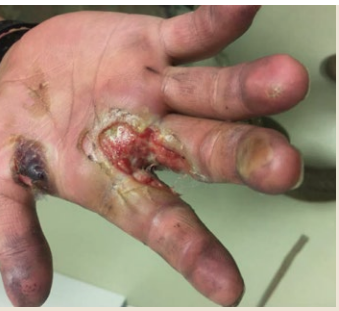
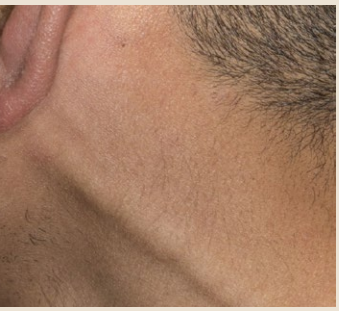
DECEMBER 2019

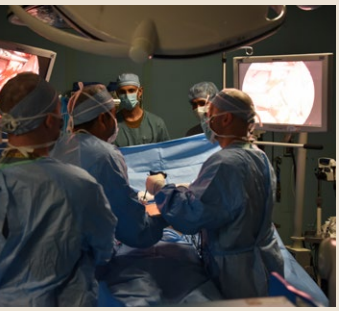
Volume 26
Number 12

MSMR

MEDICAL SURVEILLANCE MONTHLY REPORT







Case Report

Hansen's Disease in an Active Duty Soldier Presenting with Type 1 Reversal Reaction

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Leprosy, or Hansen's disease (HD), is caused by the bacterium *Mycobacterium leprae* and is a significant cause of morbidity worldwide. Clinical manifestations range from isolated skin rash to severe peripheral neuropathy. Treatment involves a prolonged course of multiple antimicrobials. Although rare in the U.S., with only 168 new cases reported in 2016, HD remains a prevalent disease throughout the world, with 214,783 new cases worldwide that same year.[1] It remains clinically relevant for service members born in and deployed to endemic regions. This report describes a case of HD diagnosed in an active duty soldier born and raised in Micronesia, a highly endemic region.

CASE REPORT

In May 2018, a 21-year-old male soldier presented with right hand swelling and ulcer formation along the interspace between his index and middle fingers while he was deployed to Eastern Europe **(Figure 1)**. He first developed a blister at that site after washing a tank several days earlier, and it subsequently progressed to an ulcer. The ulcer was initially assessed as a third-degree burn, and he was transferred to Brooke Army Medical Center (Joint Base San Antonio-Fort Sam Houston, TX) for management on 11 May 2018. At that time, the patient denied any pain but described gradual loss of sensation to his right hand dating back to January 2018. The patient had been otherwise healthy except for a right hand burn injury during basic training in early 2017, which had completely healed without complications. He denied any close contacts with Hansen's disease (HD). The patient had enlisted in the Army in January 2017 from the Federated States of Micronesia and completed initial entry training in June 2017 at Fort Benning, GA. He completed advanced individual training at Fort Riley, KS, and then was deployed to Europe in November 2017.

In May 2018, the patient successfully underwent full-thickness skin graft of his ulceration but continued to experience edema and eventually lost intrinsic motor function of his right hand. He remained at Fort Sam Houston, where a nerve conduction study in July 2018 revealed severe median, ulnar, and radial neuropathies in the right forearm. Around that time, the patient noticed eruption of annular, hyperpigmented, erythematous plaques on his right medial arm, which spread to his bilateral limbs and trunk **(Figures 2a, 2b)**. These symptoms coincided with new edema and numbness involving his left hand. In September 2018, magnetic resonance imaging revealed perineural edema involving nerve groups of his distal right arm **(Figure 3a, 3b)**. The patient was referred to dermatology, where examination noted thickening of peripheral nerves, including the greater auricular nerve **(Figure 4)**; a clinical diagnosis of HD was made. Skin biopsy showed tuberculoid granulomas extending along adnexal structures and nerves **(Figure 5a, 5b)**. Fite staining was negative for acid-fast organisms. Polymerase chain reaction testing at the National Hansen's Disease Program (NHDP) was also negative for *Mycobacterium leprae*. Given his histopathology, edema, and rapid progression of neurologic impairment, the patient was diagnosed with paucibacillary leprosy complicated by type 1 reversal reaction. In consultation with the NHDP, the patient was started on clarithromycin 500 mg daily and minocycline 100 mg daily in October 2018. Prednisone 60 mg daily was started for the patient's type 1 reversal reaction and neuropathy. Steroids were tapered over the ensuing 6 months, while methotrexate 12.5 mg weekly was added as a steroid-sparing agent.

At follow-up in December 2018, the patient showed improvement in the appearance of his skin lesions and the edema in both hands, with some improvement in motor and sensory exam. At follow-up in May 2019, he remained on clarithromycin, minocycline, and methotrexate. He showed further improvement in the appearance of his skin lesions. However, he continued to have persistent right hand weakness and persistent left ulnar neuropathy. He was referred to the medical evaluation board and was discharged from the Army in August 2019.

EDITORIAL COMMENT

HD is caused by *M. leprae*. While the disease is endemic in the southern U.S., the majority of cases found here are

FIGURE 1. Ulcer along the interspace between the patient's right index and middle fingers. Photograph courtesy of Brooke Army Medical Center Medical Photography.

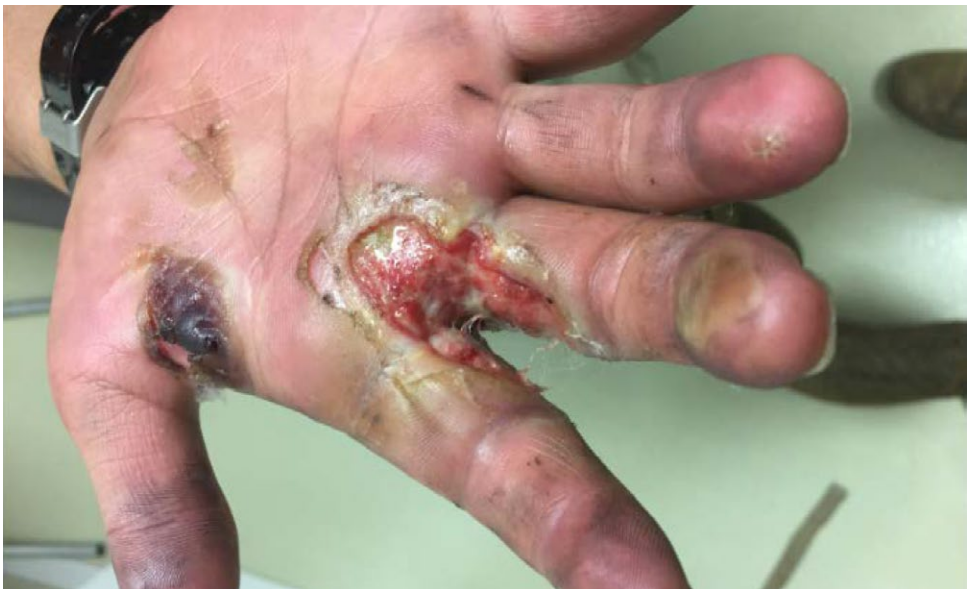


FIGURE 2a. Multiple, large, irregular, well-demarcated, scaly, erythematous plaques on the left arm. These lesions were noted to have diminished sensation compared to surrounding normal skin. Photograph courtesy of Brooke Army Medical Center Medical Photography.

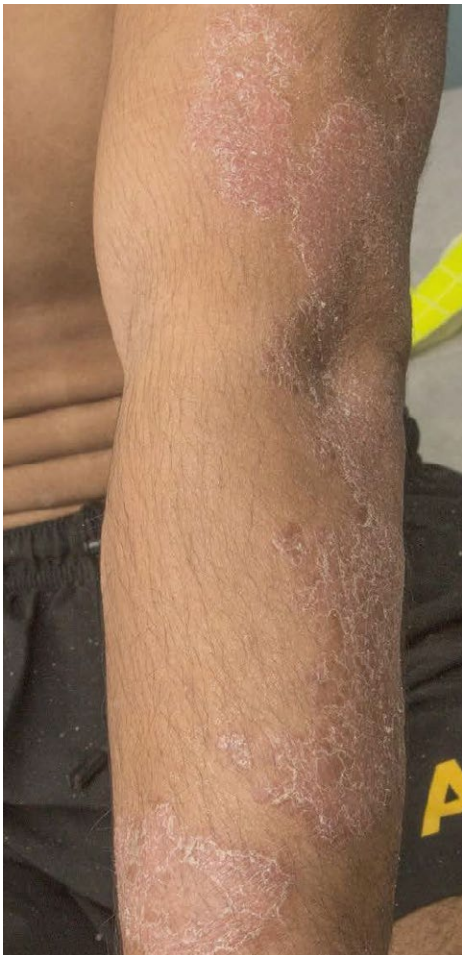
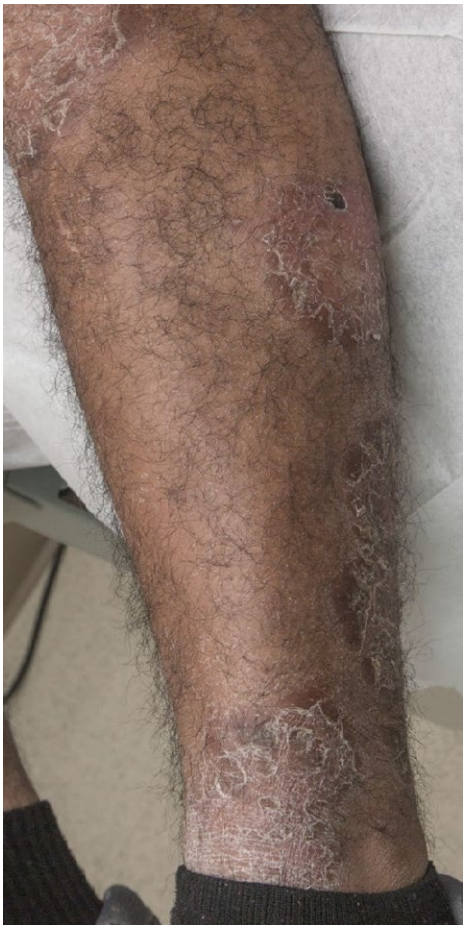


FIGURE 2b. Multiple, large, well-demarcated, annular, hyperpigmented, scaly plaques with relative central clearing on the left leg. These lesions were noted to have diminished sensation compared to surrounding normal skin. Photograph courtesy of Brooke Army Medical Center Medical Photography.



diagnosed in individuals born outside of the U.S., where exposure is thought to have occurred.[2] The Federated States of Micronesia has a high prevalence of HD, and immigrants from Oceanic countries have the highest rates of diagnosis in the U.S.[2,3]

Skin lesions and peripheral nerve damage are hallmarks of HD. The diagnosis can be made clinically, though histopathology is the gold standard.[4] Complications of HD include type 1 reversal reactions, which are associated with increased cell-mediated immune response to *M. leprae,* leading to increased edema and swelling of peripheral

FIGURE 3a. Magnetic resonance imaging of the distal right arm. Coronal short T1 inversion recovery (STIR) image showing diffuse ulnar nerve enlargement (red arrow).

