HHS Public Access

Author manuscript

*Pharmacoepidemiol Drug Saf*. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

*Pharmacoepidemiol Drug Saf*. 2018 August ; 27(8): 921–925. doi:10.1002/pds.4569.

# Safety of repeated doses of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine in adults and adolescents

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## Abstract

In light of waning immunity to pertussis following receipt of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine, maintaining protection may require repeated Tdap vaccination. We evaluated the safety of repeated doses of tetanus-containing vaccine in 68 915 nonpregnant adolescents and adults in the Vaccine Safety Datalink population who had received an initial dose of Tdap. Compared with 7521 subjects who received a subsequent dose of tetanus toxoid, reduced diphtheria (Td) vaccine, the 61 394 subjects who received a subsequent dose of Tdap did not have significantly elevated risk of medical visits for seizure, cranial nerve disorders, limb swelling, pain in limb, cellulitis, paralytic syndromes, or encephalopathy/encephalitis/meningitis. These results suggest that repeated Tdap vaccination has acceptable safety relative to Tdap vaccination followed by Td vaccination.

### Keywords

pharmacoepidemiology; vaccination; whooping cough

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ETHICS STATEMENT

Institutional Review boards at each MCO approved this study.

CONFLICT OF INTEREST

MLJ has received research funding from Sanofi unrelated to the current project. The other authors report no conflicts of interest. The study sponsor participated in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the report for publication.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

## 1 | INTRODUCTION

The Advisory Committee on Immunization Practices recommends 1 dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine for adolescents aged 11 to 18 years and for all adults aged ≥19 years not previously vaccinated.[1,2] The Advisory Committee on Immunization Practices does not recommend repeated vaccination with Tdap except in pregnant women, who are recommended to receive Tdap during every pregnancy.[3] However, repeated Tdap vaccination may be necessary to maintain protection against pertussis, possibly with intervals of <10 years. Antibody concentrations to pertussis antigens wane to pre-Tdap levels within 10 years after Tdap vaccination,[4] and vaccine effectiveness may wane within 5 years of Tdap receipt.[5-7]

Limited data are available regarding the safety of repeated Tdap vaccination. In adults and adolescents who had received Tdap as part of Tdap licensure trials, 4 studies did not find an elevated risk of local or systemic reactions to a second dose of Tdap, compared either with Tdap-naïve subjects or with subjects receiving a dose of tetanus toxoid and reduced diphtheria toxoid (Td) vaccine alone.[4,8-10] However, these studies were small (between 82 and 769 subjects) and unable to evaluate rare adverse events. A study of pregnant women found that women who received Tdap with an interval of <2 years since a prior dose of tetanus-containing vaccine did not have an elevated risk of medically attended local reactions relative to women with an interval of >5 years.[11] Among nonpregnant adults and adolescents who received a first dose of Tdap, we assessed the safety of subsequent Tdap compared with subsequent Td, particularly at intervals <10 years between doses.

## 2 | METHODS

### 2.1 | Study population

We conducted a longitudinal cohort study within the Vaccine Safety Datalink (VSD), a collaboration between the Centers for Disease Control and Prevention and multiple managed care organizations (MCOs) in the United States.[12] This study included 6 MCOs: Kaiser Permanente Washington, Kaiser Permanente Northwest, Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Colorado, and the Marshfield Clinic. Managed care organization members were eligible to enter the study population when they met all the following criteria:

- **a.** received a dose of Tdap between January 1, 2005 and December 31, 2014 on or after their 11th birthday but before their 65th birthday;
- **b.** received a subsequent dose of any tetanus-containing vaccine between January 1, 2005 and December 31, 2015 on or after their 11th birthday but before their 65th birthday; and
- **c.** continuous enrollment in the MCO from 1 year prior to a dose of Tdap through a subsequent dose of any tetanus-containing vaccine.

