

Diphtheria and tetanus immunity among blood donors in Toronto

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Evidence

Études

Abstract

Objective: To determine the diphtheria and tetanus antitoxin levels among blood donors in Toronto.

Design: Cross-sectional seroprevalence study.

Setting: Two fixed-site blood-donation clinics in Toronto from September to November 1994.

Participants: Blood donors 20 years of age or older were eligible to participate; of the 781 eligible donors, 710 (90.9%) participated in the study.

Main outcome measures: Diphtheria and tetanus antitoxin levels and factors associated with disease susceptibility, such as vaccination history, country of birth, age and sex. A diphtheria antitoxin level lower than 0.01 IU/mL and a tetanus antitoxin level lower than 0.15 IU/mL were considered nonprotective.

Results: Among the participants, 147 (20.7%) had a diphtheria antitoxin level in the nonprotective range, and 124 (17.5%) had a tetanus antitoxin level that was nonprotective. Increasing age and lack of written vaccination records were associated with susceptibility to the 2 diseases. Birth outside Canada was significantly related to tetanus susceptibility.

Conclusion: Adults over 50 years of age who did not know their vaccination history were the least likely to be protected against diphtheria and tetanus. The greatest benefit of any immunization strategy would be gained by targeting this group.

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Résumé

Objectif : Déterminer les taux d'antitoxine diphtérique et tétanique chez les donneurs de sang à Toronto.

Conception : Étude transversale de séroprévalence.

Contexte : Deux cliniques fixes de donneurs de sang à Toronto, de septembre à novembre 1994.

Participants : Les donneurs de sang âgés de 20 ans ou plus étaient admissibles; sur les 781 donneurs admissibles à l'étude, 710 (90,9 %) y ont participé.

Principales mesures des résultats : Taux d'antitoxine diphtérique et tétanique et facteurs liés à la vulnérabilité à la maladie, comme les vaccins antérieurs, le pays d'origine, l'âge et le sexe. On a jugé non protecteurs un taux d'antitoxine diphtérique inférieur à 0,01 UI/mL et un taux d'antitoxine tétanique inférieur à 0,15 UI/mL.

Résultats : Parmi les participants, 147 (20,7 %) présentaient un taux d'antitoxine diphtérique non protecteur, et 124 (17,5 %), un taux d'antitoxine tétanique non protecteur. On a établi un lien entre le vieillissement et l'absence de dossiers de vaccination, d'une part, et la vulnérabilité aux 2 maladies, de l'autre. On a établi un lien solide entre la naissance à l'étranger et la vulnérabilité au tétanos.

Conclusion : Les adultes âgés de 50 ans et plus qui ne connaissaient pas leurs vaccins antérieurs étaient les moins susceptibles d'être protégés contre la diphtérie et le tétanos. On maximiserait l'avantage de toute stratégie d'immunisation en ciblant ce groupe.

Diphtheria and tetanus are now rare in Canada.¹ Since the introduction of diphtheria toxoid vaccine in 1926 and tetanus toxoid vaccine in 1940,² routine vaccination programs have led to marked declines in the incidence of these diseases.¹ For both vaccines, a primary series of 4 doses is recom-



mended, with a booster at 4 to 6 years of age; a primary series of 3 doses is required if the vaccine is first administered after 7 years of age. Thereafter, boosters are recommended every 10 years.^{2,3}

In Canada from 1984 to 1993, 42 cases of diphtheria and 43 cases of tetanus were reported, for an annual incidence rate of less than 0.04 cases per 100 000 population.² One death from diphtheria was reported in a woman who was over 40 years of age, and 2 deaths from tetanus occurred in people over 70.⁴ Of the diphtheria cases, 22 (52.4%) were in people under 20 and 8 (19%) were in people over 40 years of age. By contrast, of the tetanus cases, 14 (32.6%) were in people 20 to 39 and 27 (62.8%) were in people over 40. Cases have generally occurred in people who were unvaccinated or inadequately vaccinated.⁵⁻⁷

During the past 2 decades, despite the low incidence of diphtheria in developed countries, localized outbreaks have been reported in the United States and parts of Europe.⁸⁻¹¹ An epidemic of diphtheria, involving more than 50 000 cases, was recently reported in the New Independent States (NIS) of the former Soviet Union.^{12,13} The NIS epidemic has rekindled international concern about the possibility that the disease could be imported by infected travellers.^{12,13} During the past 4 years, at least 20 diphtheria cases have been imported to European countries, such as Finland, Germany, Norway and Poland, from the NIS. In addition, 2 US citizens acquired the disease while travelling in the NIS.¹³ To date, no imported cases have been reported in Canada or the US. However, given the large Ukrainian population in Canada and the extent of travel between the 2 countries, the risk of diphtheria being imported to Canada is cause for concern.

