisconsin adolescents born during 1998–2000, Tdap effectiveness in preventing laboratory-confirmed pertussis during the 2012 statewide outbreak decreased rapidly with increasing time since Tdap receipt, with values of 75.3%, 68.2%, 34.5%, and 11.9% among those who received Tdap during 2012, 2011, 2010, and 2009/2008, respectively. Our estimates of Tdap effectiveness within 2 years of receipt are similar to estimates previously reported among adolescents within 2 years of receipt (57.6%–74.4%) [27–29]. Our observations of decreasing effectiveness with increasing time since Tdap receipt were corroborated with adjusted analyses among the Tdap cohort and are similar to estimates from a case-control study conducted during the 2012 pertussis outbreak in Washington state among adolescents aged 11–14 years; estimated Tdap VE declined from 75% to 41%, respectively, <1 and ≥2 years after vaccination [30]. Together with observations of waning immunity following DTaP receipt [11–13], our results provide additional evidence of a limited duration of protection induced by acellular pertussis vaccines and the need for new pertussis vaccines that provide long-lasting protection [6, 31].

Our results are the first to suggest a difference in Tdap effectiveness by brand, with apparent waning of immunity among recipients of both brands. Among our cohort, Boostrix appeared to be more effective than Adacel in preventing pertussis, and in sensitivity analyses, including adjusted analyses among the Tdap cohort, the trends were similar. It is possible that unknown provider- or patient-related factors associated with the brand of Tdap recorded in WIR and having reported, laboratory-confirmed pertussis could have contributed to our observed differences in effectiveness by brand; however, it is also biologically plausible that Tdap effectiveness varied by brand because the products differ in composition (Supplementary Table 3).

Results of epidemiologic [9, 10] and antibody-response studies [32, 33] suggest that the formulations of the priming doses of pertussis vaccine received influence future immunity to pertussis, perhaps by linked epitope suppression [32, 34]. Following pertussis infection or Tdap vaccination, antibody responses to *B. pertussis* antigens were more robust if the antigens had been received during priming [32, 33]. These findings suggest

Table 2. Incidence Rate Ratios (IRRs) of Pertussis During 2012 and Vaccine Effectiveness (VE) Estimates Among the Full Cohort, by Year of Tetanus-Diphtheria-Acellular Pertussis Vaccine (Tdap) Receipt and Tdap Brand

Year of Tdap Receipt[a]	Cases, No.	Cohort Size, Subjects, No.	Unadjusted		Adjusted[b]		*P* Value[c]
			IRR (95% CI)	Estimated VE, % (95% CI)	IRR (95% CI)	Estimated VE, % (95% CI)	
No Tdap received	201	25 171	Reference	Reference	Reference	Reference	
Any Tdap brand							<.0001
2012	12	27 948	0.25 (.14–.45)	75.1 (54.8–86.2)	0.25 (.14–0.45)	75.3 (55.2–86.5)	
2011	173	65 909	0.33 (.27–.40)	67.2 (59.8–73.3)	0.32 (.26–.39)	68.2 (60.9–74.1)	
2010	293	64 013	0.57 (.48–.68)	42.8 (31.6–52.2)	0.66 (.54–.80)	34.5 (19.9–46.4)	
2009/2008	261	42 089	0.78 (.65–.93)	22.4 (6.8–35.5)	0.88 (.70–1.11)	11.9 (−11.1 to 30.1)	
By known Tdap brand[d,e]							
Adacel							<.0001
2012	8	12 262	0.39 (.19–.79)	61.3 (20.7–81.1)	0.38 (.19–.79)	61.8 (21.5–81.4)	
2011	91	27 128	0.42 (.33–.54)	58.1 (46.3–67.3)	0.41 (.32–.52)	59.4 (47.9–68.4)	
2010	134	22 903	0.73 (.59–.91)	26.8 (9.0–41.2)	0.86 (.68–1.09)	14.0 (−9.4 to 32.4)	
2009/2008	112	15 934	0.88 (.70–1.11)	12.0 (−10.9 to 30.2)	1.02 (.77–1.34)	−1.8 (−34.0 to 22.7)	
Boostrix							<.0001
2012	2	12 592	0.09 (.02–.38)	90.6 (62.0–97.7)	0.09 (.02–.38)	90.7 (62.4–97.7)	
2011	46	27 180	0.21 (.15–.29)	78.9 (70.9–84.7)	0.20 (.15–.28)	79.6 (71.8–85.2)	
2010	86	26 496	0.41 (.32–.52)	59.5 (47.8–68.5)	0.47 (.36–.61)	53.4 (39.2–64.3)	
2009/2008	75	15 638	0.60 (.46–.78)	40.1 (21.9–54.0)	0.70 (.52–.94)	30.5 (6.2–48.5)	

Abbreviation: CI, confidence interval.

