

Food-allergy Anaphylaxis and Epinephrine Autoinjector Prescription Fills, Active Component Service Members, U.S. Armed Forces, 2007–2016

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CE/CME

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Food-allergy anaphylaxis is an immunoglobulin E-mediated, systemic reaction that is often unanticipated and can rapidly lead to death. Active duty service members with a history of food-allergy anaphylaxis or a systemic reaction to food do not meet military accession or retention standards. In spite of this, the incidence rate of food-allergy anaphylaxis among active component service members approximates that found in the general population and appears to be increasing. The overall incidence of food-allergy anaphylaxis among active component service members was 39.1 cases per 100,000 person-years (p-yrs) during the 2007–2016 surveillance period. The incidence increased over the surveillance period from 32.0 per 100,000 p-yrs in 2007 to 55.8 per 100,000 p-yrs in 2016. First-line treatment of anaphylaxis includes rapid administration of epinephrine. In this study, 29% and 58% of incident anaphylaxis cases had filled a prescription for an epinephrine autoinjector (EAI) within 18 months before or 3 months after the incident diagnosis, respectively. Increasing awareness of food-allergy anaphylaxis, properly identifying at-risk individuals, and ensuring availability of EAIs have the potential to mitigate the risk associated with anaphylaxis.

Food-allergy anaphylaxis is an immunoglobulin E (IgE)-mediated, systemic reaction that is often unanticipated and can rapidly lead to death. Prevention of anaphylaxis includes identification of individuals at risk for anaphylaxis and avoidance of both the offending agent as well as cofactors that have the potential to induce or exacerbate reactions to an otherwise tolerated allergen.¹ The Joint Task Force on Practice Parameters recommends that patients with a history of food-allergy anaphylaxis and those who are at risk for anaphylaxis due to a previous systemic reaction to foods or other factors be prescribed an epinephrine autoinjector (EAI).^{2,3} In spite of this recommendation, studies indicate that EAIs are underutilized.^{4,5}

Knowledge related to the epidemiology of anaphylaxis in the general population

comes from multiple sources, including surveys,⁶ medical claims data from hospital admissions,^{7,8} emergency room visits,⁹ and medically coded encounters from population-based databases (Table 1).^{10–18} Incidence rate estimates vary widely due to variable case definitions, populations, data sources, and study design. Among retrospective studies utilizing medically coded encounters, rates range from 6.7 per 100,000 person-years (p-yrs) in the general population¹⁷ to 109.0 per 100,000 p-yrs among asthmatics.¹³ Studies in the U.S. and elsewhere suggest that the incidence of anaphylaxis is increasing (Table 1).^{11,14,15,17}

Individuals with a history of anaphylaxis or a systemic reaction to food do not meet military accession standards.¹⁹ Waivers may be granted, however, based on the severity of a reaction, risk of recurrence,

occupation, and the needs of the military. Service members with a history of food-allergy anaphylaxis who are not identified at accession, and those who develop food-allergy anaphylaxis while on active duty warrant referral to a medical evaluation board for a fitness for duty determination.

Establishing the incidence of anaphylaxis within the U.S. military and tracking trends over time would increase awareness of the condition, including the risk of potentially devastating outcomes in austere environments. It may also assist with development and implementation of accession and retention standards. Quantifying EAI prescription fill rates could guide prevention and treatment efforts. To date, there are no studies related to the epidemiology of food-allergy anaphylaxis or EAI prescription fill rates among active component service members. The purpose of this study is to determine the incidence of food-allergy anaphylaxis over time, and to describe EAI prescription fill rates.