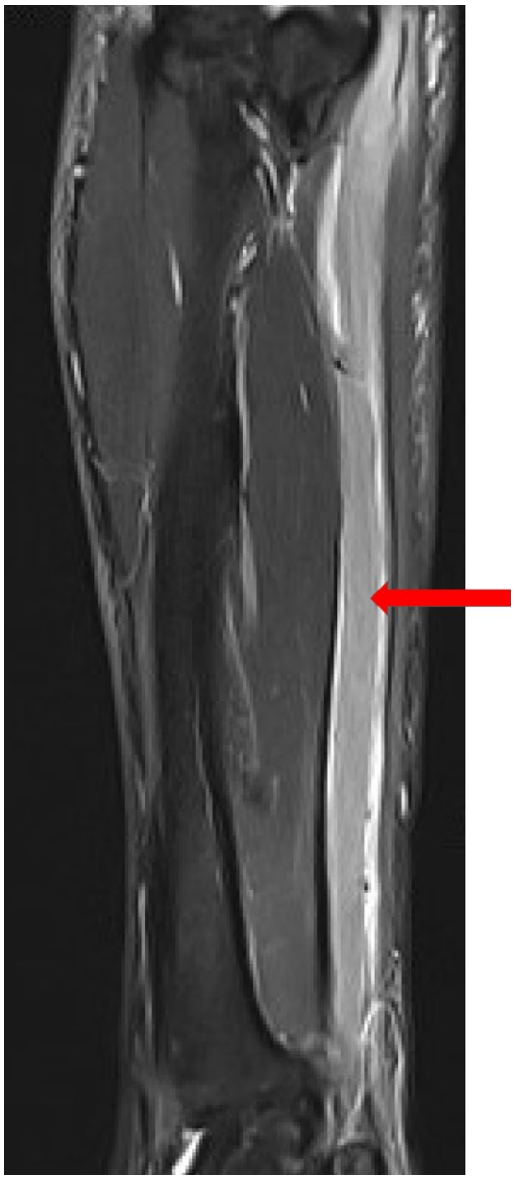


FIGURE 3b. Magnetic resonace imaging of the distal right arm. Coronal short T1 inversion recovery (STIR) imaging showing diffuse median nerve enlargement (red arrow).

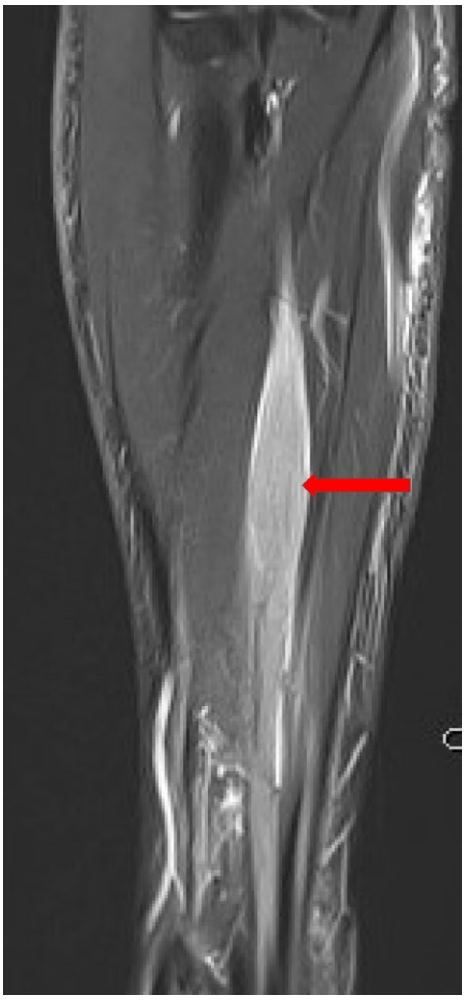
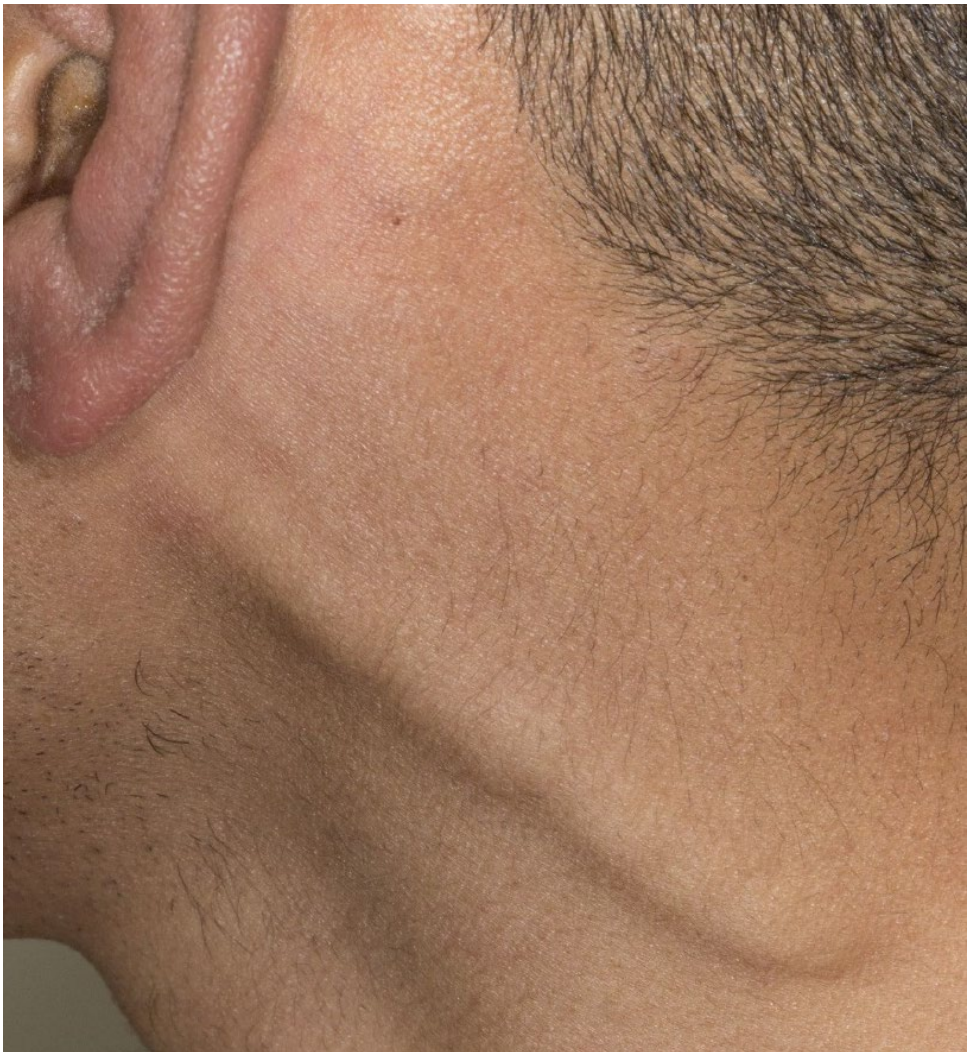


FIGURE 4. Thickening of the left greater auricular nerve. Photograph courtesy of Brooke Army Medical Center Medical Photography.



nerves and increased erythema of existing skin lesions.[4] This patient's presenting symptoms of hand edema and ulceration **(Figure 1)** represented a type 1 reversal reaction that led to significant neurologic impairment.

The treatment of HD typically involves dapsone and rifampin, with or without clofazimine, based on the disease classification.[5] Minocycline and clarithromycin are bactericidal against *M. leprae*[6] and have been used as alternative treatments when first-line agents cannot be used because of drug intolerance or, as in this case, drug interactions between rifampin and prednisone.[4] The treatment of type 1 reversal reaction typically involves corticosteroids, though the overall efficacy and duration of therapy remain uncertain.[7,8]

The military provides a unique environment for exposure, as soldiers are often deployed into endemic areas. However, reported cases of HD among U.S. military personnel are rare. The first such reported cases occurred in the Spanish-American War (1898) despite prior conflicts in endemic areas.[9,10] Among the 323 reported cases of leprosy in veterans between 1920 and 1968, less than 80 were thought to be service related.[9] Among those cases not involving infections after receiving tattoos, only 2 cases involved service members whose length of exposure was reported as less than 1 year.[9,10] The Vietnam War brought U.S. soldiers into combat in endemic areas of Southeast Asia, but there are even fewer reported cases among veterans of this conflict, with at least 3 service-related cases.[11–13] The low number of cases likely reflected decreased exposure time due to shorter deployments and the use of dapsone for malaria prophylaxis.[14] Since the start of the current Global War on Terrorism, there have been at least 6 published cases of HD among active duty U.S. military members, the majority of which were not service related.[15–18] Five of the 6 published cases involved service members from Micronesia. (Currently, there are 2 other active cases of HD being treated in service members in conjunction with the NHDP.) In a case series of 3 active duty soldiers from Micronesia with HD, the average time to diagnosis was 8 months.[15] This observation illustrates that HD's indolent course of skin lesions and neurologic deficits can lead to a delay in diagnosis.[19] Given the potential morbidity

FIGURE 5a. Photomicrograph of punch biopsy specimen demonstrating superficial and deep dermal, non-caseating, epithelioid cell granulomas (black arrow), some forming preferentially around adnexal structures and nerves (hematoxylin and eosin stain, original magnification x 4).

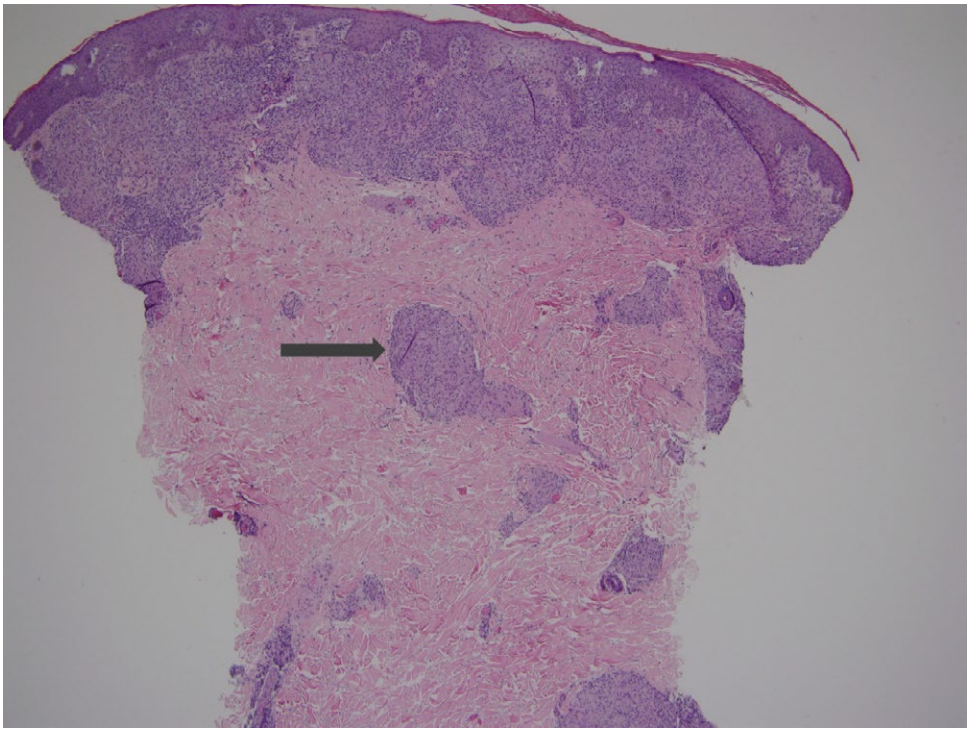
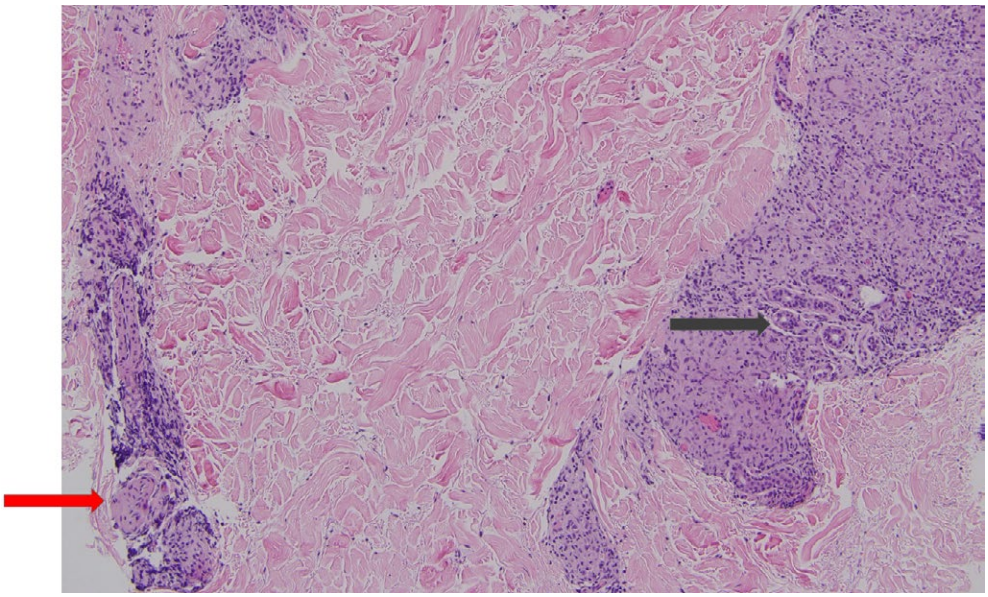