Serologic surveys of diphtheria and tetanus antitoxin levels have often been used to measure the susceptibility to the 2 diseases in a population. In many studies, the researchers have chosen specific antibody levels to indicate susceptibility. However, Ipsen¹⁴ has shown that no single diphtheria antitoxin level protects all people; rather, the level that provides individual protection varies. In addition, previously vaccinated people who have undetectable diphtheria antitoxin levels may be able to mount an anamnestic response when challenged. Thus, antitoxin levels do not provide absolute measures of underlying susceptibility; rather, they serve as surrogate measures.

In North America and Europe, surveys conducted since 1980 have shown that diphtheria antitoxin levels are lower than 0.01 IU/mL in 20% to 50% of adults^{10,15-25} and that tetanus antitoxin levels are lower than 0.01 IU/mL in 11% to 51% of adults.^{15,17,19-22,24-27} In a recent population-based survey conducted in the US, 30.3% of people over the age of 6 had tetanus antitoxin levels of lower than 0.15 IU/mL.²⁸ Susceptibility has been shown to increase with age; girls and women are more often susceptible than

boys and men; and people with a history of military service are more often protected than others.^{10,11,14-27}

Few data are available about the diphtheria and tetanus susceptibility of Canadians. The most recently published serologic surveys were conducted among Ontario schoolchildren and their parents more than 25 years ago¹⁹ and among Manitoba adults and children more than 10 years ago.²⁸ In light of the risk of imported diphtheria in Canada, up-to-date knowledge of the susceptibility of Canadians is important in guiding future vaccination policy. This study was conducted to determine the prevalence of diphtheria and tetanus susceptibility among blood donors in Toronto.

Methods

During an 8-week period from September to November 1994, all blood donors 20 years or older who attended 2 fixed-site blood-donation clinics run by the Canadian Red Cross Society in downtown Toronto were invited to participate in the study. Informed consent was obtained from all participants, and the study was conducted according to the ethical guidelines of the University of Toronto. At enrolment, participants were interviewed about their previous vaccination history, history of military service, country of birth and date of immigration, if applicable. Participants gave written permission for the researchers to use any sera that remained after completion of donor screening tests for analysis of diphtheria and tetanus antitoxin levels and to contact health care providers concerning previous vaccinations if a written vaccination record was unavailable. Only participants who had a written vaccination record or whose vaccination history could be verified by a health care professional were deemed to have documented vaccination.

All laboratory testing was conducted by Connaught Laboratories. A microtissue culture neutralization method was used to determine diphtheria antitoxin levels. This method involves analysis of the pH change resulting from the metabolism of surviving VERO cells after exposure to a toxin-antitoxin mixture in sterile tissue-culture plates.²⁹ A checkerboard titration of the diphtheria reference antitoxin (National Institutes of Health standard) was performed to determine the minimum detectable level. The final result for a sample was obtained by multiplying the minimum detectable antitoxin level in the reference antitoxin titration by the highest serum dilution with a pH of 7.2 or lower.

A solid-phase enzyme-linked immunoassay was used to measure the level of tetanus antitoxin.³⁰ Serum samples were tested in duplicate with 4 2-fold serial dilutions. Starting dilutions ranged from 1:50 to 1:2000. Samples that did not have a detectable antibody concentration in the 1:50 dilution were reported as lower than 0.01



IU/mL. The final result reported was the mean antibody concentration of the 4 dilutions for each serum sample.

In general, a diphtheria antitoxin level lower than 0.01 IU/mL^{10,15-24} and a tetanus antitoxin level lower than 0.01 IU/mL are deemed to indicate susceptibility. Some studies have used a level of 0.01 to 0.09 IU/mL to indicate the presence of antitoxin and a level of 0.1 IU/mL to indicate protection.¹⁰ However, when enzyme-linked immunoassay is used to determine the tetanus antitoxin level, a higher cutoff is generally chosen^{10,29} because, below 0.2 IU/mL, results of neutralization assay are much lower than those of enzyme-linked immunoassay.³¹ In this study, people with a diphtheria antitoxin level lower than 0.01 IU/mL and a tetanus antitoxin level lower than 0.15 IU/mL were deemed to be susceptible.

We used the χ^2 test to compare categorical variables and Student's *t*-test and analysis of variance to compare continuous variables. Multiple logistic regression analysis was conducted to examine factors associated with nonprotective antitoxin levels. SAS software (version 6.10, SAS Institute Inc., Cary, NC, 1994) was used for data entry and analysis.