[a] Separate Poisson regression models were used to determine IRR and VE estimates for clients with Tdap receipt dates during 2008–2011 and clients with Tdap receipt dates during 2012. Because few clients were vaccinated during 2008, Tdap receipt years 2008 and 2009 were combined.

[b] Adjusted for birth year.

[c] Test for linear trend in adjusted VE from 2012 to 2009/2008.

[d] Excludes those with Tdap brands that were unspecified (183 cases and 38 385 noncases) or diphtheria-tetanus-acellular pertussis vaccine (DTaP) (2 cases and 1256 noncases).

[e] The 95% CIs of the IRR and VE point estimates among Adacel and Boostrix recipients do not overlap during Tdap receipt years 2011 and 2010. The 95% CIs of the IRR and VE point estimates among Adacel and Boostrix recipients do overlap during Tdap receipt years 2012 and 2009/2008.

Tdap vaccines may boost antibody responses most effectively to the antigens received during priming; therefore, the effectiveness of Adacel and Boostrix may depend on which vaccine antigens (pertussis toxin [PT], filamentous hemagglutinin [FHA], pertactin, and fimbriae 2/3) were received during priming and on the quantities of these antigens in the Tdap vaccines received.

A limitation of our study is lack of specific data regarding DTaP formulations received by each client during childhood. Because WIR data collection began during 2000, the last birth year among our cohort, and because providers are not required to transmit brand information to the WIR, data regarding specific formulations received were missing for 78% of all DTaP doses documented among the Tdap cohort. During 1998–2001, when our cohort would have received priming doses, DTwP was no longer recommended for use, and multiple DTaP products containing 1–4 pertussis antigens were available (Supplementary Table 3). Infanrix, the DTaP analogue to Boostrix, may have been more frequently received among Wisconsin's 1998–2000 birth cohorts than in other states because the Wisconsin Vaccines for Children Program exclusively provided Infanrix to public vaccine providers, who vaccinated approximately 30% of DTaP recipients in Wisconsin.

PT and FHA quantities (micrograms/dose) are greater in Boostrix than Adacel. Both antigens would have been received among the majority of the cohort during priming. Adacel contains fimbriae 2 and 3, whereas Boostrix does not, but fimbriae 3 was not available in DTaP priming formulations, and fimbriae 2 was available in only 1 vaccine. Pertactin quantity is greater in Adacel, but the effectiveness of this antigen may vary by geographic location and time because the prevalence of *B. pertussis* strains that do not express pertactin, currently unknown in Wisconsin, appears to be increasing in the United States [35–37].

Results of a study conducted in Italy demonstrated that immunoglobulin G responses to PT persisted longer following receipt of Boostrix among children primed with Infanrix-containing vaccine than among children primed with a 2-component (PT and FHA) DTaP-containing vaccine (Hexavac, Sanofi Pasteur), despite Infanrix and Hexavac having the same quantity of PT [33]. These data suggest that protection

Table 3. Characteristics of the Tetanus-Diphtheria-Acellular Pertussis Vaccine (Tdap) Cohort, by Tdap Brand Received