FIGURE 5b. Photomicrograph of punch biopsy specimen demonstrating discrete, non-caseating, epithelioid cell granulomas around adnexal structures (black arrow, eccrine glands) and nerves (red arrow) within the dermis (hematoxylin and eosin stain, original magnification x 10).



associated with delayed diagnosis, providers should consider HD in a patient from an endemic region with rash and neuropathy.

There have been no published reports among U.S. troops of HD secondary to exposure to other infected service members. However, there have been reported cases of family members contracting HD from service members.[9] Such examples indicate that prolonged, close exposure to an infected individual or prolonged travel to endemic countries is needed for infection with HD.

Before effective therapies were widely available, a diagnosis of HD resulted in discharge from the U.S. Army.[9] However, currently, if the HD responds to treatment and does not lead to physical limitations, affected service members may be retained.[20]

In summary, HD is rare in the U.S. military and its veterans. However, because of the potential significant morbidity associated with delayed diagnosis and treatment of HD, this condition should be considered in patients presenting with skin lesions and peripheral neuropathy, especially if the patients are from HD-endemic regions.

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Put a FREEZE on Winter Holiday Fires

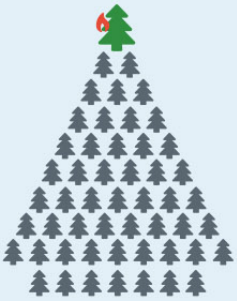
It's fun to decorate for the winter holidays, but holiday decorations can increase your risk for a home fire. As you deck the halls this season, be fire smart.

More than half of the home decoration fires in December are started by candles.

More than 1/3 of home decoration fires are started by candles.

The top 3 days for home candle fires are **Christmas Day, New Year's Day** and **New Year's Eve.**

Keep candles at least **12 inches** away from anything that burns.



Although Christmas tree fires are not common, when they do occur, they are dangerous.

On average, **1 of every 52** reported home Christmas tree fires resulted in death.

A heat source too close to the Christmas tree causes **1 in every 4** winter fires.

Read manufacturer's instructions for the number of light strands to connect.

Make sure your tree is **at least 3 feet away** from heat sources like fireplaces, radiators, space heaters, candles or heat vents. Also, make sure your tree does not block exits.

Get rid of your tree after Christmas or when it is dry.

FEMA | U.S. Fire Administration

Fire is Everyone's Fight®

NFPA®

For more information on how to prevent winter fires, visit **www.usfa.fema.gov/winter** and **www.nfpa.org/winter.**

Update: Gallbladder Disease and Cholecystectomies, Active Component, U.S. Armed Forces, 2014–2018

Donna K. Lormand, MPH; Valerie F. Williams, MA, MS; Alyssa Fedgo, MPH; Shauna Stahlman, PhD, MPH

The term gallbladder disease refers to a variety of conditions of the gallbladder and the biliary tract. The more common of these conditions are cholelithiasis (gallstones) and cholecystitis (inflammation of the gallbladder), and these conditions often are treated with cholecystectomy (gallbladder removal). During the 2014–2018 surveillance period, 8,008 active component service members were identified as incident cases of gallbladder disease. The crude overall incidence rate of gallbladder disease was 1.2 per 1,000 person-years; the crude annual rate decreased very slightly during the period. A total of 6,470 active component service members underwent incident cholecystectomies. Almost all (97.4%) were performed laparoscopically, and the majority were performed in outpatient settings (65.2%). The number of hospital bed days per open cholecystectomy far exceeded those per laparoscopic cholecystectomy. However, the number of hospital bed days per open cholecystectomy markedly decreased throughout the period. Gallbladder disease and cholecystectomies were more common among service members who were female, American Indian/Alaska Native or Hispanic, older, in the Air Force, and in healthcare occupations. Clinicians should continue to advocate for lifestyle changes, such as maintaining a healthy weight and a diet low in fat and cholesterol, that could prevent gallbladder disease. Similarly, continued Department of Defense-wide initiatives to promote healthy lifestyles could also help prevent gallbladder disease and maintain the health of the force.

WHAT ARE THE NEW FINDINGS?

Annual rates of gallbladder disease in active component service members during the 2014–2018 period declined slightly compared to the 2004–2013 period, when rates increased. About 1,601 new cases of gallbladder disease and 1,294 cholecystectomies occurred annually during the surveillance period. Over 97% of cholecystectomies were performed via laparoscopy, a technique that reduces the duration of recovery compared to an open surgical approach.

WHAT IS THE IMPACT ON READINESS AND FORCE HEALTH PROTECTION?

Gallbladder disease and cholecystectomy are not rare, affecting approximately 1 out of every 1,000 service members per year. Their availability for duty and deployability are adversely impacted during the evaluation, surgical treatment, and convalescence associated with gallbladder disease. Risk factors for such disease that are susceptible to modification include excess body weight, a diet with a high fat or cholesterol content, diabetes, and certain medications.

The gallbladder is a small (3-inch long), hollow, pear-shaped organ located in the upper right section of the abdomen, just under the right lobe of the liver. The gallbladder stores bile produced by the liver and releases it into the small intestine after a meal to help dissolve fat. Gallbladder disease, including cholelithiasis (gallstones), is common in the U.S. and often results in cholecystitis (inflammation of the gallbladder). Cholecystitis can result in severe pain in the upper right or center abdomen, pain that spreads in the right shoulder or back, tenderness over the abdomen when touched, nausea, vomiting, or fever, particularly after a large or fatty meal. Although these symptoms may be avoided by reducing the amount of fatty and highly processed foods as well as whole milk dairy products consumed, gallbladder removal (cholecystectomy) is recommended when symptoms become frequent, recurrent, or more severe. Gallbladder removal is typically achieved with the minimally invasive laparoscopic technique, which involves inserting a camera and dissection tools through several small incisions in the abdominal wall.[1] Open cholecystectomy, which requires a 4- to 6-inch incision[1] and longer hospitalization and convalescence periods, is only used if the laparoscopic method is not possible or cannot be completed safely because the gallbladder is severely inflamed, infected, or scarred from other operations.

Gallbladder disease is related to nonmodifiable risk factors, such as being female, being older than 40 years of age, having a family history of gallbladder disease, and being of American Indian or Hispanic descent,[2–8] as well as modifiable risk factors, such as being overweight or obese, rapid fluctuations in body weight, a high-fat or high-cholesterol diet, diabetes, and certain medications.[2–8] Pregnancy and parity have also been shown to be associated with an increased risk of gallstone formation.[2,7,8]

It is estimated that over 20 million people in the U.S. have gallstones, and symptoms caused by gallstones are a primary gastrointestinal cause for hospital admissions and healthcare utilization.[3,7,9] Furthermore, over 500,000 laparoscopic cholecystectomies are performed annually in the U.S., making it one of the most common abdominal surgeries performed, costing roughly $6.5 billion per year.[7,10]

A previous *MSMR* report showed very slight increases in the crude annual incidence rates of gallbladder disease and cholecystectomies among active component members of the U.S. Armed Forces from 2004 through 2013.[11] Although outcomes related to laparoscopic cholecystectomy are generally good, an increase in the rates of gallbladder disease could negatively impact the readiness of the force. This report updates the counts and rates of newly diagnosed gallbladder disease and cholecystectomies among U.S. active component service members during 2014–2018.

METHODS

The surveillance period was 01 January 2014 through 31 December 2018. The surveillance population included all active component service members of the Army, Navy, Air Force, and Marine Corps who served at any time during the surveillance period. For the purposes of this report, "gallbladder disease" included not only cholelithiasis and cholecystitis, but also other or unspecified disorders of the gallbladder and other or unspecified disorders of the biliary tract **(Table 1)**. An incident (first-ever) case of gallbladder disease was defined as an inpatient encounter with a case-defining International Classification of Diseases (ICD) code in the primary diagnostic position or 2 outpatient encounters with a relevant ICD code in the primary diagnostic position **(Table 1)**. An individual was considered a case once per lifetime. The type of gallbladder disease was categorized based on the diagnosis specified in the primary diagnostic position for the incident encounter. A prevalent case was defined in the same manner as an incident case, but it occurred before the start of the surveillance period. Individuals with 1 encounter before the start of the surveillance period and 1 after were classified as prevalent cases. Person-time was censored at the incident event and prevalent cases were removed from the study population. Those with diagnoses in non-primary positions were also excluded.

A case of cholecystectomy was defined as an inpatient encounter with a procedure code (PR code) for cholecystectomy in any position or an outpatient encounter with a Current Procedural Terminology (CPT) code for cholecystectomy in any position **(Table 1)**. An individual was considered a case of cholecystectomy only once per lifetime; cholecystectomies were analyzed separately from gallbladder disease cases. For each incident case of cholecystectomy, if an individual had records of multiple procedures performed, inpatient encounters were preferentially selected over outpatient encounters and open cholecystectomies were prioritized over laparoscopic cholecystectomies.

Among the incident gallbladder disease cases that were identified during the surveillance period, the number and percentage of cases with a cholecystectomy encounter whose date was on or after their incident gallbladder disease diagnosis were identified. The average time between incident gallbladder disease diagnosis and first subsequent cholecystectomy encounter was calculated. Similarly, for all individuals with an incident cholecystectomy identified during the surveillance period, the number and percentage of cases with gallbladder disease diagnoses (made in any diagnostic position) during an encounter on or before the date of their incident cholecystectomy were identified. The average time between incident cholecystectomy and first gallbladder disease diagnosis was calculated.

