

Adverse event reporting rates following tetanus–diphtheria and tetanus toxoid vaccinations: data from the Vaccine Adverse Event Reporting System (VAERS), 1991–1997

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Abstract

Since 1966, the Advisory Committee on Immunization Practices (ACIP) has recommended tetanus–diphtheria toxoid (Td) be used instead of single antigen tetanus toxoid (TT) because, while both vaccines protect against tetanus, only Td protects against diphtheria. Despite this recommendation, approximately 2.5 million doses of TT were distributed annually from 1991 to 1997. One possible explanation for the continued use of TT is concern about the relative safety of Td. Small clinical trials found Td to be associated with a higher rate of local vaccine-associated adverse events (VAEs) than TT. To determine if the findings from the trials would hold up on a larger scale, we compared the rate of reporting to the Vaccine Adverse Event Reporting System (VAERS), a passive reporting system, after either vaccine from 1991 to 1997. There were 40 reports per million doses of Td, and 27 reports per million doses of TT, for a reporting rate ratio of 1.4. Reporting rates to VAERS are lower than the rates of VAEs identified in the clinical trials, but the magnitude of the difference in VAEs following TT versus Td is similar. While reporting rates are lower after TT than Td, rates of reported VAEs after both vaccines are low.

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1. Introduction

Effective vaccinations for tetanus and diphtheria have made these diseases rare in the US and most industrialized countries worldwide [1]. About 50 cases of tetanus have been reported to the Centers for Disease Control and Prevention (CDC) each year from 1991 to 1997, with more than 90% of these occurring in persons greater than 20 years of age [2,3]. Five or fewer cases of diphtheria have been reported in the US each year since 1980, and 70% of these are in persons greater than 15 years of age [4]. While toxigenic strains of diphtheria are infrequently detected in the US, the risk for importation of these strains persists. The recent diphtheria epidemic in the Newly Independent States of the former Soviet Union (and endemicity in many other coun-

tries) continues to be a concern [5–10]. Serological studies suggest that there are US adults susceptible to both tetanus and diphtheria, with a higher percentage of adults susceptible to diphtheria than to tetanus [11–16]. Neither disease is a likely candidate for eradication because of the ubiquitous nature of the organisms that cause them, so vaccinations for tetanus and diphtheria will be necessary into the foreseeable future [17,18].

Two types of vaccines are available in the US for the immunization of adults against tetanus. One is a combined, adsorbed tetanus and diphtheria toxoid formulated for adult use (Td), and the second is a single antigen adsorbed tetanus toxoid (TT). Both Td and TT confer excellent tetanus protection, but Td confers the added benefit of protection against diphtheria disease [19]. Diphtheria toxoid is no longer available in the US as a single antigen vaccine. The Advisory Committee on Immunization Practices (ACIP) has recommended since 1966 that Td be used in adults for both

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primary and booster immunization against tetanus [20]. Despite the longstanding recommendation, substantial quantities of TT are still in use. Based on data from the CDC Biologics Surveillance System, approximately 15% of the tetanus-containing vaccine indicated for use in persons over 7 years of age and sold between 1991 and 1997 was in the form of TT [21,22]. Possible explanations for the continued use of TT include a lack of awareness of the difference between the two vaccines, a lack of awareness of the ACIP recommendations, and a perceived difference in cost. (Note: US vaccine manufacturers who still produce both Td and TT vaccine currently charge either the same price for the two products, or charge a lower price for Td.) Anecdotal reports suggest that some health care providers may prefer TT to Td because they believe Td is associated with an unacceptably high rate of vaccine-associated adverse events (VAEs).

