

Post-Marketing Safety Evaluation of a Tetanus Toxoid, Reduced Diphtheria Toxoid and 3-Component Acellular Pertussis Vaccine Administered to a Cohort of Adolescents in a United States Health Maintenance Organization

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Background: Prelicensure clinical studies may not include sufficient numbers of subjects to assess the potential for rare postvaccination adverse events. The aim of this postlicensure study (NCT00297856) was to evaluate uncommon outcomes following vaccination with a tetanus, reduced-antigen-content diphtheria, and acellular pertussis vaccine (Tdap, Boostrix GlaxoSmithKline) in a large adolescent cohort.

Methods: We monitored safety outcomes among 13,427 10 to 18-year-old adolescents enrolled in the Northern California Kaiser Permanente Health Care Plan who received Tdap vaccination as part of their normal health care. Subjects were evaluated using self-control analysis comparing days 0 to 29 to days 30 to 59 postvaccination for neurologic events, hematologic events and allergic reactions. We evaluated new onset chronic illnesses within 6 months of Tdap vaccination by comparing with historical Td controls matched for age at vaccination, season, sex, and geographic area. We also compared the incidence of events of interest between the Tdap and historical cohorts as exploratory analyses.

Results: No increased risk for medically attended neurologic (odds ratio [OR], 0.962; 95% confidence interval [CI], 0.533–1.733) or allergic reactions (OR, 1.091; 95% CI, 0.441–2.729) was observed following Tdap vaccination when comparing the first 30 postvaccination days to the second 30 postvaccination days. There was one hematologic event within 30 days of Tdap, compared with 0 events within days 30 to 59 ($P = 1.0$). When compared with matched historical Td recipients, no increase in new onset chronic illnesses (OR, 0.634; 95% CI, 0.475–0.840) was seen after Tdap. No deaths occurred in the Tdap cohort during the study.

Conclusions: This study provides no evidence for an increased risk for neurologic, hematologic, allergic events, or new onset of chronic illnesses among adolescents vaccinated with Tdap.

Key Words: diphtheria, tetanus, pertussis, Tdap, booster, vaccine

(*Pediatr Infect Dis J* 2010;29: 613–617)

Although childhood vaccination against pertussis is well established in the United States and elsewhere around the globe, pertussis remains an important public health concern. Reported cases of pertussis in the United States increased from 1010 cases in 1976 to a peak of 25,847 cases in 2004.^{1,2} Pertussis now primarily affects infants less than 6 months of age and individuals aged 10 years and older.^{1,3,4} As substantial, prolonged illnesses due to pertussis are not uncommon in adolescents and adults,⁵ this group can serve as the main reservoir of infection for neonates and infants who are too young to be immunized and are at high risk for the severe consequences of pertussis.^{4,6,7}

The immunity afforded by childhood pertussis vaccination begins to wane after approximately 5 years, making booster vaccination in adolescence or adulthood necessary. In June 2005, the Advisory Committee on Immunization Practices recommended that all adolescents in the United States aged 11 to 18 years receive an acellular pertussis booster vaccination in the form of a combined reduced antigen content tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine (Tdap).⁸ This recommendation was subsequently expanded to adults 19 to 64 years old,⁹ adults who have close contact with infants aged less than 12 months, health-care personnel, and in 2008, for pregnant women within the immediate postpartum period.¹⁰

Boostrix, a Tdap vaccine developed by GlaxoSmithKline Biologicals (Philadelphia, PA) containing the pertussis antigens pertussis toxoid, filamentous hemagglutinin, and pertactin, was originally licensed in 2005 in the United States as a single-dose booster for adolescents 10 to 18 years of age. The age range for use of this vaccine was extended in 2008 to include adults up to 64 years of age. This vaccine is based on GlaxoSmithKline's pediatric DTaP vaccine, Infanrix.^{11–13} The tetanus and diphtheria toxoid content of Tdap is similar to that found in currently licensed adult Td vaccines, but is reduced compared with DTaP vaccines as are the quantities of the pertussis antigens.

