Health Effects of Anthrax Vaccination in the Canadian Forces

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Objective: The objective of this study was to determine whether anthrax vaccine resulted in adverse health effects in Canadian Forces members 8 months after vaccination. Methods: A quasi-experimental, retrospective chart review was undertaken for two groups within the Canadian Forces, one group that received anthrax vaccination and another that did not. Information on symptoms, diagnoses, and injuries for 848 persons for which there were approximately 35,000 chart entries was abstracted from charts over a 4.5-year period and was coded using the *International Statistical Classification of Diseases and Related Health Problems*, 10th edition. Results: The chart retrieval rate was 84%. The mean number of chart entries per person was higher in the comparison group (43.4) than in the vaccine group (38.2). No statistically significant differences were seen in the percent change before and after vaccination in the number of chart entries for specific diagnoses and symptoms for the vaccine group compared with the comparison group. Visual inspection of the time trend in rates showed no unexplained increases in the rate of diagnosis and symptoms in the vaccine group after vaccination. Conclusion: This study found no evidence that the anthrax vaccination resulted in an increase in adverse health effects in the 8-month period after vaccination.

Introduction

The potential for the use of *Bacillus anthracis* as a biological warfare agent has been recognized for approximately 60 years, and the World Health Organization estimates that 50 kg of *B. anthracis* spores released in a population of 500,000 would result in 95,000 deaths and 125,000 hospitalizations.[1] In 1998, reports that Iraq was stockpiling chemical and biological weapons, including *B. anthracis*, resulted in a decision to vaccinate the Canadian Forces members who were to be deployed in the Persian Gulf. This decision attracted much media attention, described as an "unrelenting barrage of negative press coverage" by the physician then responsible for medical policy at the Department of National Defense.[2] In February 1999, there was sustained questioning in Parliament about the safety of the anthrax vaccine.[3]

What is known about the safety of the vaccine? A comprehensive review of published and unpublished data by an expert advisory committee of the U.S. Institute of Medicine (IOM) was published in 2002.[4] This report concluded that there was no evidence that life-threatening or permanently disabling immediate-onset adverse events occurred at higher rates in persons who had received the vaccination than in the general population and that there was no convincing evidence that persons who had received the anthrax vaccination had elevated risks of later-onset health events.[4] Nevertheless, the safety of the anthrax vaccine has been questioned in a peer-reviewed commentary published in the *American Journal of Public Health* on the basis that (1) the vaccine has never been proved safe or effective; (2) it is a cause of Persian Gulf War syndrome; (3) the production of the vaccine was substandard; and (4) the vaccine was not approved for use against inhalation anthrax.[5] These assertions have been refuted by the Assistant Surgeon General of the U.S. Army on the basis that they had been considered and dismissed by multiple government experts and civilian scientific committees, and, furthermore, that the commentary ignored the 2002 report of the IOM committee.[6]

The aim of this study was to determine whether anthrax vaccine resulted in adverse health effects in Canadian Forces members 8 months after vaccination.

Methods

A quasi-experimental, retrospective chart review of members of the Canadian Forces was carried out to assess the possible adverse effects of the vaccination against anthrax. The study population consisted of 571 persons who were vaccinated during March 1998 and 572 persons randomly selected from a larger group of 1,655 persons who were not vaccinated. Both groups were actively deployed; the vaccine group was deployed in the Persian Gulf between February and May 1998 and the comparison group was deployed in Kosovo between June and December 1999. Both missions were assumed to be comparable in terms of the anxiety and stress experienced by the participating members.

The anthrax vaccine (adsorbed) from lot 020-1 manufactured by BioPort Corporation (Lansing, MI) was administered subcutaneously in three doses on or about March 15, March 30, and April 15, 1998. Information on all diagnoses and symptoms was extracted from the members' medical records for the period of February 1, 1996 through August 31, 2000. Charts for those persons who subsequently retired were included in the study. Reservists were excluded from the study because their charts generally do not cover medical care before and after deployments.