METHODS

Anaphylaxis incidence

This was a retrospective cohort study. An incident case of food-allergy anaphylaxis was defined as any inpatient, outpatient, or Theater Medical Data Store (TMDS) medical encounter identified using ICD-9 code 995.6* and ICD-10 code T78.0* in any diagnostic position. Service members who had been diagnosed with food-allergy anaphylaxis prior to the surveillance period were excluded from the study population. The surveillance period for an incident case of food-allergy

TABLE 1. Results of similar studies evaluating the incidence of food-allergy anaphylaxis

Author (publication year)	Study period	Location	Data source	Ages studied	Incidence ^a	Time trend in incidence ^a	Food as cause of anaphylaxis	Sex with highest incidence	Age with highest incidence
Bohlke (2004) ¹⁰	1991–1997	WA	Health Maintenance Organization	<18 yrs	10.5 using codes specific for anaphylaxis; 68.4 using non-specific codes	No increase	Most frequent cause	Males (not statistically significant)	15–17 yrs (not statistically significant)
Yocum (1999) ¹⁶	1983–1987	Olmsted County, MN	Rochester Epidemiology Project	All	30	Not reported	Most frequent cause	No difference	Mean age 29 yrs ± 19 yrs
Decker (2008) ¹¹	1990–2000	Rochester, MN	Rochester Epidemiology Project	All	49.8	Increased from 46.9 to 58.9	Most frequent cause	Not evaluated	29.3 yrs ± 18.2 yrs
Lee (2017) ¹⁴	2001–2010	Olmsted County, MN	Rochester Epidemiology Project	All	42	Increased from 36.8 to 46.6	Most frequent cause in 0–9 y/o	Males 10–19 yrs; Females 30–39 yrs; no difference in other age groups	Median age 31 yrs
Yang (2017) ¹⁵	2008–2014	Republic of Korea	Korean National Health Insurance	All	22.01	Increased from 16.0 to 32.2	Second most frequent cause after unspecified	Males	40–69 yrs
Sheikh (2008) ¹⁷	2001–2005	United Kingdom	QRESEARCH	All	6.7–7.9	Increased from 6.7 to 7.9	Not reported	Males <14 yrs; Females >14 yrs	50–65 yrs
Rolla (2013) ¹⁸	2010	Piemonte Region, Italy	Regional Health System	All	9.9 in 18+ yrs; 29.0 in <18 yrs	Not reported	Rates specific for food	Males <18 yrs; Females >18 yrs	<18 yrs
Gonzalez-Perez (2010) ¹²	1996–2005	United Kingdom	The Health Improvement Network	10–79 yrs	21.28 in patients without asthma; 50.45 in patients with asthma	Not reported	Most frequent cause in those <40 yrs	Males	20–29 yrs
Iribarren (2010) ¹³	1996–2006	CA	Kaiser	All	19.9 in patients without asthma; 109.0 in patients with asthma	Not reported	Second most frequent cause after serum	Females	19–45 yrs

^aRate per 100,000 person-years

anaphylaxis was 1 January 2007 through 31 December 2016. The surveillance population included all individuals, deployed and non-deployed, who served in the active component of the Army, Navy, Air Force, or Marine Corps at any time during the surveillance period.

All data used to determine incident food-allergy anaphylaxis were derived from records routinely maintained in the Defense Medical Surveillance System (DMSS). These records document both ambulatory encounters and hospitalizations of active

component members of the U.S. Armed Forces in fixed military and civilian (if reimbursed through the Military Health System) treatment facilities.

EAI prescription fill rates

Individuals with an incident case of food-allergy anaphylaxis or an incident diagnosis of food allergy from 30 June 2008 through 30 September 2016 were considered candidates for an EAI prescription. An incident diagnosis of food allergy was defined by having a first-ever inpatient,

outpatient, or TMDS medical encounter with ICD-9 codes V15.01–V15.05 and ICD-10 codes Z91.010–Z91.013 or Z91.018 in any diagnostic position during the surveillance period. Individuals were considered candidates for an EAI prescription fill for 18 months prior to and 3 months after a diagnosis of food allergy or food-allergy anaphylaxis.