Clinical studies involving 3608 adolescents 10 to 18 years of age and 2972 adults 19 to 64 years of age have demonstrated that Tdap (Boostrix, GlaxoSmithKline) is immunogenic and well tolerated in these populations.^{14–15} The primary aim of this study was to estimate the incidence of specific categories of adverse events (medically attended neurologic and hematologic events, allergic reactions, and new onset chronic illnesses) following the administration of a single dose of Tdap to US adolescents in a postlicensure setting.

Accepted for publication December 29, 2009.

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Research support by GlaxoSmithKline, Merck & Co.: GlaxoSmithKline Biologicals was the funding source and was involved in all stages of the study conduct and analysis. GSK Biologicals also funded all costs associated with the development and the publishing of the present manuscript. The corresponding author had full access to the data and was responsible for data analysis and manuscript submission. Supported by GlaxoSmithKline, Merck & Co., Sanofi Pasteur, Novartis and Wyeth (to N.P.K.).

S. Black is a consultant for GlaxoSmithKline and Novartis; W. Weston, S. Wu, P. Li, B. Howe, L.R. Friedland are all employees of GlaxoSmithKline.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).

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ISSN: 0891-3668/10/2907-0613

DOI: 10.1097/INF.0b013e3181d581f9

MATERIALS AND METHODS

Study Design and Cohorts Studied

This open, prospective, observational study was carried out in a US Health Maintenance Organization. The study was reviewed and approved by the Kaiser Permanente Institutional Review Board. Study subjects were adolescents aged between 10 and 18 years who were enrolled in the Northern California Kaiser Permanente (NCKP) Health Care Plan and who received Tdap vaccination as part of their routine clinical care. Subject accrual began following the administration of Tdap to the first age-appropriate subject in NCKP and was planned to continue for either 10 months or until 10,000 subjects were accrued, whichever came last. We also identified a historical comparison cohort of Td vaccine recipients vaccinated between June 1, 2002 and September 21, 2005 who were matched for age, season, sex, and geographic location to Tdap recipients.

Safety Outcomes

The primary aim of this study was to estimate the incidence of medically attended neurologic events during the 30 days (days 0–29) following Tdap. The secondary aims of this study included: (1) an estimation of the incidence of medically attended hematologic events, and allergic reactions during the 30 days (days 0–29) following Tdap; (2) an estimation of the incidence of new onset chronic illnesses (eg, autoimmune disorders, asthma, type I diabetes, and allergies) in the 6-month period (days 0–180) following Tdap; (3) a determination of the relative risk for neurologic events, hematologic events and allergic reactions during the first two 30-day periods (days 0–29 and 30–59) following Tdap or Td vaccination; (4) a determination of the relative risk for new onset chronic illnesses (as defined above) in the 6-month period (days 0–180) following Tdap compared with a matched historical Td control cohort. Events of interest were identified by searching medical utilizations databases for prespecified International Statistical Classification of Diseases and Related Health Problems-9 (ICD-9) codes and text strings associated with such events, as described below.

Data Sources

Each NCKP member has a unique medical record number. All member information is stored in the clinical and institutional databases which contain data regarding vaccine administration, medical utilization, participant demographics and Health Maintenance Organization membership for all NCKP members.

After identification of Tdap recipients and their health service utilization within the protocol defined date-ranges, individuals were monitored for 6 months following vaccination for outcomes of interest, with the exception of pregnancy, which was followed to determination of its outcome. Adverse events and pregnancies were identified by searching computerized records of outpatient clinic visits, emergency room visits, and hospitalizations for prespecified ICD-9 codes, as well as by scanning prespecified text descriptors in the NCKP regional databases. We searched for events of interest during the specified time periods following vaccination with Tdap (days 0–29, days 30–59, and days 0–180). We evaluated electronic database records for the 1-year period before vaccination with Tdap to determine the presence of chronic illnesses (Appendix table for ICD-9 codes employed, Supplemental Digital Content 1, <http://links.lww.com/INF/A387>), and defined a chronic illness as being “new onset” if there were no electronic diagnoses for that condition during the 1 year before Tdap vaccination. When it was necessary, we reviewed medical records to confirm the occurrence of an event or to clarify the nature of an event.