A message from the Surgeon General of the Canadian Forces was sent to all 62 medical units in Canada referring to a "Medical File Review" and requesting that each medical unit provide a photocopy of the members medical attendance record along

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with the original copy of their full chart. The charts were then sent to Canadian Forces Base Kingston for data coding and entry. Each chart was reviewed, coded, and entered by one of two trained data abstractors who were experienced nurses and were fluent in French and English. The average length of time that the abstractors spent on each chart was 2 hours. Each record in the database represented a chart entry, so that a member might have had several diagnoses or symptoms entered arising from a single medical unit visit.

Every new diagnosis, symptom, and injury was classified using rubrics of the Canadian enhancement of the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (ICD-10-CA).[7]

The analysis consisted of a comparison of the frequency of diagnoses and symptoms between the two groups. Chart entry rates were calculated by dividing the number of events (e.g., diagnoses) for specific codes by the total number of events and multiplying this number by 1,000. The percent change in these rates between the 12-month period before deployment and the 8-month period after deployment in the vaccine group and the comparison group was calculated. Diagnosis and symptom rates were plotted by monthly intervals. Age and sex adjustment of these rates was considered and deemed unnecessary because there was insufficient variation in the age-sex composition of the study population. These rates were plotted over time to allow for visual inspection of possible changes in the rates that may have occurred after vaccination during March 1998. All analyses were carried out using procedures written in SAS (SAS Institute, Cary, NC).

A pilot study of 50 charts was undertaken to test record retrieval, data entry, the accuracy of coding, and the inter-rater reliability between the coders. Ethics approval was received from the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

Results

Of the original 1,143 persons identified for the study, 19 names were duplicated on the list and a further 111 were reservists, so that the eligible study population was 1,013. One hundred sixty-five charts were not provided by the Canadian Forces because 12 were not found, 125 were not available because they were in movement related to a posting or were currently deployed, and 27 were required for current treatment. Therefore, the final study population was 848 and the overall chart retrieval rate was 84%, slightly higher in the comparison group (86%) than in the vaccine group (82%).

Table I shows the characteristics of the study population. The mean age was 30 years and the majority of participants were between 25 and 44 years of age (79%) and were men (93%). The majority of participants (85%) were in the junior ranks. The relative proportion of members in the air element in both deployment groups was similar (36% vs. 29%), but substantial differences existed in the relative proportions of distribution of land and navy members. The vaccine group had a large proportion of navy members, 40%, compared with 2% in the comparison group. The majority of the comparison group were comprised of land forces (69%) compared with the vaccine group (24%). The mean number of chart entries per person was higher in the comparison group (43.4) than in the vaccine group (38.2).

Table II lists the leading 20 diagnosis codes, representing approximately 40% of all diagnoses. The leading diagnosis for the vaccine group was "disorders of refraction and accommodation," followed by "soft tissue disorders related to use, overuse, and pressure." In the comparison group, the leading diagnoses were "acute upper respiratory infections of multiple and unspecified sites," "other disorders of muscle" and "soft tissue disorders related to use, overuse, and pressure." In general, the percent changes in diagnoses in the vaccine group decreased or saw small increases, ranging from 0.1 to 1.5%. There were no statistically significant differences between the vaccine group and the comparison group in the percent change after deployment.

Table III shows the leading 20 symptom codes, representing approximately 90% of all symptoms. The most common symptoms recorded in the patient charts were "other symptoms and signs involving the nervous and musculoskeletal systems" followed by "other symptoms and signs involving the circulatory and respiratory systems." In the vaccine and comparison groups, there were similar small increases (+2% and +2.8%, respectively) in "other symptoms and signs involving the nervous and musculoskeletal systems." The remainder of symptom codes recorded decreased or increased to a maximum of 1.6%. In the comparison group, the remaining symptom codes decreased or increased to a maximum of 0.9%. Several of the percent differences were statistically significant, but these differences were all higher in the comparison group.