Finally, a burden analysis was performed to identify the morbidity and healthcare burden of gallbladder disease and cholecystectomy during the surveillance period. For this analysis, all inpatient and outpatient encounters with a diagnosis of gallbladder disease in the primary diagnostic position during the study period were included. No more than 1 encounter per person per day was counted. If there were multiple encounters on the same day, inpatient encounters were prioritized over outpatient encounters. The total number of encounters, hospital bed days, and individuals affected were calculated according to standard *MSMR* burden methodology.[12]

RESULTS

Gallbladder disease

During the 5-year surveillance period, 8,008 incident diagnoses of gallbladder disease were documented on inpatient or outpatient medical records of active component service members **(Table 2)**. The crude overall rate of incident gallbladder disease diagnoses was 1.2 per 1,000 person-years (p-yrs). A majority of the cases were diagnosed as cholelithiasis (65.8%); cholecystitis was reported among 14.6% of cases, and other/unspecified disorders of the gallbladder/biliary tract were reported among 19.6% **(data not shown)**. Crude annual incidence rates of all gallbladder disease diagnoses (total) decreased very slightly during the surveillance period from 1.3 per 1,000 p-yrs in 2014 to 1.1 per 1,000 p-yrs in 2018 **(Figure 1)**.

Compared to their respective counterparts, service members who were female, American Indian/Alaska Native or Hispanic, in the Air Force or Army, and in healthcare occupations had higher overall incidence rates of gallbladder disease **(Table 2)**. Overall incidence rates increased approximately linearly with increasing age **(Table 2)**.

Cholecystectomy

From 2014 through 2018, a total of 6,470 active component service members underwent cholecystectomies **(Table 2)**. The overall incidence rate of cholecystectomy was 1.0 per 1,000 p-yrs. Slightly more than three-fifths of all the procedures were performed in the outpatient setting (n=4,220; 65.2%), and the vast majority were performed laparoscopically (n=6,300; 97.4%) **(data not shown)**. There was a small decrease in the annual rate of total cholecystectomy procedures during the surveillance period from 1.1 per 1,000 p-yrs in 2014 to 0.87 per 1,000 p-yrs in 2018, with slight decreases observed in the rates of inpatient and outpatient cholecystectomies as well as open and laparoscopic cholecystectomies **(Figure 2)**.

On average, there were 0.7 hospital bed days per laparoscopic cholecystectomy

TABLE 1. Gallbladder disease case-defining ICD-9/ICD-10 codes and cholecystectomy PR codes

ICD-9 diagnostic codes[a]		ICD-10 diagnostic codes[a]	
Cholelithiasis		Cholelithiasis	
574.*	Cholelithiasis (calculus of the gallbladder or bile duct)	K80.*	Cholelithiasis (calculus of the gallbladder or bile duct)
Other disorders of gallbladder		Cholecystitis (inflammation of the gallbladder or bile duct)	
575.0	Acute cholecystitis	K81.0	Acute cholecystitis
575.1*	Other cholecystitis (unspecified/chronic/acute and chronic)	K81.1, K81.2, K81.9	Other (chronic/unspecified) cholecystitis
		Other diseases of gallbladder (chronic/acute with chronic/unspecified)	
575.2	Obstruction of gallbladder	K82.0	Obstruction of gallbladder
575.3	Hydrops of gallbladder	K82.1	Hydrops of gallbladder
575.4	Perforation of gallbladder	K82.2	Perforation of gallbladder
575.5	Fistula of gallbladder	K82.3	Fistula of gallbladder
575.6	Cholesterolosis of gallbladder	K82.4	Cholesterolosis of gallbladder
575.8	Other specified disorders of gallbladder	K82.8	Other specified disorders of gallbladder
575.9	Unspecified disorder of gallbladder	K82.9	Disease of gallbladder, unspecified
		K82.A1, K82.A2	Gangrene of gallbladder in cholecystitis, Perforation of gallbladder in cholecystitis
Other disorders of biliary tract		Other diseases of biliary tract	
576.1	Cholangitis	K83.0*	Cholangitis
576.2	Obstruction of bile duct	K83.1	Obstruction of bile duct
576.3	Perforation of bile duct	K83.2	Perforation of bile duct
576.4	Fistula of bile duct	K83.3	Fistula of bile duct
576.5	Spasm of sphincter of Oddi	K83.4	Spasm of sphincter of Oddi
576.8	Other specified disorders of biliary tract	K83.8, K83.5	Other specified diseases of biliary tract, Biliary cyst
576.9	Unspecified disorder of biliary tract	K83.9	Disease of biliary tract, unspecified
576.0	Postcholecystectomy syndrome	K91.5	Postcholecystectomy syndrome
ICD-9 inpatient PR codes		ICD-10 inpatient PR codes	
51.23, 51.24	Laparoscopic cholecystectomy	0FT44ZZ, 0FB44ZZ, 0FB48ZZ	Laparoscopic cholecystectomy
51.21, 51.22	Open cholecystectomy	0FB40ZZ, 0FB43ZZ, 0FT40ZZ	Open cholecystectomy
Outpatient CPT codes			
47562, 47563, 47564	Laparoscopic cholecystectomy		
47600, 47605, 47610, 47612, 47620	Open cholecystectomy		

[a] An asterisk (*) indicates that any subsequent digit/character is included.
ICD, International Classification of Diseases; PR, procedure; CPT, Current Procedural Terminology.

and 4.8 bed days per open cholecystectomy **(data not shown)**. The number of hospital bed days per laparoscopic cholecystectomy remained under 1 bed day during each year of the surveillance period and was stable throughout the surveillance period **(Figure 3)**. Bed days per open cholecystectomy decreased each year from a high of 6.6 bed days in 2014 to a low of 2.3 bed days in 2018.

Relationship between gallbladder disease diagnoses and cholecystectomy

Of the 8,008 individuals who were identified as incident cases of gallbladder

TABLE 2. Demographic and military characteristics of service members with gallbladder disease and cholecystectomies, active component, U.S. Armed Forces, 2014–2018

	Gallbladder disease		Cholecystectomies	
	No.	Rate[a]	No.	Rate[a]
Total	8,008	1.2	6,470	1.0
Sex				
Male	5,051	0.9	4,037	0.7
Female	2,957	2.9	2,433	2.4
Race/ethnicity				
Non-Hispanic white	4,421	1.2	3,588	1.0
Non-Hispanic black	1,063	1.0	833	0.8
Hispanic	1,587	1.7	1,288	1.4
Asian/Pacific Islander	320	1.2	261	1.0
American Indian/Alaska Native	117	1.8	89	1.4
Other/unknown	500	1.2	411	1.0
Age group (years)				
<20	185	0.4	132	0.3
20–24	1,607	0.8	1,264	0.6
25–29	1,630	1.1	1,277	0.8
30–34	1,589	1.5	1,286	1.2
35–39	1,446	2.0	1,200	1.6
40–44	929	2.3	782	1.9
45+	622	2.5	529	2.1
Service				
Army	3,244	1.4	2,690	1.1
Navy	1,813	1.1	1,555	1.0
Marine Corps	554	0.6	460	0.5
Air Force	2,397	1.5	1,765	1.1
Military status				
Enlisted	6,709	1.3	5,390	1.0
Officer	1,299	1.1	1,080	0.9
Occupation				
Combat-specific[b]	722	0.8	599	0.7
Motor transport	238	1.3	202	1.1
Pilot/air crew	220	0.9	167	0.7
Repair/engineering	2,209	1.2	1,770	0.9
Communications/intelligence	2,177	1.6	1,737	1.2
Healthcare	1,050	1.8	941	1.6
Other/unknown	1,392	1.1	1,054	0.8

[a]Number of cases per 1,000 person-years.
[b]Infantry/artillery/combat engineering/armor.
No., number.

disease, 5,720 (71.4%) were also identified as having a cholecystectomy performed following their first-ever case-defining encounter. Among the gallbladder disease cases who had cholecystectomies, 23.3% had their first-ever gallbladder encounter on record on the same day as the cholecystectomy. The average interval between first-ever gallbladder disease diagnosis and surgery was 44 days **(data not shown)**.

Among the 6,470 service members who were identified as having undergone cholecystectomy, 98.7% (n=6,388) had at least 1 gallbladder disease-related encounter before their cholecystectomy **(data not shown)**. Among the cholecystectomy cases, the average number of days between their first-ever gallbladder disease encounter and cholecystectomy was slightly more than 4 months (123 days).

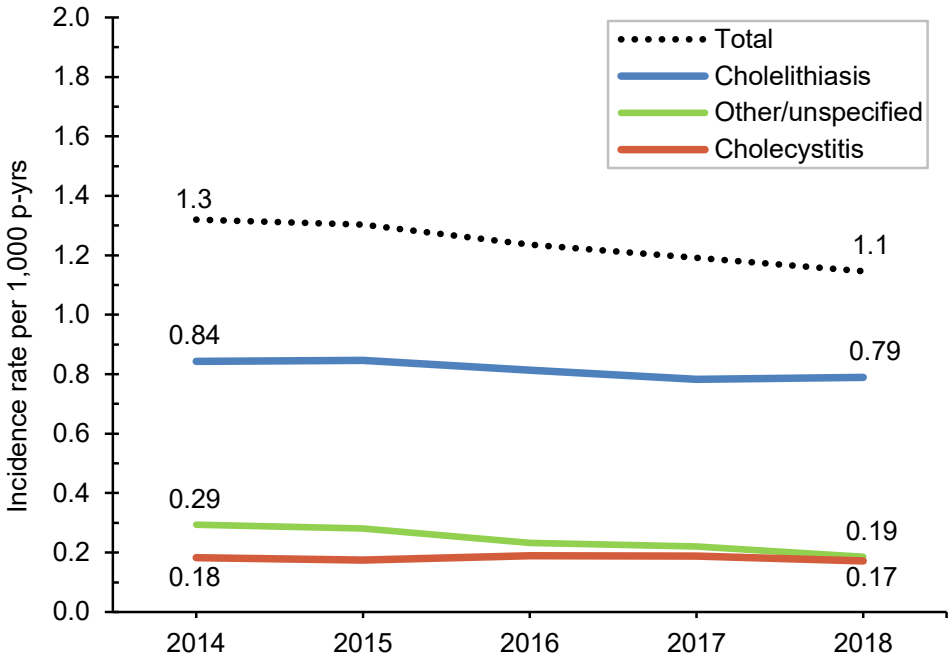
EDITORIAL COMMENT

The annual rates of gallbladder disease declined very slightly between 2014 and 2018. Gallbladder disease was newly diagnosed in approximately 1,600 active component service members on average each year between 2014 and 2018. A total of 6,470 incident cholecystectomies were performed during this period.

A previously published *MSMR* report documented a slight overall increase in the annual rates;[11] however, data toward the end of the surveillance period may have indicated the beginning of the slight decline documented in this report. It is possible that the increase shown in that 2014 report tracked with the increase in obesity rates,[11] as obesity is a known risk factor for gallbladder disease. Indeed, the Millennium Cohort study, *MSMR* analyses, and the recently published Department of Defense (DoD) Health of the Force have shown that the prevalence of obesity among service members, while still lower than the prevalence among the general U.S. population, has been increasing.[13–15] However, the current analysis cannot clarify the reasons for the decreases seen. It should be noted, though, that the increases and decreases documented in both reports represent very slight changes that may not be clinically or epidemiologically meaningful.