Vaccine

Each 0.5 mL dose of Tdap (Boostrix, GlaxoSmithKline) contained 2.5 Lf diphtheria toxoid, 5 Lf tetanus toxoid, 8 g pertussis toxoid, 8 g filamentous hemagglutinin, 2.5 g pertactin. The vaccine was preservative free.

Statistical Methods

We evaluated the occurrence of medically attended neurologic events, medically attended hematologic events, allergic reactions, and new onset chronic illnesses using 2 approaches. The first was a self-control analysis in which we compared the first 30 day (days 0–29) postvaccine period (risk period) to the second 30 day postvaccine periods (days 30–59, control period) for medically attended events of interest. Subjects who had an event within the risk period were not assessed for repeat occurrences within the control period. The risk period and the control period for each vaccinated case were treated as a matched pair. The second analytic approach was conducted by comparing the Tdap cohort matched with the historical Td cohort for events of interest during the first 30 days following vaccination, as well as for new onset chronic illnesses during the first 6 months following vaccination. Similarly, the subject in the Tdap cohort and its matched subject in the historical control cohort were treated as a matched pair.

For both approaches, matched odds ratios with 2-sided 95% CI and *P*-values were calculated using conditional logistic regression. Two-sided exact 95% confidence intervals (CI) for percentages within a cohort were calculated using the method by Clopper and Pearson.¹⁶ Since the events of interest in this study are rare, the odds ratio approximates very closely, and is therefore nearly identical to, the relative risk. The number of vaccinated subjects was used as the denominator for computing incidences.

RESULTS

The Tdap cohort accrued from September 22, 2005 through December 31, 2006 and consisted of 13,427 subjects. Cohort accrual was extended to include additional subjects over the planned 10,000 to increase the likelihood of observing rare events. Monitoring of each subject continued for 6 months after vaccination, with surveillance ending on June 29, 2007. The historical cohort included 12,509 adolescents who were vaccinated with Td between June 1, 2002 and September 21, 2005 and who could be matched with members of the Tdap cohort. We identified appropriately matched controls for approximately 93% of the Tdap cohort.

Demographic characteristics of the Tdap cohort were comparable with those of the historical cohort (Table 1). The mean age of all subjects was 13.3 years (range, 10–18 years) and 51% of subjects in each group were male. For approximately half of the subjects in each cohort, race information was either unknown or missing. Among subjects for whom race information was available, most subjects were Caucasian. The Tdap and Td cohorts had a similar seasonal distribution for the time of vaccination (data not shown).

Medically Attended Neurologic and Hematologic Events, and Allergic Reactions

For the self-controlled analysis, there were no significant differences in the incidence of medically attended neurologic and hematologic events between the 2 observation periods (Table, Supplemental Digital Content 2, <http://links.lww.com/INF/A385>). For medically attended hematologic events following Tdap, there was a single event which occurred during the postvaccination period. This subject had autoimmune anemia diagnosed 17 months before vaccination with Tdap and subsequently had a splenectomy 5 months before receiving Tdap. The visit of

TABLE 1. Summary of Demographic Characteristics

Characteristic	Category	Tdap Cohort N = 13,427		Historical Cohort N = 12,509		Total N = 25,936	
		Value or n	%	Value or n	%	Value or n	%
Age (yr)	Mean	13.32		13.30		13.31	
	SD	2.16		2.10		2.13	
Gender	Female	6550	48.8	6116	48.89	12,666	48.84
	Male	6877	51.2	6393	51.11	13,270	51.16
Race	American Indian	29	0.22	11	0.09	40	0.15
	Asian	1024	7.63	770	6.15	1794	6.92
	Black	537	4.00	569	4.55	1106	4.26
	Hispanic	537	4.00	518	4.14	1055	4.07
	White	4453	33.16	4540	36.28	8993	34.67
	Other	135	1.01	141	1.13	276	1.06
	Unknown	197	1.47	176	1.41	373	1.44
	Missing	6515	48.53	5784	46.26	12,299	47.42

N indicates total number of subjects; n, number of subjects in a given category.

interest was for routine follow-up laboratory assessment of hemoglobin and hematocrit.