Figure 1 shows the time trend in diagnosis rates (i.e., the count of diagnoses divided by the total number of persons in each group) from February 1996 to August 2000. There is a sharp increase in the diagnosis rate in the vaccine group where the monthly rates almost doubled from 169 per 1,000 in June 1998 (month 29) to 320 per 1,000 in July 1998 (month 30). In contrast, the highest rates in the comparison group were seen in the first week of 2000. Figure 2 shows the time trend in symptom rates. No clear pattern in the quarterly symptom rates was seen; the group rates rise and fall and often intersect. The monthly symptom rates were highest (687 per 1,000) in the vaccine group in May 1998 (month 28), whereas the symptom rates in the comparison group were highest in February 2000 (month 49; 843 per 1,000).

Discussion

This study reviewed approximately 35,000 medical chart entries for 848 members of the Canadian Forces between February 1, 1996 and August 31, 2000 to determine whether the administration of anthrax vaccine caused adverse health effects. In general, the leading chart entry diagnosis and symptom rates were similar in the vaccine group and the comparison group. No clear pattern was seen in the percent change of chart entries after deployment. Visual inspection of the time trend showed no important differences between the two groups. However, the limitations of this study in terms of possible biases ought to be considered before any conclusions are drawn. These limitations relate to the study design, the use of the ICD-10-CA for coding diagnoses and symptoms, and issues unique to studying persons in the Canadian Forces.

This study was a quasi-experimental, retrospective chart review and was not a true experiment. This may have affected the results in two ways. First, the groups were not strictly compa-

TABLE I

SUMMARY OF STUDY POPULATION CHARACTERISTICS AND CHART ENTRIES, BY VACCINATION STATUS, 1996–2000

	Vaccine Group		Comparison Group		Total	
	n	%	*n*	%	*n*	%
Age group (years)						
15–24	36	8.9	131	29.4	167	19.7
25–34	256	63.5	243	54.6	499	58.8
35–44	105	26.1	63	14.2	168	19.8
45–54	6	1.5	8	1.8	14	1.7
Total	403		445		848	
Sex						
Men	384	95.3	407	91.5	791	93.3
Women	19	4.7	38	8.5	57	6.7
Total	403		445		848	
Rank (missing = 1)						
Level 1[a]	228	56.6	307	69	535	63.2
Level 2[b]	99	24.6	84	18.9	183	21.6
Level 3[c]	50	12.4	36	8.1	86	10.2
Level 4[d]	25	6.2	18	4	43	5.1
Total	402		445		847	
Service						
Air	145	36	129	29	274	32.3
Land	98	24.3	307	69	405	47.8
Sea	160	39.7	9	2	179	21.1
Total	403		445		848	
Diagnoses						
Chapter headings	4,431	11	5,355	12	9,786	11.5
Level 2	4,429	11	5,352	12	9,781	11.6
Symptoms						
Chapter headings	10,474	26	12,997	29.2	23,471	27.7
Level 2	10,472	26	12,995	29.2	23,467	27.7
Level 3	8,284	20.6	10,309	23.2	18,593	21.9
Injuries	508	1.3	960	2.2	1,468	1.7
Total chart entries	15,413	38.2	19,312	43.4	34,725	41

[a] Rank level 1, Private recruit to master corporal, ordinary seaman to master seaman.
[b] Rank level 2, Sergeant to chief warrant office, petty officer 2nd class to chief petty officer 1st class.
[c] Rank level 3, Officer cadet to captain, naval cadet to lieutenant (N).
[d] Rank level 4, Major to general, lieutenant commander to vice admiral.

rable because persons were not randomly allocated to the vaccination or the comparison group. Members of the vaccination group differed from the comparison group in terms of their age, their type of service, and in the time and location of their deployment. Indeed, members in the comparison group showed a higher average number of chart entries per person than did the vaccine group, suggesting that the groups were not strictly comparable. Second, the vaccine group included a substantial number of persons who were deployed on board a ship in the Persian Gulf between February and May 1998 compared with the comparison group who were primarily air and land forces deployed in Kosovo between June and December 1999. Both groups would have been subject to differing exposures that could not have been be controlled for as they would have been in a true experiment.