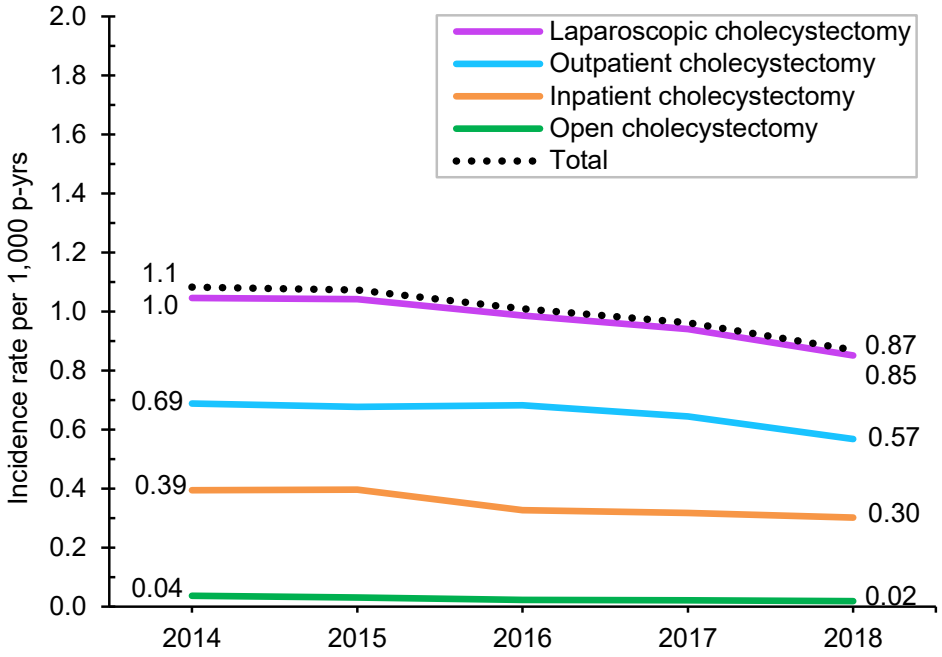
Consistent with studies of the prevalence of gallbladder disease in the U.S. and elsewhere, the overall rates of gallbladder disease were highest among females, American Indians/Alaska Natives or Hispanics, and those in the oldest age groups. As indicated in the previous *MSMR* report, the higher overall rates among those in the Air Force and healthcare occupations may be because those groups have comparatively higher proportions of females and older individuals.[11]

FIGURE 1. Incidence rates of gallbladder disease diagnoses by type, active component, U.S. Armed Forces, 2014–2018



P-yrs, person-years.

FIGURE 2. Incidence rates of cholecystectomy by type, active component, U.S. Armed Forces, 2014–2018



P-yrs, person-years.

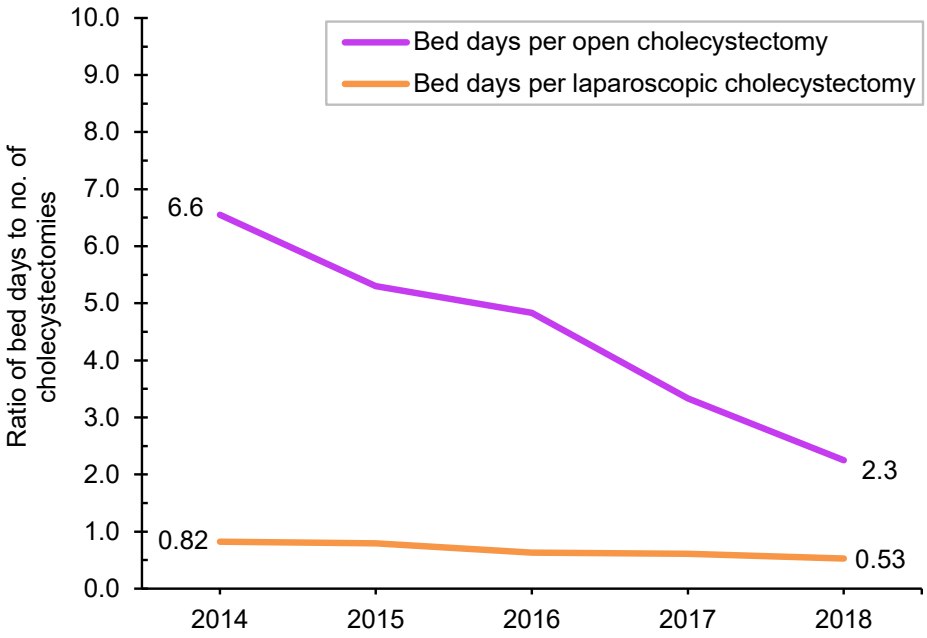
In line with the slightly declining trend observed in the crude annual rates of gallbladder disease, the rates of both inpatient and outpatient and open and laparoscopic cholecystectomies also decreased slightly. Laparoscopic cholecystectomies performed in the outpatient setting continue to be the standard of care.[1] The number of hospital bed days per laparoscopic cholecystectomy stayed under 1 bed day throughout the surveillance period. The number of bed days per open cholecystectomy in particular has shown a steep and steady decline throughout the 5-year surveillance period.

The mean number of days between the incident gallbladder disease encounter and cholecystectomy among service members with gallbladder disease was 44 days (range = 0 days–4.8 years), which suggests that clinicians and affected individuals are not waiting long before gallbladder removal. This may be related to a variety of factors, including surgical options with a very short recovery period, access to free health care, and the military's need to maintain a fit and ready force. On the other hand, the mean number of days between incident gallbladder disease encounter and cholecystectomy among all those who had a cholecystectomy (123 days; range = 0 days–18.7 years) increased slightly from the previous *MSMR* report (82 days; range = 0 days–14.8 years).

The number of cholecystectomy cases exceeded the number of incident gallbladder disease cases who underwent cholecystectomy because some individuals did not have gallbladder disease case-qualifying encounters (e.g., the individual had only 1 outpatient encounter or had a case-defining diagnosis reported in a non-primary diagnostic position) and were not counted in this report. Furthermore, other gallbladder encounters may have occurred before entrance into military service, before the surveillance period, or in healthcare settings outside the Military Health System (MHS).

Interpretation of the findings in this report should be done with consideration of some limitations. This report likely underestimates the rates of cholecystectomy after a gallbladder disease diagnosis, as some service members may have left military service or were lost to follow-up before surgery. Moreover, the surveillance period may have ended before some of the cases that were identified later in the period underwent surgery. Another limitation of the current analysis is related to the implementation of MHS GENESIS, the new electronic health record for the MHS. For 2017–2018, medical data from sites that were using MHS GENESIS are not available in the Defense Medical Surveillance System. These sites include Naval Hospital Oak Harbor, Naval Hospital

FIGURE 3. Ratio of bed days per cholecystectomy by year and type, active component, U.S. Armed Forces, 2014–2018



No., number.

Bremerton, Air Force Medical Services Fairchild, and Madigan Army Medical Center. Therefore, medical encounter and person-time data for individuals seeking care at any of these facilities during 2017–2018 were not included in the analysis.

Although the rates of gallbladder disease and cholecystectomies declined slightly among all active component service members during the study period, gallbladder disease and cholecystectomies are not rare and the rates are higher among those with identified risk factors for gallstone formation. Clinicians should continue to advocate for lifestyle changes, such as maintaining a healthy weight and a diet low in fat and cholesterol, that could prevent gallbladder disease. Similarly, continued DoD-wide initiatives to promote healthy lifestyles could also help prevent gallbladder disease and maintain the health of the force.

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Prevalence of Glucose-6-Phosphate Dehydrogenase Deficiency, U.S. Armed Forces, May 2004–September 2018

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inherited genetic disorder most commonly associated with hemolytic anemia. Among those with G6PD deficiency, hemolytic anemia may be triggered by bacterial or viral infections and by certain foods and drugs, including the 8-aminoquinoline (8-AQ) class of antimalarials. Because 8-AQ drugs remain the only drugs approved by the U.S. Food and Drug Administration for malaria relapse prevention, the Department of Defense (DoD) requires testing of all service members' G6PD status. To estimate prevalence of G6PD deficiency among DoD service members, Composite Health Care System-generated, Health Level 7-formatted laboratory records for all service members (n=2,311,223) dated between May 2004 and September 2018 were queried for G6PD testing. Corresponding demographic data were obtained from the Defense Enrollment Eligibility Reporting System. Overall prevalence of G6PD deficiency among this cohort was low, at 2.2%. Demographic trends mirrored U.S. statistics; the cohort prevalence among males (2.3%) was higher than among females (1.5%), and the prevalence among non-Hispanic blacks (9.5%) was higher than among those in any other race/ethnicity group.

WHAT ARE THE NEW FINDINGS?

Test results for 2,311,223 active duty service members over a 14-year period confirmed previous service-specific surveillance reports about the prevalence of G6PD deficiency. The deficiency was found in 2.2% of all service members, and the prevalence ranged from 11.2% among non-Hispanic black males to 0.3% among non-Hispanic white females. To the authors' knowledge, this is the first DoD report widely addressing the prevalence of G6PD deficiency among active duty service members.

WHAT IS THE IMPACT ON READINESS AND FORCE HEALTH PROTECTION?

Service members who travel or deploy to malaria-endemic regions are at risk of malaria infection. Because of the risk of hemolytic anemia from use of the 8-AQ class of antimalarial drugs (e.g., primaquine, tafenoquine), military leaders should be aware of G6PD deficiency diagnoses among service members under their purview and should continue adherence to current DoD G6PD screening policies.

Glucose-6-phosphate dehydrogenase (G6PD) is an essential enzyme for the pentose phosphate pathway in the erythrocyte because it converts glucose-6-phosphate to 6-phosphoglucono-δ-lactone. G6PD also converts nicotinamide adenine dinucleotide phosphate (NADP) to the reduced form of NADP (NADPH), a critical redox-active cofactor that mitigates oxidative damage to the erythrocytes.

G6PD deficiency is a genetic condition arising from mutations on the Gd gene on the X chromosome that encodes G6PD enzyme. As an X-linked recessive genetic disorder, G6PD deficiency has a higher prevalence in males than females.[1] Reduced G6PD activity in G6PD deficient individuals can cause hemolysis with different manifestations (e.g., kernicterus in infants and hemolytic crises) from exposures to oxidative stressors including certain medications, fava beans, and infections.[1,2] For example, members of the 8-aminoquinoline (8-AQ) class of antimalarial drugs can cause hemolysis in the G6PD deficient population.

8-AQ class antimalarial drugs (primaquine and the newly Food and Drug Administration (FDA)-approved tafenoquine for weekly chemoprophylaxis and single-dose radical cure) are important because they target hypnozoites—a dormant form of the malaria parasite common in *Plasmodium vivax* and *P. ovale* infections that can emerge from the liver and cause relapse days to years after treatment has cleared the malaria parasites from the circulating red blood cells. Although these infections are less often fatal than *P. falciparum* infections, they still can cause significant morbidity because of relapse from the dormant form of the parasites. Because the 8-AQ class drugs are the only FDA-approved drugs for malaria relapse prevention, the Department of Defense (DoD) mandated G6PD testing of service members at the time of military accession as early as 1981 (Instruction 6465.1[3,4] updated with DoD Instruction 6465.01[5] in 2015 and 6025.14[6] in 2018), and the Army implemented additional G6PD screening of soldiers deploying to malaria endemic regions as early as 2004.[7] However, given that this drug class may trigger hemolytic anemia among those who are G6PD deficient, it is important to adhere to DoD G6PD screening instructions and provide results to command leaders and tested individuals for situational awareness and force protection.