There was no significant difference in the overall incidence of allergic reactions between the postvaccine risk period (N = 12) and control risk period (N = 11) in the Tdap cohort (matched OR, 1.091; 95% CI, 0.441–2.729; $P = 1.00$, Table, Supplemental Digital Content 2, <http://links.lww.com/INF/A385>). Because we noted an imbalance in the number of the ICD-9 event “allergic reaction” between the postvaccine risk period (N = 4) and the control risk period (N = 0), we reviewed the medical records of all 12 subjects with reports of allergic events. In all but one instance, the events reported were not temporally associated with Tdap vaccination and/or were potentially attributable to other causes. One subject reported tongue swelling and headache several hours after concomitant vaccination with Tdap, meningococcal ACWY conjugate (MCV4), hepatitis A, and hepatitis B vaccines. The treating physicians noted in the medical record that the event was possibly related to vaccination.

To assess the incidence of medically attended neurologic and hematologic events, and allergic reactions, we conducted an exploratory self-controlled analysis within the historical Td cohort group. Rates of medical events of interest between days 0 to 29 and days 30 to 59 following vaccination for the historical Td cohort were comparable to those in the Tdap cohort (data not shown).

We next compared the incidence of medically attended neurologic and hematologic events, and allergic reactions during the 30 days after vaccination between the Tdap and historical Td cohorts. There were no significant differences between the Tdap and historical cohorts with respect to the incidence of medically attended neurologic or hematologic events within 30 days of vaccination with either Tdap or Td (Table, Supplemental Digital Content 3, <http://links.lww.com/INF/A386>). The incidence of allergic reactions in the first 30 days following vaccination was significantly greater in the historical cohort (N = 25) than in the matched Tdap cohort (N = 11; matched OR, 0.440; 95% CI, 0.195–0.927; $P = 0.0288$) due to a greater number of urticaria events reported in the historical cohort (N = 23) than in the matched Tdap cohort (N = 4; matched OR, 0.174; 95% CI, 0.044–0.509; $P = 0.0003$; Table, Supplemental Digital Content 3, <http://links.lww.com/INF/A386>).

New Onset of Chronic Illnesses

The incidence of new onset of chronic illnesses in the 6 months following vaccination was significantly greater in the historical cohort (N = 132) than in the matched Tdap cohort (N =

84; matched OR, 0.634; 95% CI, 0.448–0.840; $P = 0.0013$), due primarily to a greater number of asthma events in the historical cohort (N = 88) than in the matched Tdap cohort (N = 42; matched OR, 0.471; 95% CI, 0.317–0.691; $P = <0.0001$; Table 2).

There were more reports of thyroiditis in the Tdap cohort (N = 5) than in the historical cohort (N = 0, Table 4). Case investigations revealed that 3 of these individuals were diagnosed with Hashimoto thyroiditis and 2 were diagnosed with autoimmune thyroiditis. Medical record review showed that, in all cases, symptoms and/or clinical suspicion (such as fatigue or abnormal laboratory results) were present either on or before the day of vaccination (n = 4), or a family history of thyroid disease was present (n = 1).

Deaths, Serious Adverse Events, and Pregnancies

There were no deaths in the Tdap cohort during the surveillance period. Since study data were obtained through retrospective review of patient care databases, there was no real-time identification of serious adverse events (SAEs; defined as events resulting in death; that were life-threatening at the time of occurrence; required hospitalization or prolongation of hospitalization; resulted in disability/incapacity; or were a congenital anomaly in the offspring of a study subject). Retrospective application of the aforementioned SAE criteria to study outcomes of interest identified 3 events in the Tdap cohort that could be considered as SAEs. One subject (discussed above) experienced tongue swelling with potential relationship to vaccination. Another subject was diagnosed with type 1 diabetes 4½ months after receiving Tdap while a third subject developed Henoch-Schönlein purpura 3 months after receiving Tdap. Neither of these 2 events was considered to be related to vaccination.