Characteristic	Tdap Brand, No. (%)					*P* Value[a]
	Total	Adacel	Boostrix	Unspecified	DTaP	
Sex						
Female	84 778 (49.3)	32 342 (49.0)	34 302 (49.5)	17 601 (49.3)	533 (51.3)	<.01
Male	86 997 (50.6)	33 547 (50.9)	34 897 (50.3)	18 054 (50.6)	499 (48.0)	
Unknown	236 (0.1)	76 (0.1)	115 (0.2)	37 (0.1)	8 (0.8)	
Age on 1 January 2012, y						
11	41 788 (24.3)	16 043 (24.3)	17 863 (25.8)	7666 (21.5)	216 (20.8)	<.001
12	63 834 (37.1)	23 908 (36.2)	26 453 (38.2)	13 095 (36.7)	378 (36.3)	
13	66 389 (38.6)	26 014 (39.4)	24 998 (36.1)	14 931 (41.8)	446 (42.9)	
Median (IQR)	12.7 (12.0–13.4)	12.7 (12.0–13.4)	12.6 (12.0–13.3)	12.8 (12.1–13.4)	12.8 (12.1–13.5)	<.001
Region of residence[b]						
Southeastern	63 624 (37.0)	16 830 (25.5)	21 577 (31.1)	24 652 (69.1)	565 (54.3)	<.001
Southern	34 945 (20.3)	12 839 (19.5)	14 827 (21.4)	7105 (19.9)	174 (16.7)	
Northeastern	34 179 (19.9)	16 606 (25.2)	16 376 (23.6)	1080 (3.0)	117 (11.3)	
Western	22 378 (13.0)	10 521 (15.9)	10 056 (14.5)	1685 (4.7)	116 (11.2)	
Northern	15 327 (8.9)	8573 (13.0)	5770 (8.3)	941 (2.6)	43 (4.1)	
Unknown	1558 (0.9)	596 (0.9)	708 (1.0)	229 (0.6)	25 (2.4)	
Age at Tdap receipt, y						
10	19 718 (11.5)	2667 (4.0)	11 776 (17.0)	5063 (14.2)	212 (20.4)	<.001
11	132 209 (76.9)	55 140 (83.6)	49 563 (71.5)	26 868 (75.3)	638 (61.3)	
12	18 509 (10.8)	7503 (11.4)	7387 (10.7)	3466 (9.7)	153 (14.7)	
13	1575 (0.9)	655 (1.0)	588 (0.8)	295 (0.8)	37 (3.6)	
Year of Tdap receipt						
2011	65 909 (38.3)	27 128 (41.1)	27 180 (39.2)	11 211 (31.4)	390 (37.5)	<.001
2010	64 013 (37.2)	22 903 (34.7)	26 496 (38.2)	14 237 (39.9)	377 (36.3)	
2009	39 573 (23.0)	15 538 (23.6)	14 366 (20.7)	9433 (26.4)	236 (22.7)	
2008	2516 (1.5)	396 (0.6)	1272 (1.8)	811 (2.3)	37 (3.6)	
Years since Tdap receipt[c]						
Median (IQR)	1.2 (0.4–1.9)	1.2 (0.4–1.9)	1.2 (0.4–1.8)	1.3 (0.7–2.1)	1.2 (0.5–2.1)	<.001
DTaP doses received before age 10 y, no.						
≥4	156 135 (90.8)	61 098 (92.6)	64 815 (93.5)	29 369 (82.3)	853 (82.0)	<.001
<4	15 876 (9.2)	4867 (7.4)	4499 (6.5)	6323 (17.7)	187 (18.0)	
Years since last DTaP dose received before age 10 y						
Median (IQR)	7.6 (6.9–8.4)	7.6 (6.9–8.4)	7.5 (6.8–8.4)	7.8 (7.1–8.5)	8.0 (7.2–8.7)	<.001
Total	172 011 (100.0)	65 965 (100.0)	69 314 (100.0)	35 692 (100.0)	1040 (100.0)	

Abbreviations: DTaP, diphtheria-tetanus-acellular pertussis vaccine; IQR, interquartile range.

[a] For the difference between Adacel and Boostrix recipients. χ^2 tests were used for categorical variables, and Mann–Whitney *U* tests were used for nonnormally distributed continuous variables.

[b] Wisconsin Division of Public Health region of residence.

[c] Years from Tdap receipt to 1 January 2012.

following Boostrix receipt may persist longer among those primed with Infanrix and that the duration of protection may vary by priming vaccine received, perhaps as a result of differences in vaccine composition or preparation [33]. Studies among adolescents with known DTaP histories are needed to investigate whether the effectiveness of Adacel and Boostrix varies with the DTaP formulation(s) received during childhood. As data included in the WIR and other IISs become more complete through quality improvement initiatives, IISs may be useful in future investigations of this issue.

