

Anaphylaxis: Assessment of a Disease-Based Military Medical Standard

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ABSTRACT Although widespread, the use of disease-based employment medical standards is poorly understood or researched. A probabilistic model and threshold value are developed and applied to a military (Canadian Forces [CF]) medical standard for anaphylaxis. Frequency estimates of prevalence, occurrence, and impairing reactions are determined from the literature for military applicants and from medical chart review of military members identified by prescriptions for self-administered epinephrine. The prevalence of prescriptions is 1.13% (CI 1.05, 1.22) and 0.86% (CI 0.72, 1.00) in the CF Regular Force and applicant populations, respectively. The proposed model predicts the annual risk of an impairing allergic reaction in the CF population ranges from 0.1% to 0.16%/year, well below the proposed threshold of 0.5%. The majority of this risk arises from new cases and not recurrences. Requirement for care increases with recurrence. This model allows a useful method of disease-based medical standard review.

INTRODUCTION

The aging Canadian population and, until recently, low unemployment rates have been challenges to successful expansion of the Canadian Forces (CF) during a prolonged period of increased operational tempo. Re-examination of enrolment and retention medical standards is a potential way of aiding Force expansion. The development and enforcement of employment medical standards, in particular those that are disease based, have not kept pace with the present era of evidence based medicine.^{1,2} Anaphylaxis is a condition that is considered for military medical fitness; in the case of the CF, this standard is differentially applied to applicants and to serving members. A model of assessing disease-based medical standards and a risk threshold is proposed. Using literature-based estimates of anaphylaxis, this model and threshold are applied to an applicant population, and using CF experience, they are applied to a military population. This study was funded entirely by the Canadian Forces Health Services.

BACKGROUND

Medical Employment Standards

Besides protecting the worker from unacceptable risk,^{2,3} military medical standards also aim to maintain the ability to mount deployed operations. To meet these goals, the CF uses a set of enrolment and retention medical standards.⁴ Creation of these standards requires adequate and valid assessments of job requirements and worker capacity; assessments that are relatively simple to create for strength, endurance, and motor skills, and can be applied to cardiovascular and musculoskeletal functional assessments. Standards based on diagno-

sis, rather than function, are much more difficult to create. Prognostication is inexact, individualized, and dependent on the environment; even more so in medical conditions that are intermittent. Diagnoses such as depression, epilepsy, migraines, asthma, renal colic, inflammatory bowel disease, and anaphylaxis are all examples of conditions that imply potential rather than present impairment; they require a method of assessment distinct from that of functional assessments.

Military recruiting is challenged by an aging population, demographic shifts, and relatively low unemployment at a time of increased operational tempo. It has thus become increasingly important to avoid unnecessary exclusion of applicants. A model for assessment of medical fitness directed toward intermittently symptomatic medical conditions may improve risk assessment and allow a greater yield from the military applicant pool.

Model

Anecdote and physician experience play a major role in fitness to work assessment of disease-based employment standards.^{1,2} A theoretical, probabilistic model of accident risk assessment for diseases that cause sudden incapacitation has been described by Donaghue.⁵ He calculates conditional probabilities to assess risk of worker and coworker fatalities and costs of fatal injury and property damage. Each step in the chain leading to a fatal injury is assigned a probability. He suggests that the resultant probability should be compared with a standard already accepted by society such as the rates of fatalities in high-risk industries or an order of magnitude less than the national motor vehicle fatality rate. This type of probabilistic model could be modified for use in all periodically impairing medical conditions and for less dire outcomes than fatality.

Figure 1 is a diagrammatic representation of such a risk model for intermittent medical conditions. The model considers risk from the view of the military on an operation and calculates the frequency of an impairing outcome resulting from the condition of interest in the general deployed population.