Cohort members were followed for 42 days[13] from the date of their second tetanus-containing vaccine, or until they reached 65 years of age, disenrolled from the MCO, or

died, whichever came first. We did not assess risks after a third dose of tetanus-containing vaccine, as this was rarely observed. We excluded MCO enrollees if they were pregnant during their subsequent dose of tetanus-containing vaccine, as rates and detection of adverse events may differ during pregnancy than during other times.

### 2.2 | Exposures of interest

We identified vaccine type and date of receipt of tetanus-containing vaccines by using immunization databases at each MCO. These databases include all vaccinations given to enrollees at each MCO. The immunization databases at Kaiser Permanente Washington, Marshfield Clinic, and Kaiser Permanente Northwest also exchange data with state immunization information systems, allowing us to identify initial Tdap vaccines received prior to MCO enrollment or outside the MCO health-care system.

### 2.3 | Potential adverse events following vaccination

Consistent with a prior VSD study of Tdap safety,[13] we considered 7 serious potential adverse events: seizure; cranial nerve disorders; limb swelling; pain in limb; cellulitis; paralytic syndromes; and encephalopathy, encephalitis, or meningitis. We did not include Guillain-Barré syndrome as an outcome,[13,14] as preliminary analyses suggested that we would detect fewer than 5 Guillain-Barré syndrome cases in our population. We identified potential adverse events by using International Classification of Diseases, version 9, Clinical Modification (ICD-9-CM) codes assigned to inpatient, outpatient, and emergency department encounters (Table 1). For each subject, we identified first diagnosis date of each outcome occurring within the observation period after their second tetanus toxoid-containing vaccination. To exclude events which may have had onset prior to vaccination, we excluded any codes during the postvaccination observation period if those specific codes also occurred during the 30 days prior to vaccination.

### 2.4 | Covariates of interest

We used enrollment and medical utilization databases at each MCO to define demographics, MCO enrollment history, indicators of healthcare utilization (numbers of outpatient visits, well care visits, and hospitalizations in the past year), and receipt of other recommended vaccinations. We defined these covariates as of the dates of initial Tdap and of second tetanus-containing vaccine.

### 2.5 | Analysis

We compared covariate distributions between participants whose second dose of tetanus-containing vaccine was Tdap vs Td. We estimated rates of potential adverse events, with 95% CIs, assuming a Poisson distribution. To compare adverse event rates following Tdap vs Td as the second dose of tetanus-containing vaccine, we estimated rate ratios for each outcome of interest by using Poisson regression. A priori, models were adjusted for age at first receipt of Tdap, number of years between first Tdap and subsequent dose of tetanus-containing vaccine, and year of second dose of tetanus-containing vaccine. We further included any covariates that altered the rate ratios from this base model by 10% or more. As secondary analyses, we stratified by time between vaccine doses (<3 years vs ≥3 years after

Tdap, the median interval between doses). Due to the smaller number of outcomes, these analyses were only adjusted for age at first Tdap, years between doses, and year of second dose. All analyses were conducted by using SAS version 9.4 (SAS Institute, Cary NC).

## 3 | RESULTS

We identified 68 915 eligible VSD enrollees who received a dose of Tdap followed by a subsequent dose of tetanus-containing vaccine. Most (68%) received their first Tdap vaccination between 2006 and 2009. The median interval between vaccine doses was 2.9 years (interquartile range, 1.3-5.2 years). Most study participants (89.1%) received a second dose of Tdap following their initial Tdap, with only 10.9% receiving Td as their next dose of tetanus-containing vaccine. Compared with participants who received a second Tdap, participants who received Td were more likely to be male, age ≥50 years, and have had ≥1 well care visit in the prior year. Crude rates of potential adverse events after the second Tdap dose ranged from 0.8 cases per 10 000 vaccinees for encephalopathy/encephalitis/meningitis to 16.9 per 10 000 for pain in limb.

