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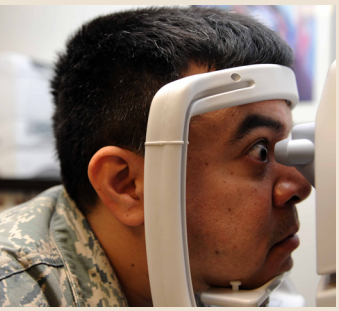
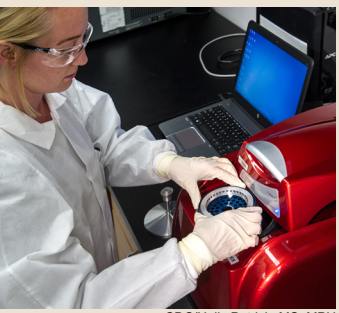




CDC/Holly Patrick, MS, MPH

Update: Malaria, U.S. Armed Forces, 2018

Malaria infection remains an important health threat to U.S. service members who are located in endemic areas because of long-term duty assignments, participation in shorter-term contingency operations, or personal travel. In 2018, a total of 58 service members were diagnosed with or reported to have malaria. This represents a 65.7% increase from the 35 cases identified in 2017. The relatively low numbers of cases during 2012–2018 mainly reflect decreases in cases acquired in Afghanistan, a reduction due largely to the progressive withdrawal of U.S. forces from that country. The percentage of cases of malaria caused by unspecified agents (63.8%; n=37) in 2018 was the highest during any given year of the surveillance period. The percentage of cases identified as having been caused by *Plasmodium vivax* (10.3%; n=6) in 2018 was the lowest observed during the 10-year surveillance period. The percentage of malaria cases attributed to *P. falciparum* (25.9 %) in 2018 was similar to that observed in 2017 (25.7%), although the number of cases increased. Malaria was diagnosed at or reported from 31 different medical facilities in the U.S., Afghanistan, Italy, Germany, Djibouti, and Korea. Providers of medical care to military members should be knowledgeable of and vigilant for clinical manifestations of malaria outside of endemic areas.

WHAT ARE THE NEW FINDINGS?

A total of 58 service members were diagnosed with or reported to have malaria in 2018 compared with 35 in 2017. Most of the malaria cases (63.8%) were caused by unspecified agents and were presumed to be acquired in Afghanistan (34.5%) or Africa (24.1%).

WHAT IS THE IMPACT ON READINESS AND FORCE HEALTH PROTECTION?

Service members are at risk of malaria infection via deployment or personal travel to endemic regions. Commanders should stress the importance of adherence to personal protective measures. Military healthcare providers in non-endemic regions should be aware of the signs and symptoms of malaria.

Globally, the incidence rate of malaria is estimated to have decreased by 18% between 2010 and 2017, from 72 to 59 cases per 1,000 population at risk.[1] However, for the second consecutive year, the World Health Organization reported a relative plateauing in the numbers of cases of malaria; in 2017, there were an estimated 219 million cases of malaria compared with 217 million in 2016.[1] During the 6 years prior, the number of people contracting malaria globally had been steadily decreasing, from 239 million in 2010 to 214 million in 2015.[1]

A total of 87 countries reported indigenous malaria cases in 2017, with countries in Africa accounting for around 92% of worldwide malaria cases and 93% of all malaria-related deaths.[1] The majority of these cases and deaths occurred in sub-Saharan Africa among children under 5 years of age and were due to mosquito-transmitted *Plasmodium falciparum*, but *P. vivax, P. ovale*, and *P. malariae* can also cause severe disease.[1,2] Globally, 3.4% of estimated malaria cases are due to *P. vivax*; however, outside of the African continent, the proportion of *P. vivax* infections is 36.8%.[1] In 2017, 82% of vivax malaria cases occurred in 5 countries including India, Pakistan, Ethiopia, Afghanistan, and Indonesia.[1]

Since 1999, the *MSMR* has published regular updates on the incidence of malaria among U.S. service members.[3,4,5] The *MSMR*'s focus on malaria reflects both historical lessons learned about this mosquito-borne disease and the continuing threat that it poses to military operations and service members' health. Malaria infected many thousands of service members during World War II (approximately 695,000 cases), the Korean War (approximately 390,000 cases), and the conflict in Vietnam (approximately 50,000 cases).[6,7] More recent military engagements in Africa, Asia, Southwest Asia, the Caribbean, and the Middle East have necessitated heightened vigilance, preventive measures, and treatment of cases.[8-16]

In the planning for overseas military operations, the geography-based presence or absence of the malaria threat is usually known and can be anticipated. However, when preventive countermeasures are needed, their effective implementation is multifaceted and depends on the provision of protective equipment and supplies, individuals' understanding of the threat and attention to personal protective measures, treatment of malaria cases, and medical surveillance. The U.S. Armed Forces have long had policies and prescribed countermeasures effective against vector-borne diseases such as malaria, including chemoprophylactic drugs, permethrin-impregnated uniforms and bed nets, and topical insect repellents containing N,N-diethyl-meta-toluamide (DEET). When cases and outbreaks of malaria have occurred, they generally have been due to poor adherence to chemoprophylaxis and other personal preventive measures.[9-12]

MSMR malaria updates from the past 6 years documented that the annual case

counts among service members after 2011 were the lowest in more than a decade.[5,17-21] In particular, these updates showed that the numbers of cases associated with service in Afghanistan had decreased substantially in the past 6 years, presumably due to the dramatic reduction in the numbers of service members serving there. This update for 2018 uses methods similar to those employed in previous analyses to describe the epidemiologic patterns of malaria incidence among service members in the active and reserve components of the U.S. Armed Forces.