Prescription information was obtained from the Pharmacy Data Transaction Service, a central data repository that contains medication records for all TRICARE

beneficiaries, regardless of point of service (i.e., military, retail, and mail-order pharmacies). Descriptive statistics were used to describe the number of EAI prescriptions dispensed to those identified as candidates for an EAI based on a prior diagnosis of food allergy or food-allergy anaphylaxis.

RESULTS

During 2007–2016, the crude overall incidence of food-allergy anaphylaxis among active component service members was 39.1 cases per 100,000 p-yrs (**Table 2**). The crude annual incidence increased during the surveillance period from 32.0 per 100,000 p-yrs in 2007 to 55.8 per 100,000 p-yrs in 2016 (**Figure 1**). The incidence of food-allergy anaphylaxis among females was almost three times that of males (85.4 and 31.1 cases per 100,000 p-yrs, respectively) and this was consistent across much of the surveillance period (**Table 2, Figure 2**). Across race/ethnicity groups, the highest overall incidence of food-allergy anaphylaxis was found among non-Hispanic blacks (72.6 cases per 100,000 p-yrs), followed by service members in the “other/unknown” category (47.0 cases per 100,000 p-yrs). Non-Hispanic blacks had the highest annual incidence rates throughout the entire surveillance period (**Figure 3**). The lowest overall incidence was found among non-Hispanic whites (28.8 cases per 100,000 p-yrs) (**Table 2**). Across the age groups, the overall incidence of food-allergy anaphylaxis was lowest among those aged 20–24 years and highest among those aged 30–34 years (34.9 cases per 100,000 p-yrs and 43.1 cases per 100,000 p-yrs, respectively). During the surveillance period, annual rates increased in all age groups (**data not shown**).

More than 10% of food-allergic individuals filled a prescription for an EAI within the 18 months prior to their food allergy diagnosis, and more than 28% of individuals with a diagnosis of food-allergy anaphylaxis filled a prescription for an EAI within the 18 months prior to being diagnosed with food-allergy anaphylaxis (**Figure 4**). There were 26,085 incident cases of food allergy during the surveillance period; of these, 23.2% (6,054) filled a prescription

for EAI within the 3 months following the diagnosis. There were 4,475 incident cases of food-allergy anaphylaxis; of these, 58.4% (2,612) filled a prescription for EAI within the 3 months following the diagnosis.

EDITORIAL COMMENT

Few studies specifically evaluate the incidence of food-allergy anaphylaxis, and comparison between studies is difficult given variable study design and populations. Still, comparison of incidence rates between military service members and the general U.S. population is informative. Given that food allergies and the risk for anaphylaxis are often identified during childhood, and that anaphylaxis medically disqualifies an individual from military service, the incidence of anaphylaxis in the military was expected to be lower than that in the general population. This expectation was tempered somewhat by generous waiver approval rates among military applicants with a history of anaphylaxis, which ranged from 54% among Air Force applicants to 91% among Navy applicants between 2008 and 2013.²⁰ The current study found that the incidence of food-allergy anaphylaxis among active component service members approximated that found in previous large, population-based studies performed in the U.S.^{11,14,16} and was higher than that found in comparable studies performed overseas.^{15,17,18} Clearly, accession standards and the medical board process do not completely address the issue of anaphylaxis in the military. Military healthcare providers, including those providing care in operational environments, must be prepared to manage at-risk and affected service members. This is especially true given that the incidence of food-allergy anaphylaxis appears to be increasing.