Three pregnancies were reported in Tdap recipients. One of the reported pregnancies ended in miscarriage at 8 weeks gestation. The mother, a 17-year-old female, had received the Tdap vaccine approximately 16 days before the estimated date of conception. The miscarriage was not considered to be related to vaccination. The other 2 pregnancies (one in a 16-year-old mother receiving Tdap at approximately 13 weeks gestation, the other in a 14-year-old mother receiving Tdap at approximately 19 weeks gestation) resulted in normal healthy offspring.

Confirmatory Analysis of Subjects Who Did/Did Not Receive Concomitant Meningococcal Vaccine

Beginning early in 2006, the Advisory Committee on Immunization Practices recommended that 11 to 18 year olds receive

TABLE 2. Percentage of Subjects With New Onset Chronic Illness in the Tdap and Historical Control Cohorts During Six Months After Tdap or Td Vaccination, Respectively

Event	Tdap Cohort N = 13,427		Tdap Cohort (Matched to Historical Cohort) N = 12,509		Historical Cohort N = 12,509		Matched Odds Ratio Tdap Cohort/Historical Control		
	n	%	n	%	n	%	Matched OR	95% CI (LL, UL)	P
New onset chronic illnesses	97	0.7224	84	0.6715	132	1.0552	0.634	0.475, 0.840	0.0013
Asthma	52	0.3873	42	0.3358	88	0.7035	0.471	0.317, 0.691	<0.0001
Asthma, cough variant	5	0.0372	5	0.0400	5	0.0400	1.000	0.230, 4.345	1.0000
Asthma, exercise induced	34	0.2532	31	0.2478	41	0.3278	0.756	0.458, 1.235	0.2888
Diabetes, type 1	1	0.0074	1	0.0080	3	0.0240	0.333	0.006, 4.151	0.6250
Henoch-Schönlein purpura	1	0.0074	1	0.0080	1	0.0080	1.000	0.013, 78.497	1.0000
Iritis	1	0.0074	1	0.0080	1	0.0080	1.000	0.013, 78.497	1.0000
Systemic lupus erythematosus	1	0.0074	1	0.0080	0	—	—	0.026, —	1.0000
Thyroiditis, Autoimmune	2	0.0149	2	0.0160	0	—	—	0.188, —	0.5000
Thyroiditis, Hashimoto's	3	0.0223	2	0.0160	0	—	—	0.188, —	0.5000
Uveitis	1	0.0074	1	0.0080	0	—	—	0.026, —	1.0000
Arteritis	0	—	0	—	1	0.0080	0.000	0.000, 39.000	1.0000
Vasculitis	0	—	0	—	1	0.0080	0.000	0.000, 39.000	1.0000

N indicates number of subjects; n/%, number/percentage of subjects with the specified events; 95% CI, exact 95% confidence interval; LL, lower limit; UL, upper limit.

meningococcal serogroups A, C, Y, and W-135 polysaccharide-diphtheria toxoid conjugate vaccine (MCV4, Menactra, Sanofi Pasteur, Swiftwater, PA) in addition to Tdap vaccination. As this recommendation overlapped with the surveillance period of this study (routine MCV4 use began in April 2006 in NCKP), the historical Td control group had different vaccine exposures than did the Tdap cohort and the cohorts could not be matched in terms of receipt of MCV4. One-third (35.06%) of the Tdap cohort and 6.66% of the historical cohort received concomitant MCV4 vaccination. To address this imbalance, we conducted a secondary analysis with stratification according to receipt of concomitant MCV4 vaccination to account for any potential confounding of results by concomitant MCV4 vaccination.