### 3.1 | Primary analyses

Unadjusted adverse event rates were lower following a second dose of Tdap than following a subsequent Td for cellulitis (5.2 per 10 000 vaccinees after Tdap vs 5.3 after Td), limb swelling (3.4 vs 9.3 per 10 000), pain in limb (16.9 vs 33.2 per 10 000), and seizure (8.3 vs 13.3 per 10 000). Cranial nerve disorders were slightly more common following Tdap (5.4 per 10 000) compared with Td (4.0 per 10 000). In adjusted analyses, receipt of Tdap vs Td was not significantly associated with any of these outcomes (Figure 1). Only 6 cases of encephalopathy/encephalitis/meningitis were detected (5 following Tdap and 1 following Td), precluding adjusted analyses, but the crude rate ratio (0.6) was not statistically significant (95% confidence interval [CI], 0.1 to 5.2). Similarly, only 23 cases of paralytic syndromes were detected, with incidence of 2.9 per 10 000 vaccinees for Tdap and 6.6 per 10 000 for Td (crude rate ratio 0.4, 95% CI, 0.2-1.2).

### 3.2 | Stratified by time since first Tdap

Among subjects receiving a second dose of tetanus-containing vaccine <3 years after initial Tdap, receipt of Tdap vs Td was not significantly associated with any study outcome (Figure 1). Among subjects receiving a second dose ≥3 years after initial Tdap, limb swelling and pain in limb were significantly less common among recipients of Tdap vs Td (Figure 1); significant associations were not observed for cellulitis, seizure, or cranial nerve disorders.

## 4 | DISCUSSION

In light of waning immunity against pertussis following Tdap vaccination,[5,6] a possible vaccination strategy would be to recommend Tdap in place of decennial Td doses. Information about the relative safety of Tdap vs Td following an initial dose of Tdap is needed to inform decisions regarding this strategy. This study suggests that a subsequent dose of Tdap is not associated with increased risks of potential adverse events, compared with a subsequent dose of Td. Specifically, we did not observe significantly elevated risks of

medical visits for cellulitis, limb swelling, pain in limb, seizure, cranial nerve disorders, paralytic syndromes, or encephalopathy/encephalitis/meningitis for Tdap relative to Td.

Several limitations of this study are worth considering. Outcomes of interest were defined by ICD-9-CM codes assigned to clinical encounters, excluding potential adverse events that did not result in an ambulatory care visit or hospitalization. International Classification of Diseases, version 9, Clinical Modification codes are also imperfectly sensitive and specific for the underlying medical outcomes, which may bias our risk ratio estimates. As with any observational study, our results may be subject to confounding due to unmeasured factors. Strengths include the use of population-based data with near-complete capture of vaccinations and medical encounters.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGEMENTS

This work was supported by a contract (200-2012-53421) from the Centers for Disease Control and Prevention. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of Centers for Disease Control and Prevention.

Funding information

Centers for Disease Control and Prevention, Grant/Award Number: 200-2012-53421

## REFERENCES

1. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010. MMWR Morb Mortal Wkly Rep. 2011;60(1):13–15. [PubMed: 21228763]
2. 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.
3. Centers for Disease Control and Prevention (CDC). 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. [PubMed: 23425962]
4. Mertsola J, van der Meeren O, He Q, et al. Decennial administration of a reduced antigen content diphtheria and tetanus toxoids and acellular pertussis vaccine in young adults. Clin Infect Dis. 2010;51(6):656–662. [PubMed: 20704493]
5. 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. [PubMed: 24903664]
6. Acosta AM, DeBolt C, Tasslimi A, et al. Tdap vaccine effectiveness in adolescents during the 2012 Washington State pertussis epidemic. Pediatrics. 2015;135(6):981–989. [PubMed: 25941309]
7. Klein NP, Bartlett J, Fireman B, Baxter R. Waning Tdap effectiveness in adolescents. Pediatrics. 2016;137(3):e20153326. [PubMed: 26908667]
8. Booy R, van der Meeren O, Ng SP, Celzo F, Ramakrishnan G, Jacquet JM. A decennial booster dose of reduced antigen content diphtheria, tetanus, acellular pertussis vaccine (Boostrix) is immunogenic and well tolerated in adults. Vaccine. 2010;29(1):45–50. [PubMed: 20974302]