Epinephrine injection constitutes first-line treatment of anaphylaxis. U.S. studies of administrative claims data show that 46%–54% of patients being discharged from emergency departments following an episode of anaphylaxis filled a prescription for EAI within 1 year.^{5,21} Given that military service members undergo periodic examinations that potentially identify

TABLE 2. Incidence rates^a of food-allergy anaphylaxis, active component, U.S. Armed Forces, 2007–2016

	Total 2007–2016
	Rate
Total	39.1
Service	
Army	41.0
Navy	36.3
Air Force	48.2
Marine Corps	23.1
Sex	
Male	31.1
Female	85.4
Age	
≤19	42.0
20–24	34.9
25–29	40.8
30–34	43.1
35–39	38.6
≥40	40.8
Race/ethnicity	
Non-Hispanic white	28.8
Non-Hispanic black	72.6
Hispanic	42.0
Asian/Pacific Islander	37.5
Other/unknown	47.0
Rank	
Jr. Enlisted (E1–E4)	38.1
Sr. Enlisted (E5–E9)	41.3
Jr. Officer (O1–O3)	37.9
Sr. Officer (O4–O10)	35.5
Warrant Officer (W01–W05)	32.4
Military occupation	
Combat-specific ^b	23.6
Motor transport	30.0
Pilot/air crew	21.3
Repair/engineer	32.1
Communications/intelligence	47.1
Health care	69.8
Other	43.2

^aNumber of cases per 100,000 person-years
^bInfantry/artillery/combat engineering/armored

EAI candidates, and the fact that there is no pre-authorization requirement or cost associated with filling a prescription for EAI, it was expected that active component service members would have a higher rate of EAI dispensing than the general population. This expectation was bolstered by the findings of a study of military beneficiaries (including dependents and active

FIGURE 1. Annual incidence rates of food-allergy anaphylaxis, active component, U.S. Armed Forces, 2007–2016

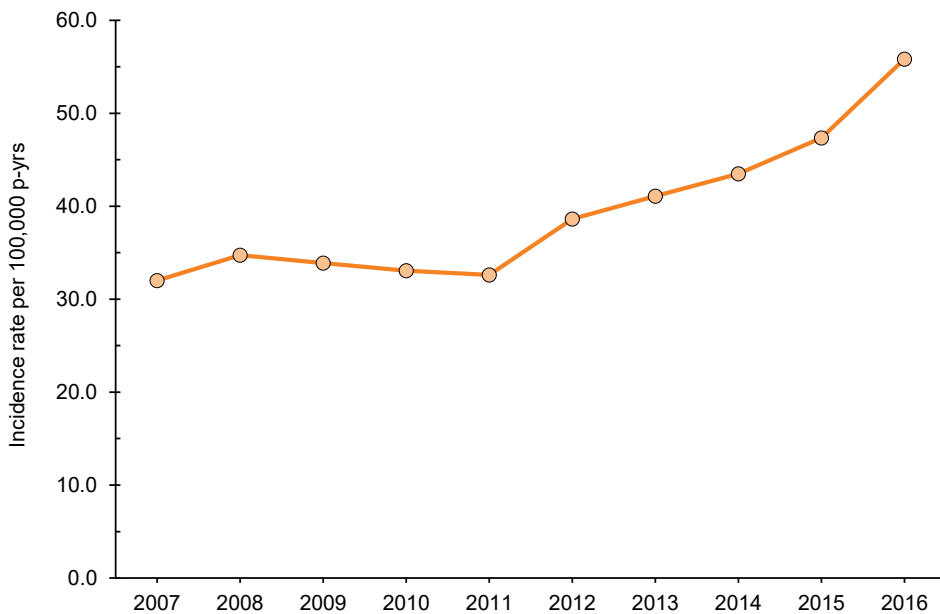
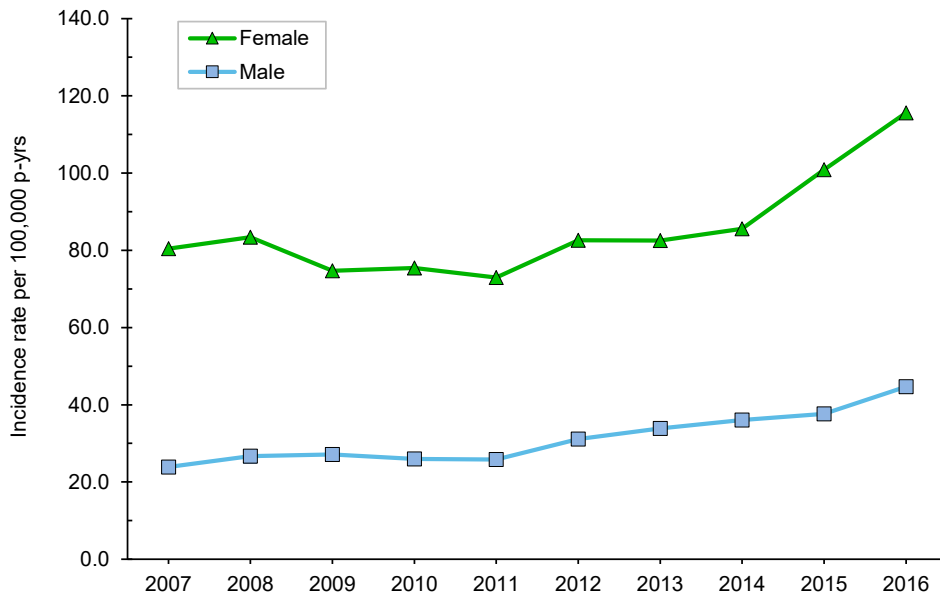