The WIR efficiently provided demographic and immunization information for this study but was limited in identifying unvaccinated clients, previously described as an IIS limitation [38, 39]. Because we could not specify precisely which full cohort clients with no record of Tdap and no case of pertussis resided in Wisconsin during 2012, our VE estimates may be

Table 4. Rates and Incidence Rate Ratios (IRRs) of Pertussis During 2012 in the Tdap Cohort, by Characteristic

Characteristic	Pertussis Case During 2012, No. (%)		Rate[a]	Unadjusted IRR (95% CI)
	No	Yes		
Sex				
Female	84 440 (49.3)	338 (46.5)	398.5	Reference
Male	86 608 (50.6)	389 (53.5)	447.1	1.12 (.97–1.30)
Unknown	236 (0.1)	0 (0.0)	. . .	. . .
Age on 1 January 2012, y				
11	41 674 (24.3)	114 (15.7)	272.5	Reference
12	63 586 (37.1)	248 (34.1)	388.3	1.43 (1.14–1.78)
13	66 024 (38.5)	365 (50.2)	550.1	2.02 (1.64–2.49)
Region of residence[b]				
Southeastern	63 357 (37.0)	267 (36.7)	419.5	Reference
Southern	34 856 (20.3)	89 (12.2)	254.4	0.61 (.48–.77)
Northeastern	34 074 (19.9)	105 (14.4)	307.0	0.73 (.58–.92)
Western	22 243 (13.0)	135 (18.6)	603.3	1.44 (1.17–1.77)
Northern	15 196 (8.9)	131 (18.0)	856.5	2.04 (1.66–2.52)
Unknown	1558 (0.9)	0 (0.0)	. . .	. . .
Age at Tdap receipt, y				
10	19 643 (11.5)	75 (10.3)	380.1	0.84 (.66–1.06)
11	131 607 (76.8)	602 (82.8)	455.3	Reference
12	18 461 (10.8)	48 (6.6)	259.0	0.57 (.42–.76)
13	1573 (0.9)	2 (0.3)	126.7	0.28 (.07–1.12)
Tdap brand				
Adacel	65 628 (38.3)	337 (46.4)	511.0	Reference
Boostrix	69 107 (40.3)	207 (28.5)	298.3	0.58 (.49–.69)
Unspecified	35 511 (20.7)	181 (24.9)	507.2	0.99 (.83–1.19)
DTaP	1038 (0.6)	2 (0.3)	192.1	0.38 (.09–1.51)
Year of Tdap receipt[c]				
2011	65 736 (38.4)	173 (23.8)	262.2	Reference
2010	63 720 (37.2)	293 (40.3)	457.6	1.75 (1.45–2.11)
2009/2008	41 828 (24.4)	261 (35.9)	620.7	2.37 (1.95–2.87)
Number of DTaP doses received before age 10 y				
≥4	155 465 (90.8)	670 (92.2)	429.0	Reference
<4	15 819 (9.2)	57 (7.8)	358.9	0.84 (.64–1.10)
Years since last DTaP dose received before age 10 y[d]				
Median (IQR)	7.6 (6.9–8.4)	8.0 (7.3–8.6)	. . .	1.18 (1.12–1.24)
Total	171 284 (100.0)	727 (100.0)	422.5	. . .

Abbreviations: CI, confidence interval; DTaP, diphtheria-tetanus-acellular pertussis vaccine; IQR, interquartile range; Tdap, tetanus-diphtheria-acellular pertussis vaccine.

[a] Incidence of pertussis during 2012 per 100 000 person-years at risk.

[b] Wisconsin Division of Public Health region of residence.

[c] Because few clients were vaccinated during 2008, Tdap receipt years 2008 and 2009 were combined.

[d] Analyzed as a continuous variable.

biased or confounded by uncontrolled client-level factors (eg, geographic location).

Using WIR data, our estimate of Tdap uptake among clients becoming 13–14 years old during 2012 was similar to estimates for Wisconsin adolescents from the 2012 National Immunization Survey-Teen (point estimate [95% CI], 89.8% ± 4.4%) [40], and the high proportion of corroborating LNs and TNs indicates there was likely not a widespread systematic misrecording of brand information in the WIR. Any misclassification of Tdap receipt or brand would be expected to be nondifferential between case- and noncase-clients because Tdap information was collected from the same source (WIR) for case- and noncase-clients, Tdap information and pertussis case information were collected using separate reporting mechanisms, and, among

Table 5. Adjusted Incidence Rate Ratios (IRRs) of Pertussis During 2012 in the Tetanus-Diphtheria-Acellular Pertussis Vaccine (Tdap) Cohort, by Tdap Brand and Year of Receipt