Three clinical trials conducted during the 1980s compared the reactogenicity of Td and TT, and demonstrated that while both vaccines were well-tolerated, Td recipients generally experienced a higher rate of local reactions than TT recipients [23–25] (Table 1). More serious VAEs were not reported in any of the study participants. The largest of these studies included fewer than 1500 participants, however, and the ability of these studies to evaluate rare events was limited. To determine if the findings from the smaller studies hold true on a larger scale and to look for possible rare VAEs, we reviewed postmarketing surveillance data for both vaccines from the Vaccine Adverse Event Reporting System (VAERS). VAERS is a national reporting system that receives more than 10,000 reports each year from public and private clinics, vaccine manufacturers, the general public, and other sources. Recent studies using VAERS data

have detected signals of rare events that are potentially associated with vaccinations (e.g. Guillain-Barre syndrome after influenza vaccination and intussusception after rotavirus vaccine) [26,27]. VAERS data have also been used to compare the occurrence of VAEs after different vaccines (e.g. relative safety of acellular pertussis vaccine versus whole-cell pertussis vaccine) [28].

2. Methods

VAERS is a spontaneous reporting system for adverse events following immunizations, jointly administered by the CDC and the Food and Drug Administration (FDA), and fully operational since 1 November 1990. The National Childhood Vaccine Injury Act of 1986 mandates its existence. The VAERS report form requests information about the patient, the adverse event and its outcome, and information about the vaccines administered, including who gave the vaccines and how they were purchased (i.e. public funds versus private funds). Whether the vaccine or vaccines administered were responsible for the adverse events described typically cannot be determined from the VAERS report alone [29,30].

The VAERS database was searched for reports following the receipt of Td or TT vaccination (alone or in combination with other vaccines) using the following parameters: date of vaccination between 1 January 1991 and 31 December 1997; vaccinee age 7 years or older (because Td is not indicated for use in persons under 7 years of age, and TT is infrequently used in young children); and an indication on the report that the vaccines were purchased with private funds (because TT is not purchased with public funds). Reporting rates were calculated, using as denominators the net doses of Td and TT distributed to private vaccine purchasers as reported to the CDC Biologics Surveillance System [21,22]. Net doses distributed is a proxy for doses administered and is equal to the number of vaccine doses distributed minus the number of doses returned to the manufacturer. We compared Td and TT reporting rates for all reports and then for only those reports meeting a pre-established definition of serious: a death, a life-threatening illness, an event that resulted in either hospitalization or prolongation of a hospital stay, or a permanent disability. Reporting rates for individual events were also calculated. Individual events on VAERS reports are coded based on the text supplied by the reporters in their description of the adverse events. For example, if the text in a VAERS report states that the vaccinee had “redness at the injection site”, the codes for this report would include both ‘redness’ and ‘injection site reaction’.

3. Results

Approximately 72.8 million net doses of Td and 18.0 million net doses of TT were distributed to private vaccine

Table 1
Results of previous studies comparing the reactogenicity of Td and TT

	Td recipients (%)	TT recipients (%)	P-value
Deacon et al. [23] (n = 60)			
Local: pain and/or redness and/or swelling on any day	79	68	NS
Systemic: headache, fever/myalgia	10	16	NS
Macko and Powell [24] (TT: n = 93; Td: n = 100)			
Pain	75	48	<0.001
Redness	25	19	NS
Swelling	30	26	NS
Itch	18	13	NS
Fever	7	2	NS
Zurrer and Steffen [25] (TT: n = 773; Td: n = 653)			
Redness	19.4	12.4	<0.001
Swelling	31.8	25.0	0.025
Pain or heaviness	63.0	58.2	NS
Tiredness	13.9	13.2	NS
Headache	7.7	6.5	NS
Arthralgia	4.1	3.0	NS
Elevated temperature	5.8	4.8	NS
Any reaction	69.7	63.4	0.014

Table 2

Td and TT vaccine doses distributed and VAERS reports received, 1991–1997

	Td	TT	RRR ^a
Net doses distributed ^b	72790280	18087905	
VAERS reports listing Td or TT	2947	516	
Rate of reports per million net doses	40	27	1.4
Serious VAERS reports listing Td or TT	175	38	
Rate of serious reports per million net doses	2.4	2.1	1.1

^a RRR = reporting rate ratio.^b Numbers reported to the CDC Biologics Surveillance System [21,22].