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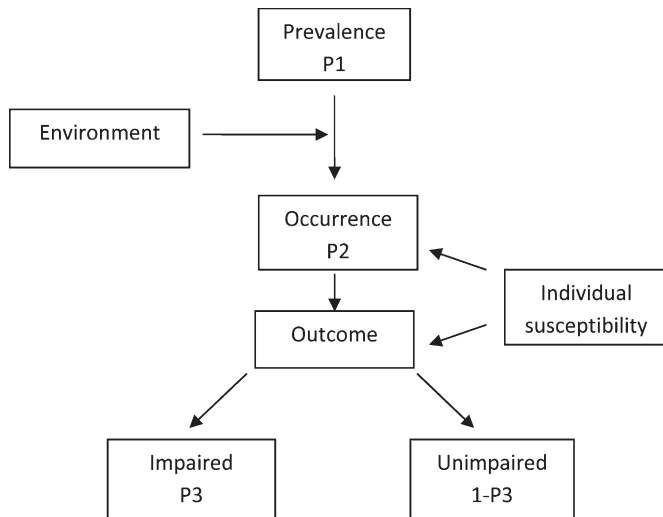


FIGURE 1. Representation of risk model.

Unlike Donaghue's model, no attempt is made to calculate time at work; it is assumed that an operation is continuous. The frequency of an operationally impairing event is $P1 \times P2 \times P3$, where $P1$ is the population prevalence of the condition, $P2$ is the rate of condition occurrence among those affected per unit time, and $P3$ is the proportion of those occurrences expected to be impairing. The model considers population prevalence with the same weight as individual risk of occurrence—the result is an estimate of population rather than individual risk. From the individual (with the condition) perspective, the frequency of an impairing outcome is $P2 \times P3$. The environmental modifying factors would include the physical environment as well as medical treatment factors (level of care locally and ability to reach higher levels of care). Individual susceptibility is the other modifying factor and includes past history of occurrences, control (and side effects) with medication, and condition specific factors. Operational impairment, or inability to perform required tasks, is chosen as the outcome of interest. This is a dichotomous outcome reflecting functional military ability.

Threshold

The model only provides a probability of an impairing event. To be useful, a decision threshold should be determined. This cutoff could be as proposed above: a fraction of an accepted community annual risk level. Alternatively, the impact of excluding workers with a condition could be calculated (number needed to exclude) to prevent an occurrence per unit time. This value reflects lost recruit numbers (and ultimately troop strength). A risk threshold and its "price" in terms of decreased manpower can be developed from literature estimates.

The community of interest in this case is a deployed military. A large cross-sectional study of illness and noncombat injuries occurring in recent U.S. military deployments⁶ provides baseline proportions of medical events. In this survey of more than 15,000 troops returning from deployment (median

length 340 days), 25.2% reported having been given intravenous fluids, 10.4% were hospitalized, 12.7% reported missing a patrol because of illness, 5.2% required medical evacuation, and 3.6% had experienced an asthma attack. Any of these reported conditions could be considered impairing. Here, the medical evacuation rate is used as a "community standard"; 1/10th this rate (0.5%/year) is proposed as an acceptable level of risk. The annual risk of 0.5% would be expected to result in 75 extra episodes of impairment (and potential evacuation) resulting from a history of anaphylaxis over 1 year based on this survey of 15,000 troops.

The cost of an attempt to eliminate the risk depends on the prevalence of history of anaphylaxis. The risk of 0.5% is half that of the approximate 1% population prevalence (as below). Of the 15,000 surveyed troops, 150 would have a history of anaphylaxis and 75 would become impaired over a year; the remaining 75 would be able to replace those impaired. The 2:1 ratio of prevalence to risk results in no net loss of manpower because of the condition.

This risk formulation is admittedly simplistic; not all reactions will occur remotely and require evacuation, and the manpower impact of risk reduction is supply dependent. However, it does allow communication of relative risk and cost of risk reduction by exclusion.

