Side Effects of Diphtheria-Tetanus Toxoid in Adults

JOHN P. MIDDAUGH, MD.

Abstract: During a mass diphtheria-tetanus immunization campaign in November 1975, more than 220,000 doses of diphtheria-tetanus toxoid, adult type were administered to adults throughout Alaska. In Anchorage, where more than 87,000 doses were given, a survey was conducted to determine the frequency of side effects. Postcard questionnaires were mailed to 2,000 randomly selected Anchorage residents; 467 questionnaires were returned by the post office as undeliverable, and 697 questionnaires were completed and returned. A follow-up survey was done of a random sample of the 836 non-responders.

Of those responding, 57.8 per cent reported at least one reaction to the toxoids. The most frequent side effects were sore arm (42.7 per cent), swelling at the site of injection (34.8 per cent), and itching (24.2 per cent). Serious side effects occurred less frequently—swelling of the arm below the elbow (1.1 per cent) and abscess or infection (0.7 per cent). Of those vaccinated, 0.5 per cent saw a physician. There were no statistically significant differences in reaction rates by age group, except for sore arms. The jet injector produced more arm swelling at the site of injection, hives, and itching. More women than men reported adverse reactions, especially sore arm, swelling at the site of injection, and itching. Fear of adverse side effects should not preclude mass vaccination of adults. (Am. J. Public Health (69:246-249, 1979.)

Background

Although first available in 1923, diphtheria-tetanus (td) toxoid was not widely used in the United States until military inductees were inoculated in the 1940s. Numerous (unrandomized) studies conducted in the intervening years documented the effectiveness of the vaccines.[1, 2] However, a high incidence of side effects occurred in adults, correlated with the amount of antigen in the toxoid and with the pre-existing immune status of those receiving inoculation.[3-6]

Advances in technology allowed for many improvements in the vaccine, primarily in purification and determination of standard antigen dose.[3, 4, 7] By reducing the amount of diphtheria antigen from 25 Lf units to 2 Lf units, an adequate antibody response could be achieved in adults while greatly decreasing the incidence of side effects.[4, 8-10] In recent years, outbreaks of diphtheria have resulted in the mass administration of Td to both adults and children.[11-13]

In the fall of 1975, 12 cases of diphtheria occurred in widely scattered areas of Alaska. Epidemiologic investigation failed to link any of the cases; and contact culturing uncovered numerous asymptomatic carriers of toxicogenic organisms. Extensive news coverage resulted in widespread public awareness and concern. Public health officials seized this opportunity to institute mass immunization clinics to update diphtheria-tetanus vaccinations in adults.

The Td vaccine used was obtained primarily from Merrell-National as Tetanus and Diphtheria Toxoids Adsorbed, U.S.P. (For Adult Use), lot numbers 1147EH, 1235EL, 1306EM. The vaccine contains alum precipitated diphtheria toxoid and tetanus toxoid in isotonic sodium chloride solution, preserved with 1 : 10,000 thimerosal. Each 0.5 ml injection contained not more than 0.25 mg of aluminum added in the form of aluminum potassium sulfate.

More than 220,000 people were vaccinated with Td during the immunization program held throughout Alaska in November 1975. In Anchorage, where more than 87,000 adults were vaccinated in a two-day period, a survey was done to determine the incidence of adverse reactions in adults.

Methods

A prepaid postcard questionnaire was mailed to 2,000 randomly selected Anchorage adult residents within three weeks after the initiation of the immunization campaign. The sample population was obtained from the State of Alaska driver's license registry and included only persons holding valid 1975 licenses. A follow-up survey was done by telephone of a random sample of 92 non-respondents to the postcard questionnaire.

The questionnaire asked if the respondent had been vaccinated in the November campaign, the route of administration of the toxoid, and the occurrence of any adverse reac-

Address reprint requests to Field Services Division, Bureau of Epidemiology, Center for Disease Control, Public Health Service, DHEW, Atlanta, GA 30333. Dr. Middaugh, a medical epidemiologist with the Field Services Division, is currently located at the Alaska Department of Health & Social Services, Anchorage, Alaska. This paper, submitted to the Journal March 21, 1978, was revised and accepted for publication June 14, 1978.