9. Halperin SA, McNeil S, Langley J, et al. Tolerability and antibody response in adolescents and adults revaccinated with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap) 4-5 years after a previous dose. Vaccine. 2011;29(46): 8459–8465. [PubMed: 21803091]
10. Halperin SA, Scheifele D, de Serres G, et al. Immune responses in adults to revaccination with a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine 10 years after a previous dose. Vaccine. 2012;30(5):974–982. [PubMed: 22115634]
11. Sukumaran L, McCarthy NL, Kharbanda EO, et al. Association of Tdap vaccination with acute events and adverse birth outcomes among pregnant women with prior tetanus-containing immunizations. JAMA. 2015;314(15):1581–1587. [PubMed: 26501534]
12. Baggs J, Gee J, Lewis E, et al. The Vaccine Safety Datalink: a model for monitoring immunization safety. Pediatrics. 2011;127 (Suppl 1: p): S45–S53. [PubMed: 21502240]
13. 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(32):4257–4262. [PubMed: 19486957]
14. Chang S, O'Connor PM, Slade BA, Woo EJ. U.S. Postlicensure safety surveillance for adolescent and adult tetanus, diphtheria and acellular pertussis vaccines: 2005-2007. Vaccine. 2013;31(10): 1447–1452. [PubMed: 23142308]

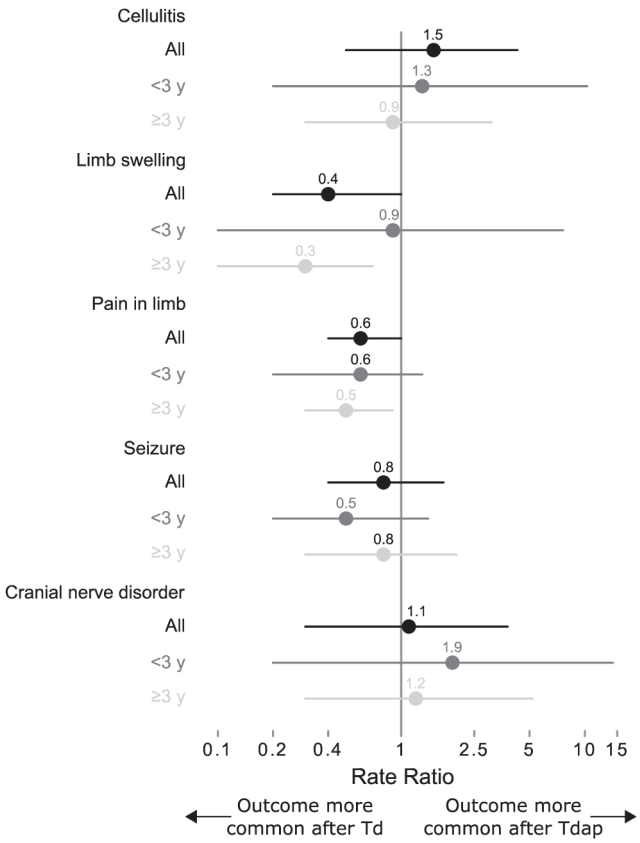


**FIGURE 1.**

Adjusted* rate ratios of adverse events following toxoid and acellular pertussis (Tdap) vs Td as a second dose of tetanus-containing vaccine following an initial dose of Tdap, overall and stratified by years between vaccine doses*Overall risk ratios adjusted for age at first Tdap, years between first Tdap and second tetanus-containing vaccine, sex, study site, receipt of human papillomavirus vaccine, and hospitalizations in the prior year. Stratified risk ratios adjusted for age at first Tdap and years between first Tdap and second tetanus-containing vaccine.