METHODS

The surveillance period was 1 January 2009 through 31 December 2018. The surveillance population included Army, Navy, Air Force, and Marine Corps active and reserve component members of the U.S. Armed Forces. The records of the Defense Medical Surveillance System (DMSS) were searched to identify reportable medical events and hospitalizations (in military and nonmilitary facilities) that included diagnoses of malaria. A case of malaria was defined as an individual with 1) a reportable medical event record of confirmed malaria, 2) a hospitalization record with a primary diagnosis of malaria, 3) a hospitalization record with a non-primary diagnosis of malaria due to a specific *Plasmodium* species, 4) a hospitalization record with a non-primary diagnosis of malaria plus a diagnosis of anemia, thrombocytopenia and related conditions, or malaria complicating pregnancy in any diagnostic position, 5) a hospitalization record with a non-primary diagnosis of malaria plus diagnoses of signs or symptoms consistent with malaria (as listed in the *Control of Communicable Diseases Manual*, 18th Edition)[22] in each diagnostic position antecedent to malaria, or 6) a positive malaria antigen test plus an outpatient record with a diagnosis of malaria in any diagnostic position within 30 days of the specimen collection date. The relevant ICD-9/ICD-10 codes are shown in **Table 1.** Laboratory data for malaria were provided by the Navy and Marine Corps Public Health Center.

This analysis allowed 1 episode of malaria per service member per 365-day period. When multiple records documented a single episode, the date of the earliest encounter was considered the date of clinical onset, and the most specific diagnosis recorded within 30 days of the incident diagnosis was used to classify the *Plasmodium* species.

Presumed locations of malaria acquisition were estimated using a hierarchical algorithm: 1) cases diagnosed in a malarious country were considered acquired in that country, 2) reportable medical events that listed exposures to malaria endemic locations were considered acquired in those locations, 3) reportable medical events that did not list exposures to malaria endemic locations but were reported from installations in malaria endemic locations were considered acquired in those locations, 4) cases diagnosed among service members during or within 30 days of deployment or assignment to a malarious country were considered acquired in that country, and 5) cases diagnosed among service members who had been deployed or assigned to a malarious country within 2 years prior to diagnosis were considered acquired in those respective countries. All remaining cases were considered acquired in unknown locations.

RESULTS

In 2018, a total of 58 service members were diagnosed with or reported to have malaria **(Table 2)**. This represents a 65.7% increase from the 35 cases identified in 2017 **(Figure 1)**. The percentage of cases of malaria caused by unspecified agents (63.8%; n=37) in 2018 was the highest during any given year of the surveillance period. Of all malaria cases identified, 6 (10.3%) were attributed to *P. vivax* and 15 (25.9%) to *P. falciparum*. In 2018, the percentage of malaria cases caused by *P. vivax* was the lowest percentage observed during the 10-year surveillance period. The percentage of malaria cases caused by *P. falciparum* in 2018 was comparable to that observed in 2017 (25.7%), although the number of cases increased. There were no cases identified as having been caused by *P. malariae* or *P. ovale* in 2018 **(Figure 1)**.

Similar to 2017, the majority of U.S. military members diagnosed with malaria in 2018 were male (96.6%), active

TABLE 1. ICD-9 and ICD-10 codes used in defining cases of malaria

	ICD-9	ICD-10
Malaria (*Plasmodium* species)		
P. falciparum	84.0	B50
P. vivax	84.1	B51
P. malariae	84.2	B52
P. ovale	84.3	B53.0
Unspecified	84.4, 84.5, 84.6, 84.8, 84.9	B53.1, B53.8, B54
Anemia	280–285	D50–D53, D55–D64
Thrombocytopenia	287	D69
Malaria complicating pregnancy	647.4	O98.6
Signs, symptoms, or other abnormalities consistent with malaria	276.2, 518.82, 584.9, 723.1, 724.2, 780.0, 780.01, 780.02, 780.03, 780.09, 780.1, 780.3, 780.31, 780.32, 780.33, 780.39, 780.6, 780.60, 780.61, 780.64, 780.65, 780.7, 780.71, 780.72, 780.79, 780.97, 782.4, 784.0, 786.05, 786.09, 786.2, 786.52, 786.59, 787.0, 787.01, 787.02, 787.03, 787.04, 789.2, 790.4	E87.2, J80, M54.2, M54.5, N17.9, R05, R06.0, R06.89, R07.1, R07.81, R07.82, R07.89, R11, R11.0, R11.1, R11.2, R16.1, R17, R40, R41.0, R41.82, R44, R50, R51, G44.1, R53, R56, R68.0, R68.83, R74.0

component members (84.5%), in the Army (77.6%), and in their 20s (58.6%) **(Table 2)**.