Anaphylaxis

Anaphylaxis is an example of an intermittent medical condition—the CF does not enroll applicants with a history of anaphylaxis, but will most often retain, without deployment restriction, enrolled members who later develop this condition. The literature can support both standards. Anaphylaxis can result in rapid incapacitation and requirement for immediate medical care,^{7,8} which supports an exclusionary standard. There is also support for the retention standard: not all allergic reactions reported as anaphylaxis are severe; 29% were rated as mild (reactions not requiring emergency room treatment)⁹ and, of recurrences, 49% were self rated as mild,¹⁰ and 59% were felt not severe enough to warrant self-administered epinephrine.¹¹ The reported frequency of recurrence varies from 21% to 42.8%.^{10,12} Reported case fatality rates are low and vary almost tenfold from 0.15%⁹ to 1.2%,¹³ and the population mortality rate is estimated at 1 to 3 per million per year.¹⁴ It is difficult to weigh the well-known risk of sudden impairment against the reported natural history to arrive at a rational medical standard policy—a model such as the above can help add perspective. A predetermined risk threshold will allow decision making and ongoing evaluation.

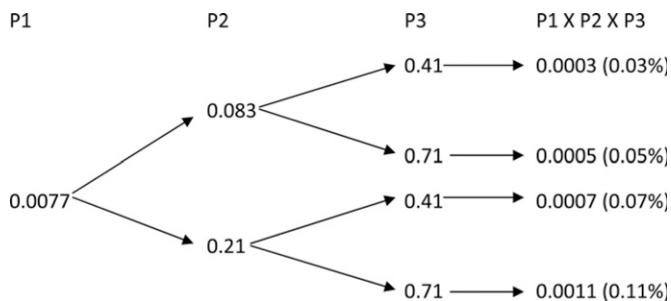
Example of Model Use in Applicant Population

As above, there is a wide range of reported anaphylaxis history prevalence (P_1), occurrence (P_2), and severity rates (P_3) in the literature reflecting differences in definition,¹⁵ recording, and heterogeneous sample populations (in-patients, emergency, and allergy specialty practices). The reported values, however, can be used to estimate a range of risk values using the above

model. The model can be applied to the CF applicant population to determine annual risk of impairing anaphylaxis if no exclusionary screening occurred. The following literature-based estimates (and ranges for recurrence and impairment) are used to determine values for P_1 , P_2 , and P_3 :

- (1) Prevalence (P_1)—is age and sex dependent with higher rates in children and in adult women. In a Canadian study (in Manitoba), prevalence (based on epinephrine prescription) was found to be 0.7% and 1.2% for men and women, respectively, in the age range of most interest for military applicants (20–24 years of age).¹⁶ The CF in 2006 was 13% female; a gender-weighted prevalence estimate would therefore be 0.77%.
- (2) Rate of occurrence per year (P_2)—of those with anaphylaxis annual rate of recurrence per year is 1/12 (8.3%) in Mullins' study¹⁰ but 21% in that of Decker¹² (21% of his series had a second occurrence with a median time to recurrence of 395 days). Both these frequencies are used to provide a range of estimates.
- (3) Severity of occurrence (P_3)—varies in definition from self report to review of medical files. Mild reaction rates are estimated at between 29% (not requiring emergency room treatment) and 59% (not warranting self-administered epinephrine) as above. The probability of reactions that are not mild (and taken as a proxy for impairing in this instance) therefore ranges from 71% to 41%. Both of these frequencies are used to provide a range of estimates of impairment.

Calculation of Annual Risk of Anaphylaxis in Unscreened Applicant Population



Using these estimates, if the CF did not screen applicants for a history of anaphylaxis, between 3/10,000 and 1/1000 enrollees would suffer from an impairing (requiring medical care or epinephrine self-injection) in the next year. These estimates are less than the threshold of 0.5% (0.005) discussed above. Of those with a history of anaphylaxis between 3.4% and 14.9%, ($P_2 \times P_3$) would be expected to have an impairing reaction in the following year. To prevent one impairing reaction per year, (1/probability of impairing reaction), between 7 and 29 applicants with a history of anaphylaxis would need to be excluded.

In this study, the prevalence of anaphylaxis in CF applicants as well as CF population prevalence (P_1), occurrence

(P_2), and outcome rates (P_3) are determined. The risk model is applied and results compared with the threshold risk level of 0.5%/year.