FIGURE 2. Annual incidence rates of food-allergy anaphylaxis, by sex, active component, U.S. Armed Forces, 2007–2016



component service members) in which 82% of individuals prescribed an EAI filled their prescriptions within 1 year.²² The current study found that only 58.4% filled their prescriptions for EAI within 3 months of incident anaphylaxis. It is unclear whether the 58.4% fill rate found in the current

study is due to failure to prescribe, failure to fill, or the relatively short window used to evaluate prescription fill rates. Regardless of the reason, there is room for improvement. Pharmacist-led interventions have been found to improve medication management and may play a role in improving

fill rates among those who are prescribed an EAI.²³

Approximately 28% of service members with food-allergy anaphylaxis filled prescriptions for an EAI within the 18 months prior to being diagnosed. This observation may reflect recognition of the service member's risk for anaphylaxis based on a previous, less severe food reaction, or the existence of another allergy warranting an EAI prescription. More worrisome is the potential for this to reflect a failure to identify at-risk individuals and appropriately document the condition in the member's medical record as may be seen when avoidance of a medical board and potential separation from the military is desired.

Current guidelines recommend that all patients experiencing food-allergy anaphylaxis be prescribed an EAI. Other patients for whom an EAI is indicated include patients with a history of a prior systemic allergic reaction; patients with food allergy and asthma; and patients with a known food allergy to peanut, tree nuts, fish, and crustacean shellfish (i.e., allergens known to be associated with more fatal and near-fatal allergic reactions).³

Given difficulties associated with identifying food-allergic individuals who are at risk for anaphylaxis, as well as difficulties predicting the severity of future IgE-mediated reactions, guidelines also recommend that providers consider prescribing an EAI to all patients with IgE-mediated food reactions.^{3,24}

It is important to note that the current study did not differentiate between food-allergic individuals who met the above criteria from those who did not. As a result, it is difficult to interpret EAI fill rates among those diagnosed with food allergy. What is notable is that at least 23% of individuals with a documented history of food allergy were considered to be at risk for anaphylaxis and candidates for an EAI by their treating provider.