Results

Of the 781 blood donors who were approached, 725 (92.8%) agreed to participate. Of these, 15 (2.1%) were excluded because insufficient sera remained after routine screening tests. The remaining 710 donors constituted the study participants, and a detailed description of their characteristics is provided in Table 1. Their age ranged from 20 to 70 years (mean 40.8 years, standard deviation [SD] 12.8 years). In general, foreign-born participants (mean 44.5 years) were older than Canadian-born donors (mean 39.0 years, $p < 0.005$). We found that 194 donors (27.3%) had written documentation of diphtheria vaccination and 216 (30.4%) had documentation of tetanus vaccination (Table 2). Among those with documentation of diphtheria vaccination, 25.8% had at least 3 doses recorded and 18.6% had been vaccinated within the past decade (and their vaccination was therefore considered up to date). Among those with documentation of tetanus vaccination, 45.7% had at least 3 doses documented and 39.6% had up-to-date vaccinations.

Diphtheria antitoxin levels

Of the 710 participants, 147 (20.7%) had a diphtheria antitoxin level lower than 0.01 IU/mL. Men and women were equally likely to be susceptible (20.4% and 20.5%, respectively, were susceptible) as were those with and without a history of military service (18.8% and 20.6%, respectively). However, susceptibility increased with age;

about 35% of donors over 50 years of age had an antibody level lower than 0.01 IU/mL, whereas less than 20% of donors under that age were susceptible (Table 3). In addition, a higher proportion of people born outside Canada than born in Canada were susceptible (26.3% and 17.6%, respectively, $p = 0.01$).

In the logistic regression model, age and lack of documentation of diphtheria vaccination were significantly related to susceptibility, but birth outside Canada was no longer a significant variable. Of the 194 donors who had written documentation of vaccination, 88.1% of those under age 50 and 76.5% of those over age 50 had a diphtheria antitoxin level higher than 0.01 IU/mL. These levels may be compared with those of the donors who were unaware of their vaccination history, of whom 82.4% under age 50 and 63.9% over age 50 had protective antitoxin levels.

Tetanus antitoxin levels

Among participants, 124 (17.5%) had a tetanus antitoxin level lower than 0.15 IU/mL. Susceptibility did not differ between the sexes but increased with age (Table 3). As with diphtheria susceptibility, susceptibility to tetanus did not differ between those with and without a history of military service (17.2% and 16.6%, respectively, were susceptible). Donors born outside Canada were, again, more likely to be susceptible than those born in Canada (26.8% and 11.8%, respectively, $p < 0.0001$).

Table 1: Characteristics of blood donors participating in study of diphtheria and tetanus immunity

Characteristic	No. (and %) of donors*		
	Men <i>n</i> = 456	Women <i>n</i> = 254	All <i>n</i> = 710
Age, yr			
< 30	78 (11.0)	75 (10.5)	153 (21.5)
30-39	144 (20.3)	74 (10.4)	218 (30.7)
40-49	111 (15.6)	47 (6.6)	158 (22.2)
50-59	69 (9.7)	33 (4.7)	102 (14.4)
≥ 60	54 (7.6)	25 (3.5)	79 (11.1)
Birthplace			
Canada	303 (42.7)	179 (25.2)	482 (67.9)
US	15 (2.1)	6 (0.9)	21 (3.0)
Europe	85 (12.0)	47 (6.6)	132 (18.6)
Asia	16 (2.2)	9 (1.3)	25 (3.5)
Caribbean	8 (1.1)	4 (0.6)	12 (1.7)
Middle East	7 (1.0)	3 (0.4)	10 (1.4)
South America	9 (1.3)	2 (0.3)	11 (1.6)
Africa	7 (1.0)	0	7 (1.0)
Australia/New Zealand	2 (0.3)	1 (0.1)	3 (0.4)
Not stated	4 (0.6)	3 (0.4)	7 (1.0)
Previous military service			
	57 (8.0)	6 (0.9)	63 (8.9)

*Percentages may not sum to 100 because of rounding.

In the logistic regression model, increasing age, lack of documentation of tetanus vaccination and birth outside Canada were significantly related to having a tetanus antitoxin level lower than 0.15 IU/mL. Of the 216 donors who had written documentation of vaccination, 93.6% of those under age 50 and 83.7% of those over 50 had a tetanus antitoxin level higher than 0.15 IU/mL. These rates of protection were significantly higher than those among participants in the same age ranges who did not know their vaccination histories (89.6% of those under age 50 and 54.3% of those over age 50).