The ICD-10-CA is the international standard for coding health conditions and has been enhanced by the Canadian Institute for Health Information to meet administrative, epidemiological, and public health research requirements in Canada.[8] Despite its recent adoption in Canadian hospitals, it has not, to our knowledge, been used for primary care research, nor has it been tested for its reliability and validity with respect to the coding of diagnoses and symptoms. The use of the ICD-10-CA is complex and its coding schemes created some difficulties for the coders.

A number of specific issues resulted from the unique nature of the population under study. Service in the Canadian Forces is characterized by routine postings and members are often on the move. In this study, movement of members created two problems. First, it made the retrieval of charts difficult, and 125 charts could not be located because they were in transit to their "owners" next posting. Second, it meant that the vaccine and comparison groups did not necessarily remain together after deployment and that members may have been posted to different places. This issue is important because it meant that other possible exposures could not be controlled for in the analysis.

Several strategies were undertaken to minimize bias that might have arisen from awareness of the aim of this study. First, the original charts were completed by clinicians in base medical units as part of a routine patient assessment. They would not have been aware that the charts were going to be used to study the possible effects of vaccination because the study had yet to be proposed at that stage. Second, the data abstractors were not told the purpose of the study and were unaware that there were two study groups. They were told they were doing a health

TABLE II

LEADING 20 ICD-10 DIAGNOSIS (LEVEL 2) CODES, NUMBER OF CHART ENTRIES, BY VACCINATION STATUS 12 MONTHS BEFORE DEPLOYMENT AND 8 MONTHS AFTER DEPLOYMENT

	Vaccine Group				Comparison Group					
		Pre	Post			Pre	Post			
ICD-10 Diagnosis (Level 2)	*N* (%)	%	%	% Change	*N* (%)	%	%	% Change	χ^2	*p*
Disorders of refraction and accommodation	103 (13)	6.1	4.2	−1.9	87 (9)	4.7	4.5	−0.2	3.17	0.08
Acute upper respiratory infections of multiple and unspecified sites	46 (6)	2.3	2.6	0.3	116 (12)	6.7	5.1	−1.6	0.24	0.627
Soft tissue disorders related to use, overuse, and pressure	74 (9)	3.6	4.2	0.6	102 (10)	4.4	6.7	2.3	2.48	0.115
Other disorders of muscle	72 (9)	3.5	4.2	0.7	104 (11)	5.6	5.5	−0.1	0.01	0.915
Dorsalgia	56 (7)	2.4	3.8	1.4	35 (4)	2	1.7	−0.3	0.73	0.394
Mental and behavioral disorders due to use of tobacco	44 (6)	1.9	2.8	0.9	49 (5)	2.3	3	0.7	0.1	0.751
Other disorders involving the immune mechanism, not elsewhere classified	50 (6)	2.4	2.8	0.4	46 (5)	2.9	1.8	−1.1	0.9	0.342
Influenza, virus not identified	39 (5)	2	2	0	51 (5)	2.9	2.4	−0.5	0.01	0.942
Other disorders of synovium and tendon	45 (6)	1.9	3.1	1.2	53 (5)	2.6	3	0.4	0.08	0.779
Other viral diseases, not elsewhere classified	31 (4)	1.2	2.2	1	42 (4)	2.4	2.1	−0.3	1.17	0.28
Disorders of patella	24 (3)	1.2	1.3	0.1	17 (2)	0.7	1.2	0.5	1.17	0.279
Disorders of lipoprotein metabolism and other lipidemias	52 (7)	2.5	3	0.5	52 (5)	2.2	2.3	0.1	0.08	0.776
Other noninfective gastroenteritis and colitis	16 (2)	0.9	0.7	−0.2	36 (4)	1.9	1.9	0	0.8	0.371
Acute sinusitis	22 (3)	0.9	1.5	0.6	41 (4)	2.4	1.9	−0.5	0.7	0.401
Diarrhea and gastroenteritis of presumed infectious origin	27 (3)	1.4	1.3	−0.1	21 (2)	1.5	1.1	−0.4	0.01	0.938
Other dermatitis	27 (3)	1.6	1.1	−0.5	22 (2)	1.1	1.2	0.1	1.31	0.253
Viral warts	14 (2)	0.9	0.4	−0.5	23 (2)	1.3	1.1	−0.2	0.57	0.22
Other disorders of bone	15 (2)	0.2	1.7	1.5	28 (3)	0.7	2.5	1.8	0.25	0.61
Other bullous disorders	9 (1)	0.5	0.4	−0.1	38 (4)	1.7	2.4	0.7	0.45	0.25
Acute pharyngitis	13 (2)	0.5	0.9	0.4	24 (2)	1.3	1.2	−0.1	0.5	0.478
Leading 20 diagnoses[a]	779	1,188	745		987	1,060	826			