Thus, the objectives of this surveillance report are to describe the prevalence of G6PD deficiency among active duty DoD service members who were screened during 2004–2018 and remind the DoD medical community to consider the risk of hemolytic anemia when prescribing the use of the 8-AQ class of antimalarial drugs.

METHODS

This cross-sectional study used Composite Health Care System-generated, Health Level 7-formatted chemistry laboratory records from 01 May 2004 through 30 September 2018 and queried for G6PD laboratory test results among all active duty, recruit, and active reserve DoD service members tested at fixed military treatment facilities (MTFs). Generally, G6PD testing occurs during accession (recruit training), which is reflected in over 90% of these records.

Key terms used to identify G6PD assays were "G6" or "glucose 6" in the test ordered or test name fields. G6PD tests are often run in panels with other genetic and hemoglobin tests. Records were excluded from the analysis if the test name field contained text indicating other genetic testing (e.g., "sickle cell anemia"), "red blood count," "hemoglobin testing," "miscellaneous," or if the test type could not be determined.

G6PD laboratory test result fields were alpha character–based or numeric. Character-based records with a test result of "Not Deficient," "High," or "Normal" were classified as "Not Deficient." Records with a test result of "Deficient" or "Low" were classified as "Deficient." Because of laboratory testing variations between MTFs, numeric test results were classified based upon the reference ranges indicated in the record. If a record had no reference range but units of measure were noted, the reference range was inferred based on other tests with the same unit of measure. In an effort to provide an accurate denominator, if the test result was numeric and the units of measure and the reference ranges could not be extrapolated from the data, the record result was classified as "Unknown." To avoid misclassification of results, if the test result field referred to the free-text result notes field, the record was classified as "Unknown."

If a service member had more than 1 record and the test results differed, the records were prioritized as follows: a "Deficient" record was retained over a "Not Deficient" or "Unknown" record, and a "Not Deficient" record was retained over an "Unknown" record. Only 1 record per service member was retained for analysis.

Final records were matched to the most recent Defense Enrollment Eligibility Reporting System (DEERS) record for each service member to obtain race/ethnicity and service affiliation. Records were not included in the final dataset if there were no matching DEERS records (n=29,642). Demographic frequencies and distributions for the final cohort were calculated using SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Overall results are presented in **Table 1**. G6PD laboratory test results for 2,311,223 service members were evaluated. Examination of laboratory records indicated that the vast majority (97.7%) of service members tested were not G6PD deficient. Only 0.13% of all records could not be classified. The majority of service members represented in this analysis (89.5%) had 1 record for G6PD testing, 8.7% had 2 records, and the remaining 1.8% had 3 or more records **(data not shown)**. Of those with more than 1 record where the classification changed, the following changes were observed: "Not Deficient" to "Deficient" (4.6%), "Unknown" to "Deficient" (3.7%), and "Unknown" to "Not Deficient" (91.7%) **(data not shown)**.

Of the 2,311,223 service members identified in the laboratory records as having been tested, 83.3% were male and 16.7% were female. Sex was not indicated in 3,070 records (0.13%). Males were more likely to be classified as G6PD deficient (2.3%) than females (1.5%).

Race/ethnicity was classified as "other/unknown" in 3.0% of all records **(Table 1)**. Non-Hispanic blacks were most likely to be classified as G6PD deficient (9.5%), followed by Asians/Pacific Islanders (2.9%) and Hispanics (1.5%). Non-Hispanic whites were the least likely to be classified as G6PD deficient (0.4%).

The G6PD classifications stratified by race/ethnicity and sex are shown in **Table 2**. Among males, non-Hispanic black service members were the most likely to be classified as G6PD deficient (11.2%), followed by Asian/Pacific Islander and Hispanic service members (3.3% and 1.7%, respectively). Non-Hispanic black males were more than twice as likely as non-Hispanic black females (4.7%) to be classified as G6PD deficient. Non-Hispanic black females had the highest proportion of G6PD deficiency of all female race/ethnicity groups. Although the non-Hispanic white race/ethnicity group represented the largest proportion of service members tested (59.8%), males and females in this race/ethnicity group were least likely to be G6PD deficient (0.4% and 0.3%, respectively).

Table 3 illustrates the G6PD results by service. The proportions of service members who tested positive for G6PD deficiency were broadly similar among the services. The Army had the highest percentage of service members with G6PD deficiency (2.7%), followed by the Air Force (2.3%) and Navy (2.2%). The Coast Guard (1.2%) and the Marine Corps (1.1%) had the lowest rates of service members with G6PD deficiency.

EDITORIAL COMMENT

The current study found an overall G6PD deficiency prevalence rate of 2.2% (n=49,897) among the 2,311,223 active and reserve component service members with laboratory results. To the authors' knowledge, this is the largest study of G6PD deficiency screening among DoD service members. The results of the current analysis are consistent with other studies that have found that non-Hispanic black males are more likely to be G6PD deficient than any other race/ethnicity group.[7–10]

Before adoption of the newly FDA-approved tafenoquine as the primary force health protection measure for DoD service members against malaria infection, it is critical to understand the indications for prevention and treatment as well as the limitations.[11] Regardless of an improved drug performance, including a radical curative efficacy, longer drug half-life, and once-weekly dosing regimen, tafenoquine still retains the risk of inducing hemolytic anemia in G6PD deficient individuals.

The results of this study must be interpreted within the context of several

TABLE 1. Results of G6PD deficiency laboratory testing among active duty DoD service members, 2004–2018

	G6PD deficient		G6PD not deficient		G6PD status unknown		Total	
	No.	%	No.	%	No.	%	No.	%
Total	49,897	2.2	2,258,256	97.7	3,070	0.13	2,311,223	100.0
Sex								
Male	43,979	2.3	1,878,756	97.6	2,570	0.13	1,925,305	83.3
Female	5,918	1.5	379,500	98.3	500	0.13	385,918	16.7
Race/ethnicity								
American Indian/Alaska Native	349	0.8	41,177	99.1	27	0.06	41,553	1.8
Asian/Pacific Islander	3,831	2.9	130,276	97.0	242	0.18	134349	5.8
Non-Hispanic black	33,781	9.5	321,321	90.4	467	0.13	355,569	15.4
Hispanic	4,898	1.5	323,745	98.4	364	0.11	329,007	14.2
Non-Hispanic white	5,485	0.4	1,374,856	99.5	1,894	0.14	1,382,235	59.8
Other/unknown	1,553	2.3	66,881	97.6	76	0.11	68,510	3.0

Data are from the Composite Health Care System (CHCS), Health Level 7-formatted chemistry and the Defense Enhancement Electronic Reporting System (DEERS) databases.
Prepared by the EpiData Center, Navy and Marine Corps Public Health Center, July 2019.
G6PD, glucose-6-phosphate dehydrogenase; DoD, Department of Defense; No., number.

TABLE 2. Classification of G6PD laboratory records among active duty DoD service members, by race/ethnicity and sex, 2004–2018

	G6PD deficient				G6PD not deficient				G6PD status unknown				Total	
	Male		Female		Male		Female		Male		Female		No.	%
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
American Indian/Alaska Native	301	0.9	48	0.6	32,932	99.0	8,245	99.3	19	0.06	8	0.10	41,553	1.8
Asian/Pacific Islander	3,471	3.3	360	1.5	105,917	96.7	24,359	98.4	205	0.19	37	0.15	134,349	5.8
Non-Hispanic black	29,463	11.2	4,318	4.7	233,247	88.7	88,074	95.2	344	0.13	123	0.13	355,569	15.4
Hispanic	4,469	1.7	429	0.7	264,049	98.2	59,696	99.2	306	0.11	58	0.10	329,007	14.2
Non-Hispanic white	5,005	0.4	480	0.3	1,193,105	99.5	181,751	99.6	1,635	0.14	259	0.14	1,382,235	59.8
Other/Unknown	1,270	2.5	283	1.6	49,506	97.4	17,375	98.3	61	0.12	15	0.08	68,510	3.0
Total	43,979	2.3	5,918	1.5	1,878,756	97.6	379,500	98.3	2,570	0.13	500	0.13	2,311,223	100.0

Data are from the Composite Health Care System (CHCS), Health Level 7-formatted chemistry and the Defense Enhancement Electronic Reporting System (DEERS) databases.
Prepared by the EpiData Center, Navy and Marine Corps Public Health Center, July 2019.
G6PD, glucose-6-phosphate dehydrogenase; DoD, Department of Defense; No., number.

TABLE 3. Classification of G6PD laboratory records among active duty DoD service members, by service, 2004–2018

	G6PD deficient		G6PD not deficient		G6PD status unknown		Total	
	No.	%	No.	%	No.	%	No.	%
Air Force	10,011	2.3	425,229	97.5	746	0.17	435,986	18.9
Army	22,231	2.7	789,423	97.1	1,688	0.21	813,342	35.2
Coast Guard	297	1.2	24,016	98.0	204	0.83	24,517	1.1
Marine Corps	5,511	1.1	497,278	98.9	145	0.03	502,934	21.8
Navy	11,824	2.2	521,620	97.7	263	0.05	533,707	23.1
Other	23	3.1	690	93.6	24	3.26	737	0.03
Total	49,897	2.2	2,258,256	97.7	3,070	0.13	2,311,223	100.0

Data are from the Composite Health Care System (CHCS), Health Level 7-formatted chemistry and the Defense Enhancement Electronic Reporting System (DEERS) databases.
Prepared by the EpiData Center, Navy and Marine Corps Public Health Center, July 2019.
G6PD, glucose-6-phosphate dehydrogenase; DoD, Department of Defense; No., number.

limitations. Laboratory records queried for this analysis were derived from fixed MTFs and do not include records from in-theater, shipboard, battalion aid station, or purchased care providers, although inclusion of these records, were they available, would not be expected to alter the findings presented herein. Genetic testing is generally performed during the accession phase of military service, so very few tests would need to be performed at austere or remote locations. Although validation steps were taken to avoid misclassification, it is possible that some results were misclassified. Because less than 1.0% of all records were classified as "Unknown," it is unlikely that these results would change the overall prevalence rates. Final laboratory records were matched to the most recent DEERS record for each service member; a service member may have changed service affiliation after the laboratory testing, but this practice is uncommon. Additionally, laboratory data were derived from DoD service members and may not be generalizable to a larger U.S. civilian population.

Given the findings of the current analysis, DoD healthcare providers, Combatant Commanders, and their command surgeons in areas of responsibility that include malaria-endemic regions should remain aware of the risks of 8-AQ hemolytic anemia in G6PD deficient service members. In addition, targeted health education and risk management instruction should be provided to G6PD deficient service members in order to mitigate adverse health outcomes. Furthermore, continued implementation of the DoD's G6PD screening instruction is required to mitigate G6PD deficiency-associated adverse events.

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Acknowledgments: The authors thank LTC Chad C. Black, LTC Mara Kreishman-Deitrick, COL James E. Moon, COL Viseth Ngauy, MAJ Brandon S. Pybus, and Angela D. Schlein for their support of this analysis and report.