METHODS

Using a prescription for self-administered epinephrine as a proxy for the diagnosis of anaphylaxis, a descriptive chart review of a cohort of CF Regular Force members with prescriptions was performed. Prevalence, recurrence, and treatment requirements of allergic incidents were the variables of primary interest. To estimate prevalence of anaphylaxis in the military applicant population, a review of applicants who had been found medically unfit for enrolment because of a diagnosis of anaphylaxis was also performed. After internal CF approval, the study protocol was reviewed and approved by an external Research Ethics Board (ethica Research Ethics Board).

Data Sources

Regular Force Members

Medical files of Regular Force CF members were reviewed. The military is exclusively responsible for Regular Force medical (and pharmacy) care; at the time of data collection, all medical records were paper and were colocated at the member's base. A centralized electronic pharmacy dispensing database was used to identify members with at least one prescription of self-administered epinephrine (Epipen, Twinject) during the calendar year 2006. Excluded files included those used for the pilot study or those unavailable after request. Two data collectors, a nurse and a pharmacy technician manually searched each entire file for treatment of any allergic reaction. Although all study members had filled a prescription for epinephrine in 2006, it was not possible to determine the date of any prescriptions before this time. Data collection occurred in the first quarter of 2008.

Basic demographic data included age, gender, and full years served in the CF. Treatment location was categorized as civilian or military based, office (with an appointment), in the "MIR" (Medical Inspection Room—equivalent to a walk-in-clinic) or in an emergency department. Ambulance use (either patient or physician requested) was noted. Treatment while on deployment was recorded. Treatment requirements were stratified to no treatment (except ice), oral antihistamine (H1 blocker) only, and provider required treatments; these groups were mutually exclusive. Provider-required treatments included parenteral treatment (epinephrine, H2 blocker), any treatment (oral or parenteral) with steroid, and admission; these groups were not mutually exclusive. Lastly, all allergens listed in the medical file were recorded.

Prevalence of epinephrine prescription (P_1) was calculated using the count of all members with at least one prescription in 2006 using the December 31, 2006 CF Regular Force paid strength as a denominator. CF population first incident rate was calculated using all first allergic reactions in

2006 with paid strength as a denominator. Annual incidence of allergic reactions within the prescription group (P_2) was calculated using all allergic reactions in 2006 as the numerator with the number of all those with a prescription as a denominator. Impairment (P_3) was defined as either requiring more than “no treatment” or requiring more than “no treatment” and “oral antihistamine only.” First and subsequent allergic incidents treatment requirements were compared. No adjustment was made for environmental or individual susceptibility.

Military Applicant Data

The Recruit Medical Office reviews all CF applicant medical information and determines medical fitness to enroll. A search of the correspondence database of the Recruit Medical Office was performed to identify all applicants (Regular and Reserve Force) who had been sent a letter of medical rejection because of a history of anaphylaxis between July 1, 2006 and June 30, 2007. All follow-up correspondence to December 10, 2007 was searched to determine proportion of reversal of initial decision. The correspondence included information regarding gender, allergen trigger, and the presence of comorbid conditions that may, by themselves, have precluded enrolment. The total number of applicant medical files between July 1, 2006 and June 30, 2007 was used as the denominator to determine prevalence in applicants.

Statistical Analysis

All comparisons of categorical variables were performed using a two-sided chi-square test with a significance level of 0.05 using GraphPad Prism version 5.02. Proportions are given with 95% confidence intervals calculated without continuity correction.

RESULTS

Applicant Data

Between July 1, 2006 and June 30, 2007, a total of 17,224 medicals of applicants to both the Reserve and Regular force components were reviewed in the Recruiting Medical Office. Of these, 163 were initially sent letters of rejection because of a history of anaphylaxis; 15 (9.2%) provided medical information (usually from an allergist) that effectively reversed the diagnosis of anaphylaxis. There were ultimately 148 applicants rejected because of a history of anaphylaxis; all had prescriptions for self-administered epinephrine. The prevalence rate of anaphylaxis history (and epinephrine prescription) in the CF applicant population was 0.86% (CI 0.72, 1.00). Men represented 83.1% of the rejected applicants. In 40 cases (27%), there was a comorbid condition that may have precluded enrolment—the most common was a diagnosis of asthma (26 cases). The majority (113) listed food allergies as a trigger, 31 listed insects, and 4 had unknown triggers.