purchasers in the US between 1991 and 1997 (Table 2). There were 2947 VAERS reports (40 per million net doses) listing Td as either the only vaccine or one of the vaccines given, and 516 VAERS reports (27 per million net doses) listing TT as either the only vaccine or one of the vaccines given, for a reporting rate ratio (RRR) of 1.4. There were 175 VAERS reports (2.4 per million net doses) listing Td that met at least one criterion for being serious, and 38 VAERS reports (2.1 per million net doses) listing TT that met at least one criterion for being serious, for a RRR of 1.1. The reporting rates for the five most commonly reported events after Td and TT are shown in Fig. 1. These include injection site reactions, redness, pain, fever, and pruritus. The reporting rate was higher for Td than for TT for all events except pruritus. Of the VAERS reports that met at least one criterion for being serious, the five most commonly reported events were the same as those for all reports (i.e. injection site reactions, redness, fever, pain and pruritus). Injection site reactions, redness and fever were also more common among Td recipients versus TT recipients in the serious reports (data not shown).

There were four deaths reported (three after Td and one after TT). Medical professionals determined that two of the three deaths reported after Td were in all probability due to other causes. Unfortunately, the information provided about the third death after Td and the only death after TT was so incomplete as to preclude any determination of the cause of death for these two vaccine recipients.

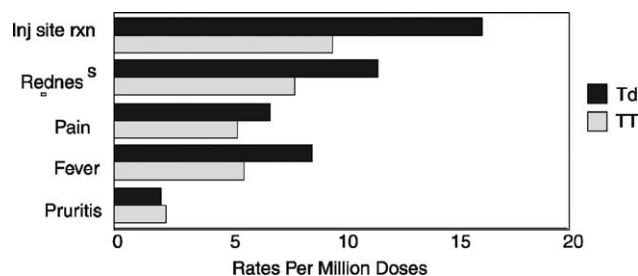


Fig. 1. Reporting rates for the five most commonly reported events after tetanus-diphtheria (Td) and tetanus toxoid (TT) vaccinations.

Table 3

Number and percentage of VAERS reports after Td and TT by age group, 1991–1997

Age group (years)	Td recipients		TT recipients	
	Number	Percentage	Number	Percentage
7–9	27	<1	6	1.2
10–19	578	19.6	60	11.6
20–29	437	14.8	82	15.9
30–39	565	19.2	118	22.9
40–49	527	17.9	103	20.0
50–59	397	13.5	65	12.6
60–69	245	8.3	47	9.1
70+	171	5.8	35	6.8
Total	2947	100.1	516	100.1

Since denominator data on the number of doses of vaccine administered by sex and age are not available, the calculation of sex- and age-specific reporting rates was not possible. The distribution of reports for Td and TT by sex was similar, with more reports after either vaccine describing female vaccinees than male vaccinees (data not shown). For Td vaccine, compared with TT, there were proportionally more reports describing younger vaccinees, with the largest difference in the 10–19 years age group. Of all the reports that listed Td, 19.6% described a vaccinee in the 10–19 years age group versus 11.6% of all the reports that listed TT (Table 3). Similar proportions for age and sex were observed in the distribution of reports classified as serious (data not shown).

Denominator data describing the number and types of vaccines given concurrently with Td or TT are not available; however, 77.3% of the 2947 VAERS reports for Td listed Td as the only vaccine given. The most common combination listed was Td and combined measles, mumps and rubella vaccine (MMR) with 192 (6.5%) of the reports. For TT vaccine, 417 (80.8%) of the 516 reports listed TT as the only vaccine given. The most common combination described was TT and hepatitis B vaccine with 16 (3.1%) of the reports. A higher percentage of the reports that listed Td and were classified as serious also listed other vaccines versus those that listed TT; 64 (36.6%) of the 175 Td reports listed Td with other vaccines while 4 (10.5%) of the 38 TT reports listed TT with other vaccines. There were 19 Td reports classified as serious (10.9%) that listed both Td and MMR.