Susceptibility to diphtheria and tetanus

Forty-nine donors (6.9%) were susceptible to both diphtheria and tetanus. Of these, 30 (61.2%)

were men and 25 (51.0%) were born in Canada. Their mean age was 48.9 (SD 14.2) years; 13 (3.5%) were under 40 years of age, 21 (8.1%) were between 40 and 59 years, and 15 (19.0%) were 60 years of age or over. Forty (81.6%) had no written documentation of vaccination against either disease.

Of the total number of participants, 69 (9.7%) were protected against diphtheria but susceptible to tetanus, 96 (13.5%) were protected against tetanus but susceptible to diphtheria, and 496 (69.9%) were protected against both diseases.

Discussion

In this study, 20.7% of the participants had diphtheria antitoxin levels lower than 0.01 IU/mL and 17.5% had tetanus antitoxin levels lower than 0.15 IU/mL. These

Table 2: Previous diphtheria and tetanus vaccination, by age group of donors

Age, yr	Total no. of donors	No. (and %) of donors with previous vaccination		
		According to written record	According to self-report	Unknown
Diphtheria vaccination	<i>n</i> = 710	<i>n</i> = 194	<i>n</i> = 249	<i>n</i> = 267
< 30	153	63 (41.2)	47 (30.7)	43 (28.1)
30–39	218	64 (29.4)	72 (33.0)	82 (37.6)
40–49	158	33 (20.9)	67 (42.4)	58 (36.7)
50–59	102	16 (15.7)	42 (41.2)	44 (43.1)
≥ 60	79	18 (22.8)	21 (26.6)	40 (50.6)
Tetanus vaccination	<i>n</i> = 710	<i>n</i> = 216	<i>n</i> = 376	<i>n</i> = 118
< 30	153	65 (42.5)	64 (41.8)	24 (15.7)
30–39	218	68 (31.2)	110 (50.5)	40 (18.3)
40–49	158	40 (25.3)	98 (62.0)	20 (12.6)
50–59	102	25 (24.5)	64 (62.7)	13 (12.7)
≥ 60	79	18 (22.8)	40 (50.6)	21 (26.6)

Table 3: Diphtheria and tetanus antitoxin levels among blood donors in Toronto, by age group

Age, yr	Diphtheria antitoxin level, IU/mL*				Tetanus antitoxin level, IU/mL†			
	No. (and %) of participants			Geometric mean titre	No. (and %) of participants			Geometric mean titre
	< 0.01	0.01 to < 0.10	≥ 0.10		< 0.01	0.01 to < 0.15	≥ 0.15	
< 30 <i>n</i> = 153	26 (17.0)	68 (44.4)	60 (39.2)	0.063	2 (1.3)	12 (7.8)	139 (90.8)	0.528
30–39 <i>n</i> = 218	29 (13.3)	88 (40.4)	101 (46.3)	0.083	4 (1.8)	14 (6.4)	200 (91.7)	0.704
40–49 <i>n</i> = 158	32 (20.3)	56 (35.4)	70 (44.3)	0.061	1 (0.6)	17 (10.8)	140 (88.6)	0.582
50–59 <i>n</i> = 102	28 (27.5)	45 (44.1)	29 (28.4)	0.031	8 (7.8)	33 (32.4)	61 (59.8)	0.200
≥ 60 <i>n</i> = 79	33 (41.8)	35 (44.3)	11 (13.9)	0.014	9 (11.4)	24 (30.4)	46 (58.2)	0.182
Total <i>n</i> = 710	147 (20.7)	292 (41.1)	271 (38.2)	0.052	24 (3.4)	100 (14.1)	586 (82.5)	0.455

*A diphtheria antitoxin level of 0.01 IU/mL or higher was considered protective.

†A tetanus antitoxin level of 0.15 IU/mL or higher was considered protective.



proportions are much lower than those reported in a Canadian study conducted more than 25 years ago, which showed that 65% of adults had no detectable level of diphtheria antitoxin and 62% had no detectable level of tetanus antitoxin.²⁰ Improved vaccination programs and the introduction of more highly immunogenic adsorbed tetanus and diphtheria toxoids since the early 1980s likely contributed to the improvement. As well, the relatively small proportion of susceptible participants could be explained by the enrolment of blood donors, a group of people who are more likely to be in good health, more interested in their health and more likely to be vaccinated than others in the population. The limitation of convenience samples such as blood donors is that they do not represent the general population.

Our findings are similar to those from studies conducted in other developed countries, which show increasing susceptibility to diphtheria and tetanus with increasing age.^{17,18,21,23-25} However, unlike other studies,^{15-17,29} our study did not show that immunologic protection was higher among men or among those with a history of military service. The lack of association with military service may be due to low statistical power, since only 9% of participants had military experience.