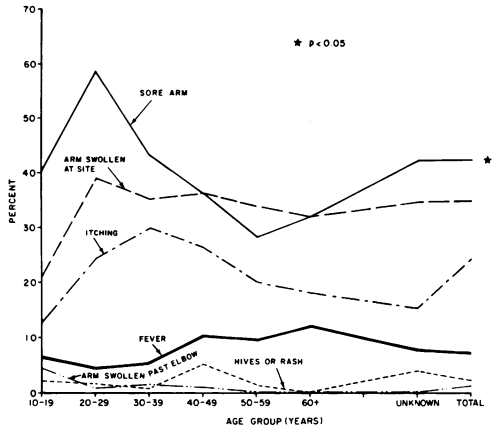

FIGURE 1—Reaction Rates: Diphtheria-Tetanus Vaccination (Td), by Age Group, Anchorage, Alaska, November 1975

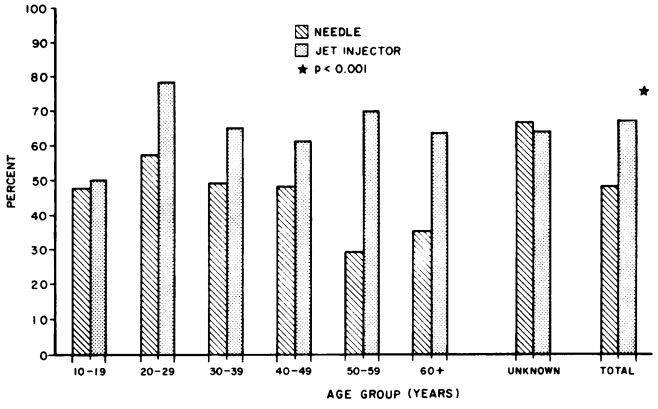

FIGURE 2—Comparison of Reaction Rates: Diphtheria-Tetanus Vaccination (Td), by Route of Administration, Anchorage, Alaska, November 1975

tions. Specific reactions listed were sore arm, swelling of the arm at the site of the injection, swelling of the arm past the elbow, fever, hives or rash, itching, and abscess or infection. Respondents were also asked to describe any other reactions. In addition to age and sex, respondents were asked to indicate whether a physician was seen, and whether they had ever had a diphtheria or tetanus shot in the past.

In an attempt to discover if serious side effects occurred but were missed by our survey, a questionnaire was mailed to over 300 city of Anchorage physicians, and telephone inquiries were made to each of the four hospitals in Anchorage (two private hospitals, the USPHS Alaska Native Hospital, and the Elmendorf Military Hospital).

Results

Of the 2,000 questionnaires mailed out, 467 were returned by the post office as undeliverable, reflecting the transient nature of Alaska's population. Of the 1,533 remaining, 697 (45 per cent) were completed and returned.

Of the 697 who answered the survey, 569 (82 per cent) were vaccinated in the November mass immunization campaign, and 58 per cent listed at least one adverse reaction. Figure 1 shows individual reaction rates in vaccine recipients, by age groups. There were no statistically significant differences in the age distribution of reactions except for sore arm, which was more frequent in the 20 to 29 year-old age group ($p < .05$). For all age groups combined, 43 per cent complained of a sore arm, 35 per cent complained of swelling of the arm at the site of injection, 24 per cent complained of itching, 7 per cent complained of fever, and 2 per cent complained of hives or rash. Serious side effects occurred less frequently—1 per cent complained of swelling of the arm past the elbow, 0.7 per cent complained of abscess or infection, and 0.5 per cent saw a physician.