Represents 40% of all level 2 diagnoses.

[a] Note that the pre- and post-column totals are for all diagnoses; multiplying these by the proportions will calculate the *N* (e.g., 1,188 × 0.061 = 72 persons in the vaccine group with disorders of refraction predeployment).

status review of Canadian Forces members. A check to determine whether one abstractor or the other was more likely to enter data from the vaccine group or the comparison group found that no systematic biases could have been introduced because the charts from the vaccine group and the comparison group were distributed equally between the two abstractors. Finally, the persons who analyzed the data were blind to which group was which. The key to the groups was only provided when the analysis was complete.

Although data were collected for a 4.5-year period, the main analyses were limited to 8 months of follow-up. This was because the comparison group was deployed later than the vaccine group and, consequently, the data for this group was not collected beyond the 8-month period.

Visual inspection of the time trend in rates showed two findings of interest in this study. First, monthly diagnosis and symptom rates in the vaccine group appeared to increase after vaccination. However, there was similar increases in diagnosis and symptom rates after deployment of the comparison group. It is likely that these increases resulted from deployment rather than from the vaccination. The usual practice in the Canadian Forces is for members to undergo a postdeployment physical examination before going on leave. It is possible that this routine physical examination explains the increases for both groups. Inspection of the time trend for all rates did not show any consistent dramatic increase in the vaccination group that would support the view that there was an effect of anthrax vaccination.

Consensus among expert groups such as the U.S. IOM and the Cochrane Collaboration have concluded that the anthrax vaccination is safe.[4,9] Our findings support this view. We found no evidence that anthrax vaccination resulted in an increase in adverse health events in the 8-month period after completion of deployment. This conclusion rests on two different findings. First, the percent change in the rates before and after deployment was similar in both groups or was within one percentage point of zero. These changes were not statistically significant. Second, visual inspection of the time trend showed no obvious unexplained increase in the rates of chart entries for diagnoses and symptoms in the vaccine group compared with the compar-

TABLE III

LEADING 20 ICD-10 SYMPTOM CODES, NUMBER OF CHART ENTRIES, BY VACCINATION STATUS 12 MONTHS BEFORE DEPLOYMENT AND 8 MONTHS AFTER DEPLOYMENT