Susceptibility was higher among participants without adequate documentation of vaccination. Not surprisingly, the rate of documentation was highest among young adults and lowest among those over 40 years of age. Although most of those without vaccination records reported previous tetanus vaccination, more than half did not know whether they had received diphtheria toxoid vaccine. In this study, as in studies of measles vaccination,^{30,32} a lack of vaccination records was significantly associated with nonprotection.^{30,32} Without documented records, there is no way of knowing whether previous vaccinations were adequate.

Another factor associated with tetanus susceptibility was birth outside Canada. Natural immunity to tetanus does not exist; it is not even conferred after infection.³³ Therefore, immunity can result only from previous vaccination. Thus, lower protection among participants born outside Canada suggests that they were inadequately vaccinated against tetanus. This lack of adequate vaccination may have been due to varying vaccination schedules or varying delivery of tetanus vaccinations among countries.³⁴

When diphtheria susceptibility among Canadian-born and foreign-born participants was compared after controlling for age, no difference was found. Unlike immunity to tetanus, natural immunity to diphtheria can develop after infection, even if the symptoms of the infection are subclinical.³⁵ Without reliable vaccination histories from most of the participants, it is difficult to know whether this lack of difference in susceptibility be-

tween Canadian-born and foreign-born participants was due to equivalent vaccination histories or to exposure to the infection and, hence, natural immunity in one of the groups.

Our data showed that a larger proportion of adults are protected against tetanus than against diphtheria. In fact, 96 participants (13.5%) were protected against tetanus but susceptible to diphtheria. Our results suggest that the use of single-antigen tetanus toxoid vaccine, instead of combined tetanus toxoid-diphtheria toxoid vaccine, may have contributed to diphtheria susceptibility. Since immunity to tetanus is likely due to vaccination, people who are protected against tetanus but remain susceptible to diphtheria afford an opportunity to examine the use of single-antigen vaccine. According to a letter to medical officers of health from the Public Health Branch of the Ontario Ministry of Health (Nov. 6, 1992), which provides vaccines free of charge to hospitals and medical practices, almost 200 000 doses of single-antigen tetanus toxoid vaccine were distributed annually. Routine use of a combined tetanus-diphtheria vaccine, instead of single-antigen tetanus toxoid vaccine, may be one means to improve the prevalence of immunity to diphtheria in the general population.

In our study, more than one-third of participants over 50 years of age did not have protective levels of diphtheria and tetanus antitoxin. Their geometric mean antibody titres were also several times lower than those of participants under 50. Thus, middle-aged and older Canadians are obvious targets for tetanus and diphtheria vaccination programs.

A closer look at participants who had documentation of vaccination against diphtheria and tetanus showed that they were more likely to be protected than participants who were unaware of their vaccination status. The observed difference may be explained by a lack of adequate vaccination in the group without documentation. Thus, the current recommendation of the National Advisory Committee on Immunization that a primary vaccination series be given to people without vaccination records appears to be sound.²

When compared with their older counterparts, younger vaccinated participants were more likely to be protected. One possible explanation for this difference is waning immunity after vaccination. However, without complete vaccination records, we do not know how many vaccine doses each person received or whether younger and older participants received comparable doses of vaccines.

Some have argued that boosters are an unnecessary expense, since so few cases of diphtheria and tetanus occur in Canada.³⁶ Others have argued that, since natural exposure to diphtheria and consequent immunity are uncommon, outbreaks can occur, and that this risk warrants periodic boosters.³⁵ Our data suggest that many previously



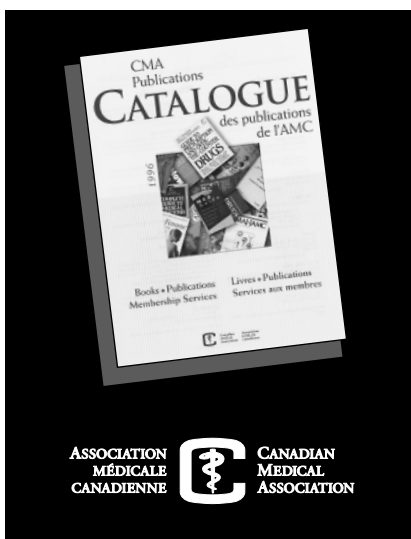
vaccinated people have serologic protection. However, without more accurate vaccination histories, we do not know how long protective levels can be maintained after a primary vaccination series. Nor do we know what proportion of people who have undetectable antitoxin levels will mount an anamnestic response or have symptoms of infection after challenge. Without this information, decisions about boosters will likely continue to be based more on judgement than on science.

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