CF Regular Force Data

The CF Regular Force paid strength was 61,797 as of December 31, 2006. During the calendar year 2006, 701 members were identified as having received at least one prescription for self-administered epinephrine. Of these, 55 member files were excluded: 15 were used in the pilot study, 31 medical files were unavailable, 7 were aboard ship, 1 was unavailable because of an administrative investigation, and 1 was that of a deceased member (not related to anaphylaxis—CF Force Health Protection, personal communication, 2008) and was also involved in an administrative investigation and not available. There were thus 646 medical files available for full review. There were no statistically significant differences in gender (chi square), mean age, and mean years of military service (*t* test) between the excluded and study populations.

Of the study population ($N = 646$), 514 (79.6%) were men, the mean age was 40.2 years (range 20, 61), and the mean number of years of military service was 16 (range 1, 38). The 2006 CF Regular Force population included 53,702 men (86.9%) and 8095 women (13.1%). Compared with the CF population, women were significantly overrepresented in the study population (chi square $p < 0.0001$).

Allergic Incident Frequency

Table I details frequency proportions for 2006. There were a total of 109 treated allergic incidents within the study population; of these, 78 were first incidents, 26 were second, and 5 were third. For all years, no allergic events were recorded in 243 (37.6%) of the prescription cohort. Of the remaining 403, a second event occurred in 131 (32.5%) and a third in 26 (6.5%). The requirement for an epinephrine prescription was determined to pre-exist enrolment in the CF in 66 (10.2%) of those with a prescription in 2006. Of all recorded allergic reactions, 8 (1.4%) were noted to have occurred while on deployment.

Care Requirement

Of all allergic incidents, recorded treatment was within military 437 (78.0%), civilian 111 (19.8%), and unknown 12 (2.1%) facilities. Table II displays treatment location and use of an ambulance. Table III displays type of treatment received; there is a significant increase in provider-dependent treatment

TABLE I. Frequency Data (2006)

Description (2006)	Count	<i>N</i>	Proportion % (CI)
Prescription Prevalence— Prescriptions/Paid Strength	701	61,797	1.13 (1.05,1.22)
First Incidents/Paid Strength	78	61,797	0.13 (0.10,0.15)
Proportion of First Incidents to All Those With Prescriptions	78	646	12.1 (9.56,14.59)
Incidence of Reactions Among All Those With Prescriptions	109	646	16.9 (13.98,19.76)
All Incidents/CF Population	109	61,797	0.18 (0.14,0.21)

TABLE II. Treatment Place

	N	Appointment (%)	Medical Inspection Room (%) ^a	ER (%)	Unknown (%)	Ambulance (%)
All 2006 Incidents	109	4 (3.7)	80 (73.4)	21 (19.3)	4 (3.7)	4 (3.7)
All First Incidents	403	14 (3.5)	307 (76.2)	73 (18.1)	9 (2.2)	12 (3.0)
All Second Incidents	131	5 (3.8)	87 (66.4)	31 (23.7)	8 (6.1)	6 (4.6)
All Third Incidents	26	0	20 (76.9)	4 (15.4)	2 (7.7)	1 (3.8)

^aWalk-in or urgent care clinic.

TABLE III. Treatment Type

	N	Provider-independent Treatment			Provider-dependent Treatment			
		No Tx (%)	PO H1 Block Only (%)	No Tx + PO H1 Block Only (%)	IM ^a	CCS ^b	Admit	Unknown
All 2006 Incidents	109	20 (18.3)	31 (28.4)	51 (46.8)	31	33	4	2
All First Incidents	403	96 (23.8)*	139 (34.5)*	235 (58.3)*	104	78	17	4
All Second Incidents	131	12 (9.2)*	43 (32.8)*	55 (42.0)*	57	35	17	0
All Third Incidents	26	1 (3.8)*	3 (11.5)*	4 (15.4)*	17	9	2	0

* $p < 0.0001$ for difference in treatment type between first and subsequent (pooled second and third) allergic incidents. ^aAny parenteral treatment (intramuscular, subcutaneous, IV). ^bOral or IV corticosteroid use.