	Vaccine Group				Comparison Group					
		Pre	Post			Pre	Post			
ICD-10 Symptom (Level 2)	*N* (%)	%	%	% Change	*N*	%	%	% Change	χ^2	*p*
Other symptoms and signs involving the nervous and musculoskeletal systems	862 (23)	19	21	2	959 (23)	19	21.8	2.8	4.69	0.03
Other symptoms and signs involving the circulatory and respiratory systems	284 (8)	6.1	7.1	1	380 (9)	8.6	7.3	−1.3	0.87	0.352
Symptoms and signs of the ear	202 (5)	5.1	4	−1.1	287 (7)	6.4	5.6	−0.8	2.19	0.138
Pain in throat and chest	193 (5)	4.6	4.2	−0.4	253 (6)	5.5	5.1	−0.4	0.88	0.347
Cough	152 (4)	3.4	3.6	0.2	212 (5)	5.1	4.1	−1	0.29	0.589
Other skin changes	217 (6)	6	3.3	−2.7	242 (6)	5	5.3	0.3	17.51	0
Headache	180 (5)	3.8	4.7	0.9	208 (5)	4.5	4.2	−0.3	0.28	0.598
Disturbances of skin sensation	185 (5)	4.9	3.2	−1.7	171 (4)	3.4	3.9	0.5	10.98	0
Localized swelling, mass, and lump of skin and subcutaneous tissue	206 (5)	5.7	3.3	−2.4	170 (4)	3.8	3.4	−0.4	7.88	0.01
Other symptoms and signs involving the digestive system and abdomen	151 (4)	3.7	3.2	−0.5	172 (4)	3.4	3.9	0.5	3.9	0.048
Symptoms and signs of the eye	152 (4)	2.9	4.4	1.5	114 (3)	2.3	2.6	0.3	0.28	0.598
Rash and other nonspecific skin eruption	116 (3)	2.8	2.5	−0.3	135 (3)	2.9	2.7	−0.2	0.55	0.457
Malaise and fatigue	145 (4)	2.7	4.3	1.6	151 (4)	3.3	3.1	−0.2	2.36	0.125
Abdominal and pelvic pain	143 (4)	3.5	3	−0.5	140 (3)	2.8	3.1	0.3	3.31	0.069
Nausea and vomiting	98 (3)	2.2	2.4	0.2	131 (3)	2.6	2.9	0.3	0.51	0.474
Abnormalities of breathing	109 (3)	2.3	2.8	0.5	108 (3)	2.3	2.2	−0.1	0.09	0.769
Fever of unknown origin	85 (2)	1.9	2	0.1	109 (3)	2.5	2	−0.5	0.13	0.723
Symptoms and signs involving emotional state	160 (4)	3.8	3.5	−0.3	60 (1)	1.5	1	−0.5	0.15	0.695
Symptoms and signs concerning food and fluid intake	73 (2)	1.6	1.8	0.2	109 (3)	2.2	2.5	0.3	0.27	0.604
Abnormalities of gait and mobility	69 (2)	1.5	1.7	0.2	102 (2)	1.8	2.7	0.9	2.14	0.144
All symptoms (level 2)[a]	3,782	2,653	1,712		4,213	2,689	2,054			

Represents 88% of all Level 2 symptoms.

[a] Note that the pre- and post-column totals are for all diagnoses; multiplying these by the proportions will calculate the *N* (e.g., 2,653 × 0.19 = 504 persons in the vaccine group with other symptoms involving the nervous and musculoskeletal systems.

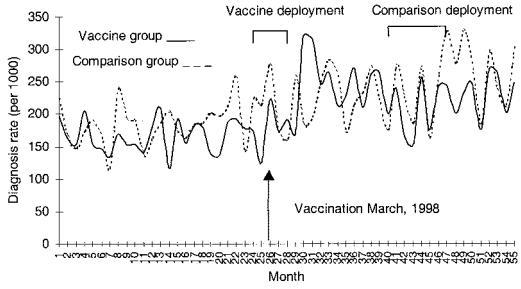

Fig. 1. Monthly diagnosis rates (per 1,000), by deployment group, 1996 to 2000.

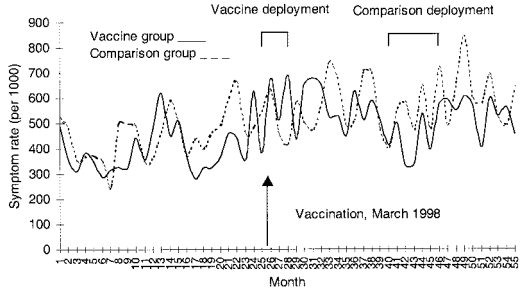

Fig. 2. Monthly level 2 symptom rates (per 1,000) by deployment group, 1996–2000.

ison group. This study suggests that anthrax vaccination did not cause adverse health effects in Canadian Forces members up to 8 months after deployment.

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