We compared time intervals—same day, 1–3, 4–7, 8–14, 15–30 and >31 days—between the date of vaccination and the reported onset of the adverse event(s). An onset interval between 0 and 3 days was reported for 68% of individuals who had received only Td versus 67% for individuals who had received only TT. A higher proportion of non-serious reports that listed both Td and MMR had onset intervals of 4–14 days versus those non-serious reports that listed either Td or TT alone (20% for Td and MMR versus 14% for Td and 13% for TT). This difference was not observed for reports classified as serious.

4. Discussion

Our study data concur with the findings of previous clinical trials that demonstrated Td is more reactogenic than TT, especially for local reactions. Our study also suggests that serious events after either vaccine are extremely rare and the distribution of such serious events is similar between Td and TT. The data used in this study reflect a time period when 72.8 million doses of Td and 18.0 million doses of TT were distributed.

The clinical trials that compared Td and TT followed subjects closely and asked about any adverse events, even minor ones such as mild local pain. Based on our previous knowledge of the reporting sensitivities of passive surveillance systems, we would expect that the reporting efficiency to VAERS would be significantly less than that found in the clinical trials, and indeed it was less than 1% of what would have been anticipated based on clinical trials for these non-serious events [31]. The relative magnitude of the reporting rate difference after Td and TT, however, was comparable to the rate differences documented in the clinical trials [23–25].

Our study has limitations, and the main one is that the numerators used in our study were the number of spontaneous reports made to VAERS. VAERS data are not collected for the purpose of conducting clinical studies, and the majority of the reports are not verified. More systematically collected data would have been preferable, but such data are not available. The comparison of individual events must not be over-interpreted since these data are based on whatever written description of the adverse events is provided by the reporter. Given the inherent limitations of VAERS data, we were pleased to find that our results were generally consistent with those of previous clinical trials. Future comparisons of the safety profiles of the two vaccines will likely become even more difficult in the future. Over the 6 years of the study, the amount of TT vaccine distributed decreased relative to the amount of Td vaccine distributed in both the public and private sectors [21,22].

A second limitation of our study was a lack of detailed denominator data that describes the population by age, sex and vaccine(s) received. This prohibited us from adjusting for possible differences between the population that received Td and the population that received TT. We noticed that the distribution of adverse event reports was similar by sex, but not by age. Td recipients with reported adverse events tended to be younger than TT recipients with reported adverse events. So, if younger persons are predisposed to have or report an adverse event regardless of which vaccine they receive, this difference may account for some of the differences between Td and TT reporting rates.

Due to a lack of denominator data on administration of multiple versus single vaccines, it was difficult to meaningfully compare reports where one vaccine was administered versus those where multiple vaccines were administered. We did notice that more non-serious reports after Td and

MMR had an onset interval between 4 and 14 days which may be more compatible with an adverse event related to MMR (because of the incubation period of the live, attenuated viruses in MMR) than to Td. Adverse events associated with Td and TT vaccines are typically noted in the first few days after administration, as these are killed vaccines. We also noted that Td was given more frequently with MMR than was TT. Therefore, for non-serious reports (but not for reports of serious events), a small amount of the observed differences in reporting rates after Td versus TT may be attributed to adverse events that are associated with MMR. It would be anticipated that children and adolescents who are behind on their immunizations would be more likely to receive Td versus TT with other vaccines needed to complete their immunization series, including the MMR vaccine.

VAEs are infrequently reported after either Td or TT, and reports of serious events are rare. Based on our findings and those from the clinical trials, however, Td appears to be associated with non-serious VAEs more frequently than TT. The potential added risk of VAEs after Td must be weighed against the known added benefit of protection against diphtheria disease. Diphtheria is currently well controlled in the US, but it is not certain what conditions are necessary to facilitate its reintroduction and spread. Maintaining population immunity against diphtheria seems especially desirable in light of the recent experiences of the Newly Independent States of the former Soviet Union [6–10]. While there may be older individuals for whom the potential risk of an adverse event from Td could theoretically outweigh the benefit of protection against diphtheria disease (because of a very low likelihood of exposure), health care providers should be reminded that only Td confers protection against diphtheria disease.

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