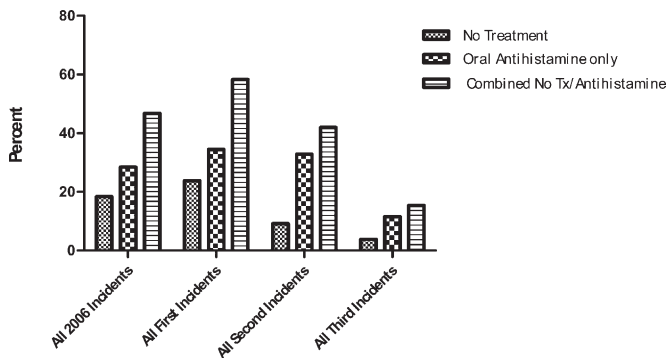


FIGURE 2. Provider independent treatment and recurrence.

for recurrences. Figure 2 graphically displays health care provider-independent treatment and recurrences. A comparison between all first reactions in 2006 (when it was certain that a prescription had been filled) and all first reactions did not demonstrate a statistically significant difference in treatment requirement (chi square $p = 0.75$).

Triggers

Food allergies and insect stings accounted for the majority of identified allergic incident triggers (30.9% and 30.3%, respectively), environmental allergies, and medications (22.7% and 16.0%) followed. A total of 1048 allergic triggers were recorded for the total of 560 allergic incidents. Figure 3 displays the triggers within each group.

Analysis Using Model

The model for CF population risk over 1 year of allergic incidents requiring a provider is as follows:

Population prevalence (P_1) $\times$ annual incidence of reactions in those affected (P_2) $\times$ proportion of provider required incidents (P_3).

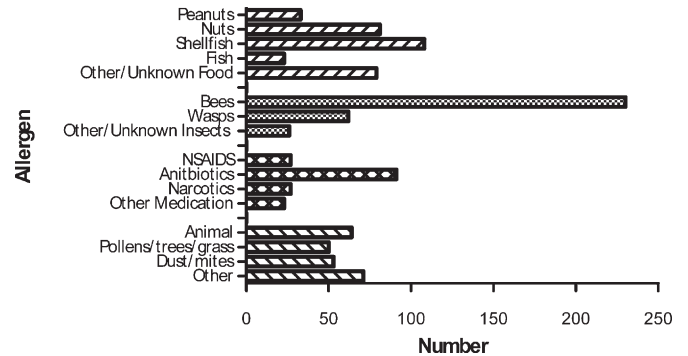


FIGURE 3. Allergic triggers.

P1—Prevalence in CF population (2006) = 1.13%

P2—Incidence of reactions among those with a prescription (2006) = 16.9%

P3—Proportion of provider required incidents (2006):

- P3a (1 – no required treatment) = 81.7%
- P3b (1 – no treatment + oral antihistamine only) = 53.2%

$P1 \times P2 \times P3a = 0.16\%$

$P1 \times P2 \times P3b = 0.10\%$

Affected population annual risk of incident occurrence requiring a provider is $P2 \times P3$.

$P2 \times P3a = 13.8\%$

$P2 \times P3b = 9.00\%$

DISCUSSION

Using prescriptions of self-administered epinephrine as a proxy for the diagnosis of prior anaphylaxis, the prevalence in the CF Regular Force population in 2006 was 1.13% (CI 1.05, 1.22); women were over represented compared with

the CF population. The prevalence of a history of anaphylaxis in the applicant population was 0.86% (CI 0.72, 1.00). Using the proposed probabilistic model, the annual risk posed by those with a prescription to the CF Regular Force population of an allergic reaction requiring either an oral antihistamine or provider required treatment was 0.16% and 0.10%, respectively; well below the discussed threshold of 0.5% per year. The risk to the cohort with prescriptions of an impairing reaction was 13.8% and 9.0% annually. To prevent one impairing reaction within the cohort per year (1/annual probability) between 7.2 and 11.1 members would need to be released. New cases represented 72% of all allergic incidents in 2006 and thus are a more important determinant of risk than prevalent (previously known) cases. As recurrence number increases, severity, as judged by required medical care, increases.