Tdap History Characteristic	Adjusted[a] IRR (95% CI)	Sensitivity Analysis 1[b] Adjusted[a] IRR (95% CI)	Sensitivity Analysis 2[c] Adjusted[a] IRR (95% CI)
Tdap brand			
Adacel	Reference	Reference	Reference
Boostrix	0.62 (.52–.74)	0.63 (.52–.76)	0.70 (.57–.87)
Unspecified	1.07 (.88–1.31)	1.06 (.86–1.31)	. . .
DTaP	0.41 (.10–1.64)	0.53 (.13–2.12)	0.40 (.10–1.61)
Year of Tdap receipt[d]			
2011	Reference	Reference	Reference
2010	1.75 (1.45–2.11)	1.78 (1.46–2.16)	1.76 (1.46–2.12)
2009/2008	2.30 (1.90–2.79)	2.47 (2.02–3.03)	2.33 (1.92–2.82)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; Tdap, tetanus-diphtheria-acellular pertussis vaccine

[a] Adjusted for region of residence, Tdap brand, and year of Tdap receipt.

[b] Sensitivity analysis 1 excludes Tdap cohort clients who received Tdap at age 10 years.

[c] In sensitivity analysis 2, unspecified Tdap brand names were imputed, using the logistic regression approach to multiple imputation, to have a value of Adacel or Boostrix.

[d] Because few clients were vaccinated during 2008, Tdap receipt years 2008 and 2009 were combined.

case-clients, Tdap doses received before pertussis onset but entered into WIR after onset were excluded. Use of WIR data may result in underestimation of Tdap receipt because WIR likely does not include all Tdap doses administered; nondifferential underestimation of Tdap receipt would underestimate Tdap VE. Nondifferential misclassification of Adacel and Boostrix would bias the difference between brands toward no difference.

B. parapertussis and *Bordetella holmesii* infections can cause pertussis-like illness [28, 41–43] that can be misclassified as pertussis and result in lower pertussis VE estimates [31, 44]. Because widespread *B. parapertussis* infections were also reported in Wisconsin during 2012 [41], we limited our case definition to laboratory-confirmed *B. pertussis* infection. It is unlikely that coinfection with *B. parapertussis* or *B. holmesii* impacted our results: coinfection with *B. parapertussis* was rare among our cohort, and *B. holmesii* was not detected among 8505 specimens tested during 2012–2013 at the Wisconsin State Laboratory of Hygiene (David Warshauer, personal communication).

Because we investigated Tdap effectiveness during a large outbreak, our results may not be generalizable to nonoutbreak settings. Additionally, it is possible the statewide pertussis outbreak during 2003–2005 impacted immunity among our cohort, resulting in decreased generalizability to other populations.

In conclusion, our results provide evidence of waning protection from Tdap vaccination among both Adacel and Boostrix recipients. Boostrix was more effective than Adacel in preventing pertussis among our cohort, but these findings may not be generalizable to cohorts of adolescents that received different DTaP vaccines during childhood and should be further examined in studies that include childhood DTaP history. Our study demonstrates the efficiency and limitations of using an IIS to examine vaccine effectiveness. Our results reinforce the needs for enhanced understanding of the correlates of protection against pertussis and for pertussis vaccines that induce durable, highly effective immunity.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We thank the many staff members of Wisconsin's local health departments, for their pertussis case investigation and data collection efforts; all immunization providers in Wisconsin who provide information to the Wisconsin Immunization Registry; the Wisconsin Division of Public Health staff members who administer the Wisconsin Immunization Registry and the Wisconsin Electronic Disease Surveillance System; the Wisconsin Division of Public Health Office of Health Informatics, for providing assistance with population estimates; and Wisconsin Division of Public Health Immunization Program staff members Jackie Nelson and Lynette Hanson, for providing historical information from the Vaccines for Children Program.

Disclaimer. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the article.

Financial support. This work was supported by the Centers for Disease Control and Prevention National Immunization Program (grant H23/CCH522563 to S. L. S.) and Sanofi-Pasteur (grant IND 8502, study M5A16 to R. K., J. C. E., R. A. A., A. B. P., and J. H. C.).