Future efforts should ensure that medical and emergency personnel are made aware of the notable number of individuals who serve in the military who have experienced or at risk for food-allergy anaphylaxis. Healthcare professionals need to properly identify, document, and code for

FIGURE 3. Annual incidence rates of food-allergy anaphylaxis, by race/ethnicity, active component, U.S. Armed Forces, 2007–2016

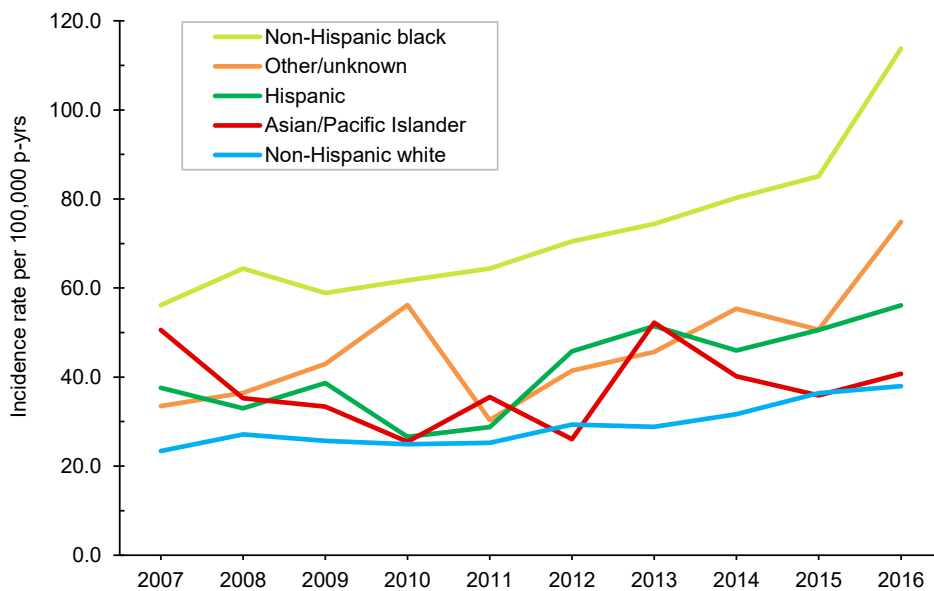
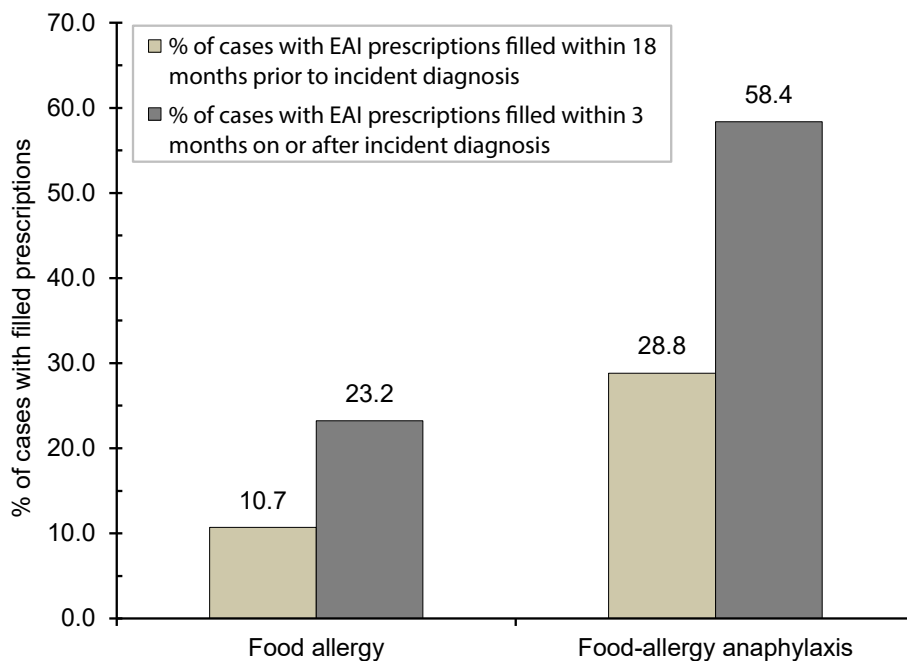


FIGURE 4. Percentages of incident cases of food allergy and food-allergy anaphylaxis with epinephrine autoinjector (EAI) prescriptions filled during specified time frames, active component, U.S. Armed Forces, 30 June 2008 through 30 September 2016



anaphylaxis so that appropriate prevention and treatment are made available.