The applicant anaphylaxis history prevalence rate was somewhat higher than that calculated from the literature; this may be resulting from age and gender mix differences in the applicant population from that used for the calculation. Despite exclusive enrolment policy, the CF prevalence of epinephrine prescriptions was higher than a gender-adjusted estimate from the Manitoba general population (at age 40, Manitoba proportions were about 0.7% and 1.15% for men and women, respectively; after adjusting for gender, this would predict a CF rate of 0.8%).¹⁶ This may, in part, be related to cost of prescription not being a barrier in the CF. It may also be that prescriptions are refilled more regularly in the CF because of mandated periodic medical examinations. Of those who had a first allergic incident in 2006 (78), only 5 (6.4%) had a second one to the end of 2007. This is lower than earlier estimates of recurrence rates^{10,12} and very likely is an underestimate resulting from short follow-up. No treatment or an oral antihistamine only was required in 46.7% of allergic incidents in 2006; this proportion is closer to the 49% of self-reported mild symptoms¹⁰ than the 29% of mild reactions (not requiring emergency room treatment) reported after chart review.⁹ The differences in severity definition make direct comparison difficult.

Misclassification of diagnosis and outcome (treatment) are potential weaknesses of this study. To our knowledge validation of prescribing data as a proxy for the diagnosis of anaphylaxis has not been performed. Although the only listed indication for self-administered epinephrine is anaphylaxis,¹⁷ no record of allergic incidents was found in 37.6% of the sample. This may reflect treatment and diagnosis outside of the CF (either pre-enrolment or from an outside source while in the CF), lack of medical record keeping or use of epinephrine for another indication. The prevalence could be inflated because of these factors. Frequency estimates could be decreased by obtaining prescriptions outside of the CF system out of concern for administrative action; this may be somewhat offset by the relatively high price of the prescriptions. Frequencies may have also been underestimated by failure to prescribe epinephrine to a patient with anaphylaxis.

Although the shelf life of dispensed epinephrine is about one year,^{18,19} it is possible that members either refilled their prescription early or late which would affect prevalence estimates. Misclassification may have occurred with the applicant data as well; a history of anaphylaxis is a barrier to enrolment and may have lead to nondisclosure resulting in a prevalence underestimate.

Misclassification of treatment may also have occurred. Although this represents a useful resource planning estimate, clinical or perceived severity may not match treatment. Treatment was reported on recorded incidents from all years. All study members had received a prescription for epinephrine in 2006, but we were unable to determine the date of their first prescription. Treatment data may have been collected from members before an epinephrine prescription—prompting incident.

The strength of this study lies in the use of a conceptual risk model for the specific population of interest. The model allows an estimate of risk and a method of evaluating this risk against a threshold. The use of a proxy marker for diagnosis and medical care received as an outcome avoids some of the concerns regarding anaphylaxis definition and severity rating. The availability of complete medical and pharmacy files of CF members added to the validity of the data.

The objective of the proposed conceptual model was to allow quantification of risk to the CF and the individual, when considering disease-based medical employment standards. No adjustment was made for environmental or individual factors. Consideration of both these factors may be more important when considering retention rather than enrolment standards when military occupation may not yet be determined. The threshold value of 0.5% was based on a fraction (1/10th) of an observed medical evacuation rate on deployment of U.S. forces.⁶ Other thresholds can be imagined and the threshold may not be appropriate for all occupations.

In summary, this study found that the military population risk of anaphylaxis is more related to new rather than recurrent cases. A model for assessment of medical employment standards was developed and using the study findings, the risk posed by a history of anaphylaxis was less than the proposed threshold for exclusion. Present exclusionary applicant standards seem to have a relatively weak risk-reduction effect at the cost of excluding otherwise acceptable military applicants. Treatment requirement for allergic incidents increases with recurrence. Although the anaphylaxis data is specific to a military population, the proposed model has potential application to all workplaces requiring medical employment standards. A prospective trial of this model applied to anaphylaxis or other disease-based medical standards is indicated.

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