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Positive Predictive Value of an Algorithm Used for Cancer Surveillance in the U.S. Armed Forces

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Recent large-scale epidemiologic studies of cancer incidence in the U.S. Armed Forces have used International Classification of Disease, 9th and 10th Revision (ICD-9 and ICD-10, respectively) diagnostic codes from administrative medical encounter data archived in the Defense Medical Surveillance System. Cancer cases are identified and captured according to an algorithm published by the Armed Forces Health Surveillance Branch. Standardized chart reviews were performed to provide a gold standard by which to validate the case definition algorithm. In a cohort of active component U.S. Air Force, Navy, and Marine Corps officers followed from 1 October 1995 through 31 December 2017, a total of 2,422 individuals contributed 3,104 algorithm-derived cancer cases. Of these cases, 2,108 (67.9%) were classified as *confirmed cancers*, 568 (18.3%) as *confirmed not cancers*, and 428 (13.8%) as *unclear*. The overall positive predictive value (PPV) of the algorithm was 78.8% (95% confidence interval [CI]: 77.2–80.3). For the 12 cancer sites with at least 50 cases identified by the algorithm, the PPV ranged from a high of 99.6% for breast and testicular cancers (95% CI: 97.8–100.0 and 97.7–100.0, respectively) to a low of 78.1% (95% CI: 71.3–83.9) for non-Hodgkin lymphoma. Of the 568 cases confirmed as not cancer, 527 (92.7%) occurred in individuals with at least 1 other confirmed cancer, suggesting algorithmic capture of metastases as additional primary cancers.

WHAT ARE THE NEW FINDINGS?

The cancer case definition algorithm published by the Armed Forces Health Surveillance Branch had a high PPV for capturing cases of common cancers and a low-to-moderate PPV for rarer cancers.

WHAT IS THE IMPACT ON READINESS AND FORCE HEALTH PROTECTION?

In the absence of a comprehensive centralized registry, cancer surveillance in the Department of Defense can rely on the Defense Medical Surveillance System for common cancer types. Algorithm-derived cases of rarer cancers may require verification by chart review.

Formal cancer surveillance dates to the early 17th century, when cancer was first recorded as a cause of death in England's *Bills of Mortality.*[1] A cancer registry for London followed in the 18th century, and the first population-based cancer registry in the U.S. appeared in 1935.[1] The Surveillance, Epidemiology, and End Results (SEER) program, established by the National Cancer Institute in 1973, was the first national cancer registry in the United States.[1] Now a conglomerate of 18 registries representing approximately 30% of the U.S. population, the SEER program utilizes the International Classification of Diseases for Oncology (ICD-O) taxonomy and incorporates demographic, clinical, histopathologic, and molecular data.[2]

The Automated Central Tumor Registry (ACTUR) has been the centralized cancer registry for the Department of Defense since its launch in 1986.[3] Several studies that have utilized this registry, however, report concerns with data incompleteness.[4–7] This incompleteness has not been quantified, but Zhu and colleagues note that some military treatment facilities (MTFs) do not comprehensively report cancer diagnoses to the ACTUR.[4] Recent large-scale epidemiologic studies of incident cancer in the U.S. Armed Forces have relied on diagnostic codes captured in the Defense Medical Surveillance System (DMSS),[8–10] using Armed Forces Health Surveillance Branch (AFHSB) case definitions.[11] This validation study provides chart review adjudication of cancer cases captured by the AFHSB cancer case definition algorithm.

METHODS

As part of a public health surveillance activity, the Epidemiology Consult Service Division (Public Health and Preventive Medicine Department, U.S. Air Force School of Aerospace Medicine), received oncological ICD 9th and 10th Revision (ICD-9 and ICD-10, respectively) codes of interest from AFHSB for active component U.S. Air Force, Navy, and Marine Corps officers who entered service as company grade officers between 1 January 1986 and 31 December 2006. The outcome period was 1 October 1995 through 31 December 2017. The outcome start date corresponds to the beginning of outpatient data capture in the DMSS, which includes diagnostic codes for all inpatient visits and outpatient encounters at MTFs (i.e., direct care) or at outside facilities reimbursed by TRICARE (i.e., purchased care).[12] All ICD codes recorded during inpatient and outpatient encounters during the outcome surveillance period were obtained regardless of beneficiary status (i.e., active duty, guard/reserve, retired, or family member).

Potential cancer cases were initially identified by searching for all cancer-related ICD-9 and ICD-10 codes in any diagnostic position from inpatient visits and outpatient encounters. Because they are not reportable to central cancer registries, basal and

squamous cell skin cancers were excluded. All other malignant cancers were categorized using the SEER site-specific ICD conversion program.[13]

As of this writing, AFHSB has published case definitions for 117 unique conditions, of which 11 are oncologic: breast cancer, cervical cancer, colorectal cancer, leukemia, lung cancer, malignant brain tumor, melanoma of the skin, non-Hodgkin lymphoma, non-melanomatous skin cancer, prostate cancer, and testicular cancer. With the exception of skin cancers, oncologic case definition algorithms specify 3 criteria by which ICD codes may classify as cases: 1) a hospitalization with a diagnostic code in the primary diagnostic position, 2) a hospitalization with a diagnostic code in the secondary diagnostic position and a therapeutic treatment V code in the primary position, or 3) 3 or more outpatient encounters within a 90-day period with a diagnostic code in the primary or secondary position. These classifications will be denoted as *inpatient*, *inpatient plus therapy*, and *outpatient*, respectively. This algorithm was applied to all site-specific cancers—including to those without an AFHSB published case definition—and to melanoma of the skin, which has a different case definition algorithm.[14] The oncological case definition was applied to melanoma of the skin in order to maximize standardization. Data were managed and analyzed using Base SAS and SAS/STAT® software, version 9.4 (2014, SAS Institute, Cary, NC). Novel code was written to apply the AFHSB case definition algorithm. For individuals identified as having more than 1 site-specific cancer, all cancers captured by the algorithm were included.

All unique cancer cases identified by the algorithm (n=3,104) were chart reviewed by 2 physicians (BJW for Air Force personnel; AER for Navy and Marine Corps personnel) using the Armed Forces Health Longitudinal Technology Application (AHLTA), Health Artifact and Image Management Solution (HAIMS), and Joint Legacy Viewer (JLV). Algorithmically captured cases were adjudicated as either *confirmed cancer*, *confirmed not cancer*, or *unclear*. A case was defined as *confirmed cancer* if it met any of these criteria: 1) a diagnosis made by an oncologist or general surgeon; 2) a diagnosis of specific cancers made by the appropriate medical or surgical specialist (i.e., melanoma of the skin by a dermatologist; thyroid cancer by an endocrinologist; eye cancer by an ophthalmologist; brain cancer by a neurologist or neurosurgeon; lung and bronchus cancer by a pulmonologist; bone and joint cancer by an orthopedist; prostate or testicular cancer by a urologist; kidney or bladder cancer by a nephrologist; colorectal, anal, or stomach cancer by a gastroenterologist; and cervical, corpus uteri, or ovarian cancer by a gynecologist); or 3) a diagnosis made by a primary care provider with substantiating documentation in the clinical note, such as histopathologic or treatment information. A case was defined as *confirmed not cancer* if an alternative diagnosis was found that explained the ICD code(s) captured by the algorithm. A case was defined as *unclear* if chart documentation was insufficient for making a determination.

All cancers were considered incident conditions, with the incident (i.e., diagnosis) date corresponding to the date of the first ICD code contributing to the case criterion. If, on chart review, the code was related to a history of cancer (i.e., a prevalent rather than incident case), the case was classified as *unclear*. These cases were not classified as *confirmed not cancer* because recurrence could not be excluded. For individuals with multiple cancers, each cancer site was assigned its own incident date.

For all malignant cancers and site-specific cancers, total and sex-specific positive predictive values (PPVs) with 95% binomial-based Clopper-Pearson confidence intervals (CIs) were calculated. PPV was also calculated after stratifying by the 3 criteria used to capture cases. PPV was defined as the number of confirmed cancer cases divided by the sum of confirmed cancer and confirmed not cancer cases; unclear cases were not included in the calculation. Although chart review resulted in site reclassification for some confirmed cancer cases, PPVs were calculated according to the original, algorithmically defined site. This study was approved by the Air Force Research Laboratory Institutional Review Board.

RESULTS

A total of 133,843 hospitalization and outpatient encounter records from 5,787 persons with a cancer ICD-9 or ICD-10 code in any diagnostic position (Air Force, n=93,174; Navy/Marine Corps, n=40,669) during the outcome period of 1 October 1995 through 31 December 2017 were abstracted by AFHSB. After application of the AFHSB algorithm, 3,104 unique cancer cases were identified among 2,422 individuals. Based on chart review, 2,108 (67.9%) were classified as confirmed cancers, 568 (18.3%) as confirmed not cancers, and 428 (13.8%) as unclear. The algorithm's PPV for all malignant cancers was 78.8% (95% CI: 77.2–80.3); for males it was 77.7% (95% CI: 75.8–79.5); for females it was 81.7% (95% CI: 78.6–84.4). For the 12 sites with at least 50 total cancer cases captured by the algorithm, the PPV ranged from a high of 99.6% for cancer of the breast and cancer of the testis (95% CI: 97.8–100.0 and 97.7–100.0, respectively) to a low of 78.1% (95% CI: 71.3–83.9) for non-Hodgkin lymphoma **(Table 1)**.

Of the 568 cases confirmed as not cancer, 527 (92.7%) occurred in individuals with at least 1 other confirmed cancer **(data not shown)**. Among the 41 cases of ruled-out cancer without a separate confirmed case, the most common situations were benign thyroid nodules algorithmically captured as thyroid cancer (n=8) and non-melanomatous skin lesions captured as melanoma of the skin (n=4) **(Table 2)**. An additional 7 cases were reclassified based on chart review: anus to other digestive (n=4), miscellaneous to colon and rectum (n=1), miscellaneous to other respiratory (n=1), and miscellaneous to small intestine (n=1) **(data not shown)**.

Confirmed cases were captured predominantly by criterion #3 (outpatient) (n=2,034), followed by criterion #1 (inpatient) (n=915) and criterion #2 (inpatient plus therapy) (n=44); some cases (n=885) were captured by multiple criteria. PPVs were 81.7% (95% CI: 79.3–83.9) for inpatient, 62.9% (95% CI: 50.5–74.1) for inpatient plus therapy, and 80.7% (95% CI: 79.1–82.2) for outpatient. Inpatient and outpatient PPVs were statistically equivalent for each cancer type **(data not shown)**.