Potential conflicts of interest. R. K., J. C. E., R. A. A., A. B. P., and J. H. C. received funding support from Sanofi-Pasteur for a study separate from the present work. J. P. D. is the coordinating investigator of a grant from Sanofi-Pasteur and does not receive salary support but did receive

funding to travel to one meeting for study purposes. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Centers for Disease Control and Prevention. U.S. vaccination coverage reported via the National Immunization Survey (NIS). http://www.cdc.gov/vaccines/imz-managers/coverage/nis/child/index.html. Accessed 18 November 2013.
2. Clark TA. Changing pertussis epidemiology: everything old is new again. J Infect Dis **2014**; 209:978–81.
3. 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**; 46:1–25.
4. Centers for Disease Control and Prevention. Recommended childhood immunization schedule–United States, 1997. MMWR Morb Mortal Wkly Rep **1997**; 46:35–40.
5. Cherry JD. Epidemic pertussis in 2012–the resurgence of a vaccine-preventable disease. N Engl J Med **2012**; 367:785–7.
6. Burns DL, Meade BD, Messonnier NE. Pertussis resurgence: perspectives from the working group meeting on pertussis on the causes, possible paths forward, and gaps in our knowledge. J Infect Dis **2014**; 209 (suppl 1):S32–5.
7. Clark TA, Messonnier NE, Hadler SC. Pertussis control: time for something new? Trends Microbiol **2012**; 20:211–3.
8. Klein NP, Bartlett J, Fireman B, Rowhani-Rahbar A, Baxter R. Comparative effectiveness of acellular versus whole-cell pertussis vaccines in teenagers. Pediatrics **2013**; 131:e1716–22.
9. Liko J, Robison SG, Cieslak PR. Priming with whole-cell versus acellular pertussis vaccine. N Engl J Med **2013**; 368:581–2.
10. Sheridan SL, Ware RS, Grimwood K, Lambert SB. Number and order of whole cell pertussis vaccines in infancy and disease protection. JAMA **2012**; 308:454–6.
11. 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**; 367:1012–9.
12. 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**; 308:2126–32.
13. Tartof SY, Lewis M, Kenyon C, et al. Waning immunity to pertussis following 5 doses of DTaP. Pediatrics **2013**; 131:e1047–52.
14. Plotkin SA. Complex correlates of protection after vaccination. Clin Infect Dis **2013**; 56:1458–65.
15. Broder KR, Cortese MM, Iskander JK, et al. 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**; 55:1–34.
16. Wisconsin Administrative Code. Chapter DHS 144: immunization of students. http://docs.legis.wisconsin.gov/code/admin_code/dhs/110/144/03. Accessed 5 June 2013.
17. Wisconsin Division of Public Health. 2012 annual pertussis surveillance summary. http://www.dhs.wisconsin.gov/immunization/pertussis.htm. Accessed 29 May 2013.
18. Schauer SL, Hopfensperger DJ, Verdon MJ, Maerz TR, Gabor GW, Davis JP. An immunization information system to meet evolving needs during the 2009–2010 Influenza A (H1N1) vaccination campaign. Disaster Med Public Health Prep **2012**; 6:402–7.
19. Schauer SL, Maerz TR, Hurie MB, Gabor GW, Flynn JM, Davis JP. The use of an immunization information system to establish baseline childhood immunization rates and measure contract objectives. J Public Health Manag Pract **2009**; 15:E6–12.
20. Schauer SL, Maerz TR, Verdon MJ, Hopfensperger DJ, Davis JP. The Wisconsin Immunization Registry experience: comparing real-time and batched file submissions from health care providers. WMJ **2014**; 113:102–6.
21. Centers for Medicare and MediCaid Services. Electronic health records incentive programs—meaningful use. http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/Meaningful_Use.html. Accessed 5 June 2013.
22. Centers for Disease Control and Prevention. Manual for the surveillance of vaccine-preventable diseases. Atlanta, GA: Centers for Disease Control and Prevention, **2012**.
23. US Census Bureau. Population and housing unit estimates, 2012 state population estimates by age, sex, and Hispanic origin. http://www.census.gov/popest/data/state/asrh/2012/index.html. Accessed 17 June 2013.
24. Wisconsin Department of Health Services. Division of Public Health—Regional Offices. http://www.dhs.wisconsin.gov/localhealth/counties/regional.htm. Accessed 25 November 2013.
25. Schafer JL. Multiple imputation: a primer. Stat Methods Med Res **1999**; 8:3–15.
26. Rubin D. Multiple imputation for nonresponse in surveys. New York: Wiley & Sons, **1987**.
27. 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.
28. Rodgers L, Martin SW, Cohn A, et al. Epidemiologic and laboratory features of a large outbreak of pertussis-like illnesses associated with cocirculating Bordetella holmesii and Bordetella pertussis–Ohio, 2010–2011. Clin Infect Dis **2013**; 56:322–31.
29. 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**; 51:315–21.
30. Acosta A, Debolt C, Tasslimi A, et al. Vaccine Effectiveness and Duration of Protection of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis among Adolescents, Washington State, 2012 IDWeek. San Francisco, CA, **2013**. https://idsa.confex.com/idsa/2013/webprogram/Paper41599.html.
31. Cherry JD. Why do pertussis vaccines fail? Pediatrics **2012**; 129:968–70.
32. Cherry JD, Heininger U, Richards DM, et al. Antibody response patterns to Bordetella pertussis antigens in vaccinated (primed) and unvaccinated (unprimed) young children with pertussis. Clin Vaccine Immunol **2010**; 17:741–7.
33. Carollo M, Pandolfi E, Tozzi AE, Buisman AM, Mascart F, Ausiello CM. Humoral and B-cell memory responses in children five years after pertussis acellular vaccine priming. Vaccine **2014**; 32:2093–9.
34. Cherry JD. Pertussis: challenges today and for the future. PLoS Pathog **2013**; 9:e1003418.
35. 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**; 21:119–25.
36. Queenan AM, Cassiday PK, Evangelista A. Pertactin-negative variants of Bordetella pertussis in the United States. N Engl J Med **2013**; 368:583–4.
37. Quinlan T, Musser KA, Currenti SA, Zansky SM, Halse TA. Pertactin-negative variants of Bordetella pertussis in New York State: A retrospective analysis, 2004–2013. Mol Cell Probes **2014**; 28:138–40.
38. American Immunization Registry Association. Management of Moved or Gone Elsewhere (MOGE) status and other patient designations in immunization information systems. Atlanta, GA: Modeling of Immunization Registry Operations Workgroup, **2005**.
39. Gowda C, Dong S, Potter RC, Dombkowski KJ, Stokley S, Dempsey AF. A systematic evaluation of different methods for calculating adolescent vaccination levels using immunization information system data. Public Health Rep **2013**; 128:489–97.
40. 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**; 62:685–93.