Although this study did not formally address risk factors for anaphylaxis, it notes that the incidence of food-allergy anaphylaxis was higher among those

aged 30–34 years, compared to other age groups; females compared to males; and non-Hispanic blacks, compared to other races/ethnicities. These findings are generally consistent with previous studies (Table 1). Other studies involving civilian

populations have explored risk factors for severe anaphylaxis (e.g., asthma^{12,13,25} and vitamin D deficiency²⁶), biomarkers,²⁷ and cofactors that induce or exacerbate reactions that might not otherwise occur (e.g., exercise, nonsteroidal anti-inflammatory drugs, and alcohol¹). Future studies aimed at identifying factors associated with severe, life-threatening anaphylaxis in the military could help stratify risk and further inform accession standards, fitness for duty determinations, and prevention and treatment efforts.

This study has several limitations. Notably, not all cases of anaphylaxis come to medical attention and the true incidence of food-allergy anaphylaxis is likely underestimated here. In addition, this study relied on medically coded encounters that were not validated by chart review or a criteria-based approach to diagnosis; this may further contribute to underestimation of the true incidence of food-allergy anaphylaxis. Of note, a study utilizing the National Electronic Injury Surveillance System found that 57% of patients presenting to an emergency department with a likely case of anaphylaxis did not receive a diagnosis of anaphylaxis.⁹ Finally, it is not clear whether the increasing incidence of food-allergy anaphylaxis reported here reflects an increase in the true incidence of anaphylaxis or increased awareness of the condition.

With regard to food allergies, it is likely that some individuals with food allergies were missed due to the failure to report, diagnose, or document their condition. In addition, the ICD-9/ICD-10 codes used to identify individuals with food allergies did not include nonspecific codes such as ICD-9: 693.1 (“Dermatitis due to food taken internally”), ICD-10: L27.2 (“Dermatitis due to ingested food”), and ICD-9: 995.7 and ICD-10: T78.1* (“Other adverse food reactions, not elsewhere classified”); this further contributes to potential underestimation of the condition.

With regard to EAI fill rates, significant information is lacking. Namely, prescription rates were not available and thus could not be used as a comparison to fill rates. In addition, EAI prescriptions were not linked to a specific diagnosis or event and prescription fills could potentially be

related to another diagnosis such as an allergy to bee stings. Finally, the reasons for fill failures, including the possibility that an EAI was not indicated or was already available to a patient, were not explored.

The incidence of food-allergy anaphylaxis among active component service members approximates that found in the general population and increased steadily over the study period. Medical accession standards and the medical board process do not completely address the issue of food-allergy anaphylaxis in the military. Properly identifying and documenting at-risk individuals, and ensuring availability of EAI have the potential to mitigate the risk of anaphylaxis. Further identifying risk factors for severe anaphylaxis, biomarkers, and cofactors could inform accession and retention standards and prevent life-threatening reactions.

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Key points

- The crude annual incidence rates of food-allergy anaphylaxis among active component service members increased over the course of the surveillance period; the rates among females were almost three times those of males, and this pattern was consistent over much of the surveillance period.
- Compared to their respective counterparts, the overall incidence of food-allergy anaphylaxis was highest among females, those aged 30–34 years, and non-Hispanic black service members.
- Of the total incident anaphylaxis cases during the surveillance period, 29% and 58% had filled a prescription for an epinephrine autoinjector within 18 months before or 3 months after the incident diagnosis, respectively.

Learning objectives

1. The reader will interpret data related to the incidence of anaphylaxis among active component service members.
2. The reader will explain how the incidence of food-allergy anaphylaxis among active component service members compares to that in the general population, and how the incidence has changed over time.
3. The reader will describe ways to prevent food-allergy anaphylaxis.

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