EDITORIAL COMMENT

Common cancers captured by the AFHSB case definition algorithm usually reflected true cases, with PPVs exceeding 95% for breast, melanoma of the skin, prostate, testis, and thyroid cancers. In the absence of tumor registry data, epidemiologic

TABLE 1. PPV of the AFHSB algorithm for incident cancer cases based on chart review, by sex, U.S. Armed Forces, 1 October 1995–31 December 2017

Site	Chart review adjudication: Confirmed cancer	Confirmed not cancer	Unclear	PPV[a]	95% CI[b]
All malignant cancers					
Male	1,520	436	322	77.7	75.8–79.5
Female	588	132	106	81.7	78.6–84.4
Total	2,108	568	428	78.8	77.2–80.3
Anus					
Male	3	3	1	50.0	11.8–88.2
Female	1	0	0	100.0	2.5–100.0
Total	4	3	1	57.1	18.4–90.1
Bladder					
Male	31	3	5	91.2	76.3–98.1
Female	3	0	1	100.0	29.2–100.0
Total	34	3	6	91.9	78.1–98.3
Bone and joints					
Male	15	10	3	60.0	38.7–78.8
Female	4	3	0	57.1	18.4–90.1
Total	19	13	3	59.4	40.7–76.3
Brain and other nervous system					
Male	79	13	10	85.9	77.1–92.3
Female	12	4	3	75.0	47.6–92.7
Total	91	17	13	84.3	76.0–90.6
Breast					
Male	6	0	1	100.0	54.1–100.0
Female	247	1	36	99.6	97.8–100.0
Total	253	1	37	99.6	97.8–100.0
Cervix					
Female	17	2	2	89.5	66.9–98.7
Colon and rectum					
Male	105	6	27	94.6	88.6–98.0
Female	19	2	2	90.5	69.6–98.8
Total	124	8	29	93.9	88.4–97.4
Corpus uteri					
Female	12	3	3	80.0	51.9–95.7
Esophagus					
Male	5	3	0	62.5	24.5–91.5
Female	0	1	0	0.0	---
Total	5	4	0	55.6	21.2–86.3
Eye					
Male	10	3	1	76.9	46.2–95.0
Female	0	2	1	0.0	---
Total	10	5	2	66.7	38.5–88.2
Gallbladder					
Male	1	1	2	50.0	1.3–98.7
Female	0	1	0	0.0	---
Total	1	2	2	33.3	0.8–90.6
Hodgkin lymphoma					
Male	64	4	4	94.1	85.6–98.4
Female	13	1	2	92.9	66.1–99.8
Total	77	5	6	93.9	86.3–98.0
Kidney					
Male	48	2	7	96.0	86.3–99.5
Female	7	0	2	100.0	59.0–100.0
Total	55	2	9	96.5	87.9–99.6
Larynx					
Male	2	3	2	40.0	5.3–85.3
Female	1	0	0	100.0	2.5–100.0
Total	3	3	1	50.0	11.8–88.2
Leukemia					
Male	53	13	13	80.3	68.7–89.1
Female	11	4	1	73.3	44.9–92.2
Total	64	17	14	79.0	68.5–87.3
Liver and bile duct					
Male	8	5	3	61.5	31.6–86.1
Female	0	1	1	0.0	---
Total	8	6	4	57.1	28.9–82.3
Lung and bronchus					
Male	16	9	6	64.0	42.5–82.0
Female	12	3	5	80.0	51.9–95.7
Total	28	12	11	70.0	53.5–83.4
Melanoma of the skin					
Male	234	6	43	97.5	94.6–99.1
Female	40	0	7	100.0	91.2–100.0
Total	274	6	50	97.9	95.4–99.2
Miscellaneous					
Male	21	233	54	8.3	5.2–12.4
Female	9	74	16	10.8	5.1–19.6
Total	30	307	70	8.9	6.1–12.4
Myeloma					
Male	15	6	4	71.4	47.8–88.7
Female	1	1	1	50.0	1.3–98.7
Total	16	7	5	69.6	47.1–86.8
Non-Hodgkin lymphoma					
Male	123	36	25	77.4	70.1–83.6
Female	16	3	4	84.2	60.4–96.6
Total	139	39	29	78.1	71.3–83.9
Oropharynx					
Male	56	5	20	91.8	81.9–97.3
Female	5	1	2	83.3	35.9–99.6
Total	61	6	22	91.0	81.5–96.6
Other digestive					
Male	1	10	0	9.1	0.2–41.3
Female	1	5	1	16.7	0.4–64.1
Total	2	15	1	11.8	1.5–36.4
Other endocrine					
Male	13	3	2	81.3	54.4–96.0
Female	2	2	0	50.0	6.8–93.2
Total	15	5	2	75.0	50.9–91.3

[a]Defined as confirmed cancer cases divided by the sum of confirmed cancer cases and confirmed not cancer cases (unclear cases were not used for the calculation).

[b]CIs were calculated using the Clopper-Pearson method.

Note: An individual could contribute multiple cancer cases but only 1 per site; calculations are based on the algorithm classification (some cancers were reclassified during chart review: anus to other digestive [n=4], miscellaneous to colon and rectum [n=1], miscellaneous to other respiratory [n=1], and miscellaneous to small intestine [n=1]).

PPV, positive predictive value; AFHSB, Armed Forces Health Surveillance Branch; CI, confidence interval.

TABLE 1. (cont.) PPV of the AFHSB algorithm for incident cancer cases based on chart review, by sex, U.S. Armed Forces, 1 October 1995–31 December 2017

Site	Chart review adjudication: Confirmed cancer	Confirmed not cancer	Unclear	PPV[a]	95% CI[b]
Other female genital					
Female	2	3	0	40.0	5.3–85.3
Other male genital					
Male	1	6	0	14.3	0.4–57.9
Other skin					
Male	0	0	1	0.0	---
Other respiratory					
Male	4	6	1	40.0	12.2–73.7
Female	0	5	2	0.0	
Total	4	11	3	26.7	7.8–55.1
Other urinary					
Male	0	1	0	0.0	---
Ovary					
Female	22	1	3	95.7	78.1–99.9
Pancreas					
Male	18	1	3	94.7	74.0–99.9
Female	1	0	2	100.0	2.5–100.0
Total	19	1	5	95.0	75.1–99.9
Prostate					
Male	188	7	54	96.4	92.7–98.5
Small intestine					
Male	3	3	0	50.0	11.8–88.2
Female	1	1	0	50.0	1.3–98.7
Total	4	4	0	50.0	15.7–84.3
Soft tissue including heart					
Male	22	23	7	48.9	33.7–64.2
Female	15	4	0	78.9	54.4–94.0
Total	37	27	7	57.8	44.8–70.1
Stomach					
Male	6	4	3	60.0	26.2–87.8
Female	2	3	1	40.0	5.3–85.3
Total	8	7	4	53.3	26.6–78.7
Testis					
Male	240	1	13	99.6	97.7–100.0
Thyroid					
Male	128	7	7	94.8	89.6–97.9
Female	113	1	8	99.1	95.2–100.0
Total	241	8	15	96.8	93.8–98.6

[a]Defined as confirmed cancer cases divided by the sum of confirmed cancer cases and confirmed not cancer cases (unclear cases were not used for the calculation).

[b]CIs were calculated using the Clopper-Pearson method.

Note: An individual could contribute multiple cancer cases but only 1 per site; calculations are based on the algorithm classification (some cancers were reclassified during chart review: anus to other digestive [n=4], miscellaneous to colon and rectum [n=1], miscellaneous to other respiratory [n=1], and miscellaneous to small intestine [n=1]).

PPV, positive predictive value; AFHSB, Armed Forces Health Surveillance Branch; CI, confidence interval.

TABLE 2. Patients with a single cancer identified by algorithm classified as confirmed not cancer based on chart review (n=41), U.S. Armed Forces, 1 October 1995–31 December 2017

Algorithm-based cancer type	Actual diagnosis	No.
Thyroid		
	Benign nodule	8
Melanoma		
	Non-melanomatous skin lesion	4
Brain and other nervous system		
	Acute disseminated encephalomyelitis	2
	Benign pineal cyst	1
	Cavernous hemangioma	1
Bone and joints		
	Fracture	2
	Cyclops lesion	1
Colon and rectum		
	Benign polyp	2
Leukemia		
	None (negative workup)	2
	Leukemoid reaction	1
Miscellaneous		
	Aplastic anemia	1
	Benign fibrous sacral mass	1
	Family history of cancer	1
	Hypereosinophilic syndrome	1
	Pterygium	1
Non-Hodgkin lymphoma		
	Benign lipoma	1
	Histoplasmosis	1
	Still disease	1
Prostate		
	Benign prostatic hyperplasia	1
	Orchitis	1
Breast		
	Prophylactic mastectomy	1
Esophagus		
	Achalasia	1
Larynx		
	Benign polyp	1
Liver and bile duct		
	Primary sclerosing cholangitis	1
Lung and bronchus		
	Idiopathic neutropenia	1
Myeloma		
	None (negative workup)	1
Soft tissue including heart		
	Neuroma	1

No., number.

studies of these cancers can rely on the AFHSB algorithm without confirmatory chart reviews. For studies of rarer cancers, such as bone and joint, esophagus, or liver and bile duct cancers—all of which had PPVs below 60%—investigators may want to confirm cases by chart review or adjust for misclassification in order to avoid overcounting cases. Such adjustment assumes that the degree of misclassification bias remains constant over time.

Investigators should also be cautious when individuals are identified by the algorithm as having more than 1 cancer. Over 92% of the cancers that were excluded during chart review were in individuals with at least 1 other confirmed cancer, suggesting capture of metastases as additional primary cancers. For surveillance purposes, investigators interested in overall cancer rates may consider limiting case counting to 1 per individual per lifetime. For site-specific cancer epidemiology, investigators may need to conduct chart reviews of individuals with multiple cancers to distinguish multiple primary cancers from solitary primary cancers with metastases. Investigators may also want to perform chart reviews of cases identified only by the inpatient plus therapy criterion, as this had a lower overall PPV than the other criteria, although this low PPV was largely driven by misclassification of miscellaneous cancers.

The high PPV for melanoma of the skin (PPV: 97.9%; 95% CI: 95.4–99.2) suggests that the standard AFHSB oncological case definition can be applied to this cancer type. Future research could determine if the AFHSB case definition for melanoma of the skin[14] outperforms the standard oncological case definition.

This study has at least 2 limitations. First, nearly 14% of all algorithm-defined cancer cases could not be definitively categorized during chart review as either cancer or not cancer. The diagnostic codes responsible for these cases may have been generated outside MTFs (i.e., in TRICARE purchased care settings), and documents from these hospitalizations or outpatient encounters were not uploaded into the HAIMS. It is unclear if their inclusion would increase or decrease PPV estimates. Second, in the absence of a registry or another database with 100% case capture, which may include cancer cases not captured by the AFHSB algorithm, this study cannot provide information on the algorithm's sensitivity. A future study should compare the AHFSB algorithm with data from the ACTUR; such a study may need to be restricted to military treatment facilities that systematically report cancer cases to the registry.

The AFHSB cancer case definition algorithm is a valuable surveillance tool for accurately identifying the most common cancers, although it has a lower PPV for rarer cancers. Since the DMSS does not provide information on critical variables such as histology and staging, the ACTUR should be funded to enhance oncology research and surveillance. Warfighters encounter unique environmental and occupational hazards, with more notable examples including herbicides in Vietnam, oil fires in Kuwait, and burn pits in Iraq and Afghanistan.[15] Tracking exposures and linking them to long-term outcomes—malignancy chief among them—is a critical capability for protecting the health of service members and veterans.[16,17]

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Reviewer Acknowledgment 2019

The *MSMR* thanks the following individuals for reviewing manuscript submissions during 2019. We value their expertise and constructive comments.

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Medical Surveillance Monthly Report (MSMR)
Armed Forces Health Surveillance Branch
11800 Tech Road, Suite 220
Silver Spring, MD 20904

MEDICAL SURVEILLANCE MONTHLY REPORT (MSMR), in continuous publication since 1995, is produced by the Armed Forces Health Surveillance Branch (AFHSB). AFHSB is a designated public health authority within the Defense Health Agency. The *MSMR* provides evidence-based estimates of the incidence, distribution, impact, and trends of illness and injuries among U.S. military members and associated populations. Most reports in the *MSMR* are based on summaries of medical administrative data that are routinely provided to the AFHSB and integrated into the Defense Medical Surveillance System for health surveillance purposes.

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ISSN 2158-0111 (print)
ISSN 2152-8217 (online)