Vaccine was administered by needle to 48.3 per cent and by jet injector to 51.7 per cent. Figure 2 shows reaction rates, by route of administration of the vaccine. In all age groups, the jet injector caused more reactions than did the needle. For all age groups combined, 67 per cent of those inoculated by jet injector reported an adverse reaction compared with 48 per cent of those inoculated by needle.

Individual reactions by method of injection are shown in Figure 3. Swelling of the arm at the site of injection, hives or rash, and itching were caused more frequently by injection with the jet injector. Figure 4 shows reactions by sex. Sore arm, swelling of the arm at the site of injection, itching, and overall reaction rates were significantly more frequent in women.

A comparison of the frequency of reactions to Td, by sex and by route of vaccine administration, reveals that: 1) in both males and females, the jet injector caused more side effects than the needle; and 2) women had more reactions than men to both the needle and jet injector. These differences are both significant ($p < 0.01$) by the Mantel-Haenszel test (Table 1).

We were interested in the influence of prior vaccination on the frequency of adverse reactions. However, only 16 people in our survey had never received diphtheria or tetanus toxoid in the past. Within the limitations of these small numbers, they had the same chance of having a reaction to Td as those who had been vaccinated in the past.

Major characteristics of respondents and non-respondents are listed in Table 2. More women than men responded to the questionnaire, but no other statistically significant differences are apparent.

Of the 77 Anchorage physicians who returned the physician questionnaire, none reported hospitalizing a patient because of an adverse reaction to the toxoid. None of the Anchorage hospitals surveyed by telephone reported an admission for a side effect of Td vaccination.

Discussion

While the frequency of minor adverse reactions to Td was high, there was a low frequency of serious reactions. Unfortunately, we were unable to verify or to quantitate any of the adverse reactions. However, as there were no reports

TABLE 1—Reaction Rate to Diphtheria-Tetanus Toxoid Injection According to Sex and Route of Administration* November 1975, Anchorage, Alaska

	Reaction	No Reaction	Total
Males			
Needle	51 (38%)	82	133
Jet Injector	68 (58%)	50	118
TOTAL	119 (47%)	132	251
	$X^2 = 8.56$	$p < 0.01$	
Females			
Needle	73 (57%)	56	129
Jet Injector	119 (74%)	42	161
TOTAL	192 (66%)	98	290
	$X^2 = 8.848$	$p < 0.01$	
Mantel-Haenszel Test	$X^2 = 7.451$	$p < 0.01$	

*Incomplete information from 28 respondents

of anaphylaxis from any immunization clinic or private doctor's office, it seems unlikely that any major side effect was overlooked. The level of awareness in both the public and medical communities was very high.

The response rate to the postcard questionnaire was low (45 per cent) and may have introduced some bias toward an overreporting of side effects. Although the data from our survey of non-respondents are reassuring, the telephone survey was carried out a month after the postcards were mailed, and the delay may have resulted in some underreporting of milder reactions. The higher frequency of sore arms, arms swollen at site, itching, and hives in the respondent group is consistent with the reporting of more adverse side effects by women, since women were more apt to respond to the questionnaire than men.

The 87,000 doses of vaccine administered in Anchorage represent 81.2 per cent of the 110,880 Anchorage residents over 18 years of age who were eligible to be vaccinated based on July 1975, population data. The finding that 81.6 per cent of the 697 respondents were vaccinated provides additional support that respondents were not biased with regard to vaccination status.

While no formal attempt was made to assess use of the jet injector, no clogging of the units occurred, and a uniform dose was delivered with prolonged use in the mass clinics. No data were collected to compare antibody response to vaccination with jet injectors or with needle administration of the vaccine. The higher rate of adverse reactions associated with jet injector use may have been due to the dispersal of an adjuvant containing vaccine in muscle, as compared to the discrete delivery of vaccine by needle injection.

Although women reported a significantly higher frequency of adverse side effects than men, the frequency of the more serious (and less subjective) reactions of arm swelling past the elbow, fever, hives or rash, and abscess did not differ by sex.