Overall, stratification by receipt of MCV4 demonstrated few differences in the incidence of outcomes of interest between subjects in the Tdap cohort who did, and who did not receive, concomitant MCV4 (data not shown). Self-controlled analysis revealed that allergic reactions (which included the terms allergic reactions; food allergy; tongue swelling [not anaphylaxis], and urticaria) were observed more frequently during the 30 days risk period after vaccination than during the control risk period (OR, 5.0; 95% CI, 1.066–46.933; $P = 0.0386$) in subjects who had received concomitant Tdap and MCV4 than among those who received Tdap without concomitant MCV4 (OR, 0.222; 95% CI, 0.023–1.074; $P = 0.0654$). Overall, there were 10 Tdap subjects who received concomitant MCV4 who had allergic reactions during the risk period. Only one of these events was temporally associated with vaccination (the same subject with tongue swelling as already described).

There were no differences detected in the incidence of new onset chronic illnesses, or the types of illnesses reported, between the Tdap cohort and the historical Td cohort, regardless of concomitant MCV4 vaccination status.

DISCUSSION

Using both a self-controlled (risk interval) and matched historical cohort design, this observational study monitored for selected medically attended outcomes following routine vaccination of 13,427 adolescents with Tdap. Both the matched cohort and risk interval approach are considered effective

methods to assess vaccine safety.¹⁷ With a sample size of more than 13,000 subjects, the study provides reasonable probability of detecting events occurring at a frequency of at least 1 in 3000. However, events occurring less frequently may not have been detected with this sample size. Taking this consideration into account, the results from this study do not indicate any increased risk for medically attended neurologic events, medically attended hematologic events, allergic reactions, or new onset chronic illness following Tdap vaccination.

Vaccination with Tdap was not associated with any significantly elevated risk for any of the outcomes evaluated in the self-controlled analysis, however, an important consideration is that routine administration of MCV4 was introduced during the study period. Because we were unable to match Tdap and historical subjects in terms of receipt of MCV4, we performed secondary self-controlled analyses with subjects stratified by MCV4 receipt. Tdap recipients who received concomitant MCV4 had a 5-fold increase in the odds of having an allergic reactions event while subjects who did not receive concomitant MCV4 had significantly lower odds for having an allergic reaction. Although the overall number of allergic reaction events was small, these results suggest that receipt of concomitant MCV4 was a confounder in this analysis.

Tdap and historical Td subjects had a similar seasonal distribution at the time of vaccination, as well as being well matched in terms of age, gender, and race. There were 2 events for which the odds in the Tdap cohort were statistically significantly decreased versus the historical Td cohort. The first was for the overall category of “New Onset Chronic Illnesses” during the 6-month follow-up period which was largely due to the decreased odds of asthma. The second event was for the overall category of “Allergic reaction” in which there was a decreased risk for urticaria during the first 30-day follow-up period when compared with the historical Td recipients. Although the results were statistically significant based on P -values for the differences between the cohorts, we attribute both of these findings to unmeasured confounding and selection bias in the utilization of healthcare resources and vaccination in that the Tdap recipients were probably more likely to have been vaccinated in the setting of well-child care than were historical Td recipients.

Serious adverse events have been rarely reported following vaccination with adult Td vaccines.¹⁸ Based on a comprehensive review of serious adverse events occurring after vaccination conducted by the Institute of Medicine in the United States during the 1990s, a causal relationship was established between administration of Td vaccine and brachial neuritis.¹⁹ The attributable risk (excess risk) of brachial neuritis in adults during the month following receipt of tetanus toxoid vaccine was estimated to be 0.5 to 1 case per 100,000 vaccines.¹⁹ This same report identified a causal relationship between Td vaccination and the recurrence of Guillain-Barré syndrome (GBS), however, further review of a large data series by the Centers for Disease Control and Prevention (CDC) concluded that an association between GBS and Td vaccines did not pose a significant public health concern since the rate of GBS following vaccination in adults and children did not exceed that expected by chance alone.²⁰ In the present study we observed no cases of GBS. Although this study does not preclude any association between Tdap and GBS, the data suggest that the occurrence of GBS after Tdap is likely to be low. A recent study conducted within the Vaccine Safety Datalink reported no increased risk for neurologic events, including GBS, seizure, and cranial nerve disorders following Tdap as compared with Td vaccine.²¹ These results provide additional support for the observations in our present study.