**TABLE 1**

Distribution of covariates at the time of initial toxoid and acellular pertussis (Tdap) vaccination, subsequent Tdap vaccination, or subsequent Td vaccination

| Characteristic | Whole Population at Time of Initial Tdap (N = 68 915) | Covariates at the Time of Subsequent Tdap (N = 61 394) | Covariates at the Time of Subsequent Td (N = 7 521) |
|---|---|---|---|
| HMO site | | | |
| Kaiser Permanente Northern California | 20 149 (29%) | 18 182 (30%) | 1 967 (26%) |
| Kaiser Permanente Colorado | 2 787 (4%) | 2 416 (4%) | 371 (5%) |
| Marshfield Clinic | 1 633 (2%) | 1 329 (2%) | 304 (4%) |
| Kaiser Permanente Northwest | 6 518 (9%) | 5 060 (8%) | 1 458 (19%) |
| Kaiser Permanente Southern California | 29 622 (43%) | 27 487 (45%) | 2 135 (28%) |
| Kaiser Permanente Washington | 8 206 (12%) | 6 920 (11%) | 1 286 (17%) |
| Male | 29 548 (43%) | 25 797 (42%) | 3 751 (50%) |
| Age (years) | | | |
| 11-19 | 23 478 (34%) | 14 531 (24%) | 1 956 (26%) |
| 20-29 | 8 583 (12%) | 11 397 (19%) | 973 (13%) |
| 30-39 | 10 390 (15%) | 10 211 (17%) | 710 (9%) |
| 40-49 | 10 439 (15%) | 8 352 (14%) | 1 084 (14%) |
| 50-59 | 13 394 (19%) | 11 149 (18%) | 1 823 (24%) |
| 60-64 | 2 631 (4%) | 5 754 (9%) | 975 (13%) |
| Well visits in prior 12 months | | | |
| 0 | 66 213 (96%) | 58 609 (95%) | 6 808 (91%) |
| 1 | 2 634 (4%) | 2 707 (4%) | 683 (9%) |
| ≥2 | 68 (0%) | 78 (0%) | 30 (0%) |
| Outpatient visits in prior 12 months | | | |
| 0 | 10 632 (15%) | 6 182 (10%) | 652 (9%) |
| 1-3 | 26 500 (38%) | 20 251 (33%) | 2 652 (35%) |
| 4-6 | 12 734 (18%) | 11 867 (19%) | 1 623 (22%) |
| 7-9 | 6 515 (9%) | 7 111 (12%) | 867 (12%) |
| 10+ | 12 534 (18%) | 15 983 (26%) | 1 727 (23%) |
| Days in hospital in prior 12 months | | | |

| Characteristic | Whole Population at Time of Initial Tdap (N = 68 915) | Covariates at the Time of | |
|---|---|---|---|
| | | Subsequent Tdap (N = 61 394) | Subsequent Td (N = 7 521) |
| No hospitalizations | 63 126 (92%) | 53 068 (86%) | 6 753 (90%) |
| <1 day | 1 420 (2%) | 1 825 (3%) | 365 (5%) |
| 1 day | 946 (1%) | 1 286 (2%) | 94 (1%) |
| 2+ days | 3 423 (5%) | 5 215 (8%) | 309 (4%) |
| Other vaccinations on/before Tdap | | | |
| Pneumococcal polysaccharide | 5 852 (8%) | 8 985 (15%) | 1 234 (16%) |
| Pneumococcal conjugate | 1 480 (2%) | 1 636 (3%) | 160 (2%) |
| Meningococcal conjugate | 13 660 (20%) | 19 020 (31%) | 2 233 (30%) |
| Human papillomavirus | 6 891 (10%) | 12 728 (21%) | 1 212 (16%) |
| Influenza | 38 136 (55%) | 46 854 (76%) | 5 256 (70%) |