Our questionnaire failed to ask if there was a past history of adverse reaction to either a diphtheria or tetanus vaccination. It is possible that people who had a severe reaction in the past avoided being vaccinated, and this could bias our finding that those vaccinated in the past had the same chance of having an adverse reaction as those never vaccinated in the past. In addition, the number of those who had never

TABLE 2—Reaction Rates of Respondents and Non-Respondents to Postcard Questionnaire

	Respondents (N=697) %	Non-Respondents* (N=92) %
1. Vaccinated/Total Surveyed	81.6	77.2
2. Sex/Vaccinated		
Male	46.4	63.2
Female	53.6	36.8
3. Reaction/Vaccinated		
Needle	48.4	42.4
Jet Injector	66.7	66.7
Total	57.8	54.9
4. Sore Arm/Vaccinated	42.7	36.6
5. Itching/Vaccinated	24.3	15.5
6. Hives/Vaccinated	2.1	1.4
7. Arm Swollen at Site/Vaccinated	34.8	26.8

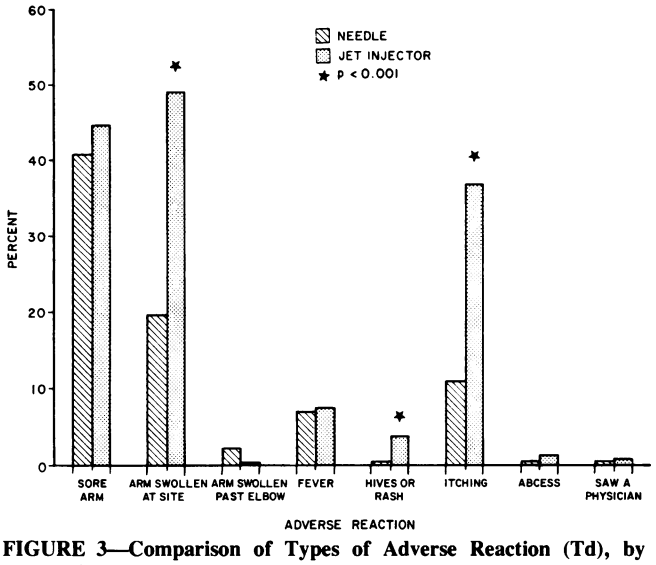

FIGURE 3—Comparison of Types of Adverse Reaction (Td), by Route of Administration, Anchorage, Alaska, November 1975

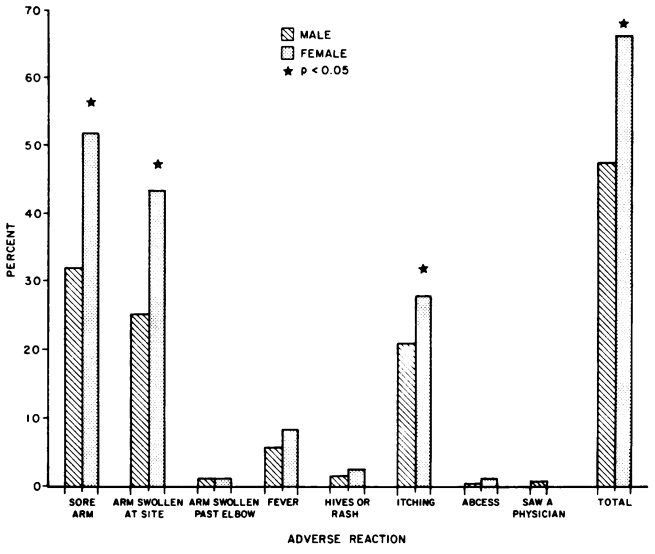

FIGURE 4—Comparison of Male-Female Reaction Rates: Diphtheria-Tetanus Vaccination (Td), Anchorage, Alaska, November 1975

been vaccinated in the past is very small and may not be meaningful.

Within these limitations, the survey shows that there was a low frequency of serious side effects to Td in adults. Concern for adverse side effects should not preclude mass vaccination of adults.

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