In summary, among the 13,427 adolescent Tdap recipients in this study, no increased risk for medically-attended neurologic, medically-attended hematologic events, or allergic reactions was observed following Tdap vaccination, nor was any increased risk for new onset chronic illnesses detected for Tdap recipients. These findings support the known safety profile of the Tdap vaccine.

REFERENCES

- Centers for Disease Control and Prevention. Pertussis—United States, 2001–2003. *MMWR Morb Mortal Wkly Rep.* 2005;54:1283–1286.
- Brooks DA, Clover R. Pertussis infection in the United States: role for vaccination of adolescents and adults. *J Am Board Fam Med.* 2006;19:603–611.
- Cherry JD. The epidemiology of pertussis: a comparison of the epidemiology of the disease pertussis with the epidemiology of *Bordetella pertussis* infection. *Pediatrics.* 2005;115:1422–1427.
- Edwards KM. Overview of pertussis: focus on epidemiology, sources of infection, and long term protection after infant vaccination. *Pediatr Infect Dis J.* 2005;24(suppl):S104–S108.
- Lee GM, Lett S, Schauer S, et al. Societal costs and morbidity of pertussis in adolescents and adults. *Clin Infect Dis.* 2004;39:1572–1580.
- Bisgard KM, Pascual FB, Ehresmann KR, et al. Infant pertussis: who was the source? *Pediatr Infect Dis J.* 2004;23:985–989.
- Wendelboe AM, Njamkepo E, Bourillon A, et al. Transmission of *Bordetella pertussis* to young infants. *Pediatr Infect Dis J.* 2007;26:293–299.
- 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(RR-3):1–34.
- Kretsinger K, Broder KR, Cortese MM, et al. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR Recomm Rep.* 2006;55(RR-17):1–37.
- Murphy TV, Slade BA, Broder KR, et al. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2008;57(RR-4):1–51.
- Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. *N Engl J Med.* 1996;334:341–348.
- Schmitt HJ, Schuind A, Knuf M, et al. Clinical experience of a tricomponent acellular pertussis vaccine combined with diphtheria and tetanus toxoids for primary vaccination in 22,505 infants. *J Pediatr.* 1996;129:695–701.
- Schmitt HJ, Wirsing von König CH, Neiss A, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. *JAMA.* 1996;275:37–41.
- Pichichero ME, Blatter MM, Kennedy WA, et al. Acellular pertussis vaccine booster combined with diphtheria and tetanus toxoids for adolescents. *Pediatrics.* 2006;117:1084–1093.
- Blatter MM, Friedland LR, Weston WM, et al. Immunogenicity and safety of a tetanus toxoid, reduced diphtheria toxoid, and 3-component acellular pertussis vaccine in adults 19–64 years of age. *Vaccine.* 2009;27:765–772.
- Clopper C, Pearson S. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika.* 1934;26:404–413.
- McClure DL, Glanz JM, Xu S, et al. Comparison of epidemiologic methods for active surveillance of vaccine safety. *Vaccine.* 2008;26:3341–3345.
- Lloyd JC, Haber P, Mootrey GT, et al. Adverse event reporting rates following tetanus-diphtheria and tetanus toxoid vaccinations: data from the Vaccine Adverse Event Reporting System (VAERS), 1991–1997. *Vaccine.* 2003;21:3746–3750.
- Stratton KR, Howe CJ, Johnston RB Jr. Adverse events associated with childhood vaccines other than pertussis and rubella. Summary of a report from the Institute of Medicine. *JAMA.* 1994;271:1602–1605.
- Tuttle J, Chen RT, Rantala H, et al. The risk of Guillain-Barre syndrome after tetanus-toxoid-containing vaccines in adults and children in the United States. *Am J Public Health.* 1997;87:2045–2048.
- Yih WK, Nordin JD, Kulldorff M, et al. An assessment of the safety of adolescent and adult tetanus-diphtheria-acellular pertussis (Tdap) vaccine, using active surveillance for adverse events in the Vaccine Safety Datalink. *Vaccine.* 2009;27:4257–4262.