41. Bartholomew M, Koepke R, Aydkio Ayele R, et al. Widespread Bordetella parapertussis infections—Wisconsin, October 2011–May 2012. Presented at: IDWeek 2013, San Francisco, CA, **2013**.
42. Bergfors E, Trollfors B, Taranger J, Lagergard T, Sundh V, Zackrisson G. Parapertussis and pertussis: differences and similarities in incidence, clinical course, and antibody responses. Int J Infect Dis **1999**; 3:140–6.
43. Heininger U, Stehr K, Schmitt-Grohe S, et al. Clinical characteristics of illness caused by Bordetella parapertussis compared with illness caused by Bordetella pertussis. Pediatr Infect Dis J **1994**; 13:306–9.
44. Cherry JD, Seaton BL. Patterns of Bordetella parapertussis respiratory illnesses: 2008–2010. Clin Infect Dis **2012**; 54:534–7.
45. Centers for Disease Control and Prevention. Pertussis vaccination: acellular pertussis vaccine for the fourth and fifth doses of the DTP series update to supplementary ACIP statement. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **1992**; 41:1–5.
46. Centers for Disease Control and Prevention. Update on the supply of tetanus and diphtheria toxoids and of diphtheria and tetanus toxoids and acellular pertussis vaccine. MMWR Morb Mortal Wkly Rep **2001**; 50:189–90.
47. Centers for Disease Control and Prevention. Food and Drug Administration approval of a fifth acellular pertussis vaccine for use among infants and young children–United States, 2002. MMWR Morb Mortal Wkly Rep **2002**; 51:574.
48. U.S. Food and Drug Administration. Vaccines Licensed for Immunization and Distribution in the US with Supporting Documents, Vaccines, Blood & Biologics. http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093830.htm. Accessed 19 November 2013.
49. Centers for Disease Control and Prevention. FDA licensure of diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant), and poliovirus vaccine combined, (PEDIARIX) for use in infants. MMWR Morb Mortal Wkly Rep **2003**; 52:203–4.