Of the 58 malaria cases in 2018, more than one-third (34.5%; n=20) of the infections were considered to have been acquired in Afghanistan, but almost one-quarter (24.1%; n=14) could not be associated with a known, specific location. Acquisition of the remaining cases was attributed mainly to Africa (24.1%; n=14) and Korea (15.5%; n=9), with 1 case (1.7%) in South/Central America **(Figure 2)**. Of the 14 malaria infections considered acquired in Africa in 2018, 4 were linked to Niger, 3 to Cameroon, 2 each to Kenya, Ghana, and Djibouti, and a single case to an unknown country **(data not shown)**.

During 2018, malaria cases were diagnosed or reported from 31 different medical facilities in the U.S., Korea, Afghanistan, Germany, Italy, and Djibouti **(Table 3)**. More than one-quarter (29.4%; 15/51) of the total cases with a known location of diagnosis were reported from or diagnosed outside the U.S., which represents a decrease from the 40.0% of malaria cases in this category in 2017. The largest number of malaria cases associated with a single medical facility during 2018 was 11 at the Womack Army Medical Center in Fort Bragg, NC.

In 2018, the percentage of malaria cases that were acquired in Africa (24.1%; n=14) was lower than the percentages of Africa-acquired cases observed in 2013 through 2017 **(Figure 2)**. The percentage of Afghanistan-acquired cases (34.5%; n=20) in 2018 was the highest that it has been since 2012. The percentage of malaria cases acquired in Korea (15.5%; n=9) in 2018 was similar to percentages during 2016–2017 but slightly lower than those during 2014–2015 **(Figure 2)**.

Between 2009 and 2018, the majority of malaria cases were diagnosed or reported during the 6 months from the middle of spring through the middle of autumn in the Northern Hemisphere **(Figure 3)**. In 2018, 82.8% (48 of 58) of malaria cases among U.S. service members were diagnosed during May–October **(data not shown)**. This proportion is higher than the 71.3% (452/634) of cases diagnosed during the same 6-month intervals over the entire 10-year surveillance period. During 2009–2018, the proportions of malaria cases diagnosed or reported during May–October varied by region of acquisition: Korea (91.9%; 57/62,); Afghanistan (80.0%; 212/265); Africa (60.0%; 114/190); and South/Central America (40.0%; 2/5) **(data not shown)**.

TABLE 2. Malaria cases by *Plasmodium* species and selected demographic characteristics, U.S. Armed Forces, 2018

	P. vivax	*P. falciparum*	Unspecified/ other	Total	% of total
Component					
Active	5	11	33	49	84.5
Reserve/Guard	1	4	4	9	15.5
Service					
Army	6	7	32	45	77.6
Navy	0	5	0	5	8.6
Air Force	0	3	4	7	12.1
Marine Corps	0	0	1	1	1.7
Sex					
Male	6	14	36	56	96.6
Female	0	1	1	2	3.4
Age group (years)					
<20	0	0	2	2	3.4
20–24	3	1	12	16	27.6
25–29	1	7	10	18	31.0
30–34	1	4	7	12	20.7
35–39	1	0	2	3	5.2
40–44	0	1	4	5	8.6
45–49	0	2	0	2	3.4
Race/ethnicity					
Non-Hispanic white	6	5	27	38	65.5
Non-Hispanic black	0	10	9	19	32.8
Other	0	0	1	1	1.7
Total	6	15	37	58	100.0

EDITORIAL COMMENT

MSMR annual reports on malaria incidence among all U.S. services began in 2007. The current report and those of the previous 5 years document that the lowest annual numbers of cases during the interval 2001–2017 were in the past 6 years,* reaching a nadir of 35 in 2017.[5,17-21] The next lowest annual number of malaria cases occurred in 2013 (n=38). Most of the marked decline in the past 7 years is attributable to the decrease in numbers of malaria cases associated with service in Afghanistan. The dominant factor in that trend has undoubtedly been the progressive withdrawal of U.S. forces from that country.

This report also documents the fluctuating incidence of acquisition of malaria in Africa and Korea among U.S. military members during the past decade. Although the predominant species of malaria in Korea and Afghanistan has been *P. vivax*, the more dangerous *P. falciparum* species is

*A recent *MMWR Surveillance Summary* reported the numbers of malaria cases among U.S. military personnel during 2009–2015, a period overlapping with the current analysis.[5] However, because the *MMWR* analysis employed a malaria case definition different from that used in the current analysis, the numbers of annual cases differ.

FIGURE 1. Numbers of malaria cases, by *Plasmodium* species and calendar year of diagnosis/report, active and reserve components, U.S. Armed Forces, 2009–2018

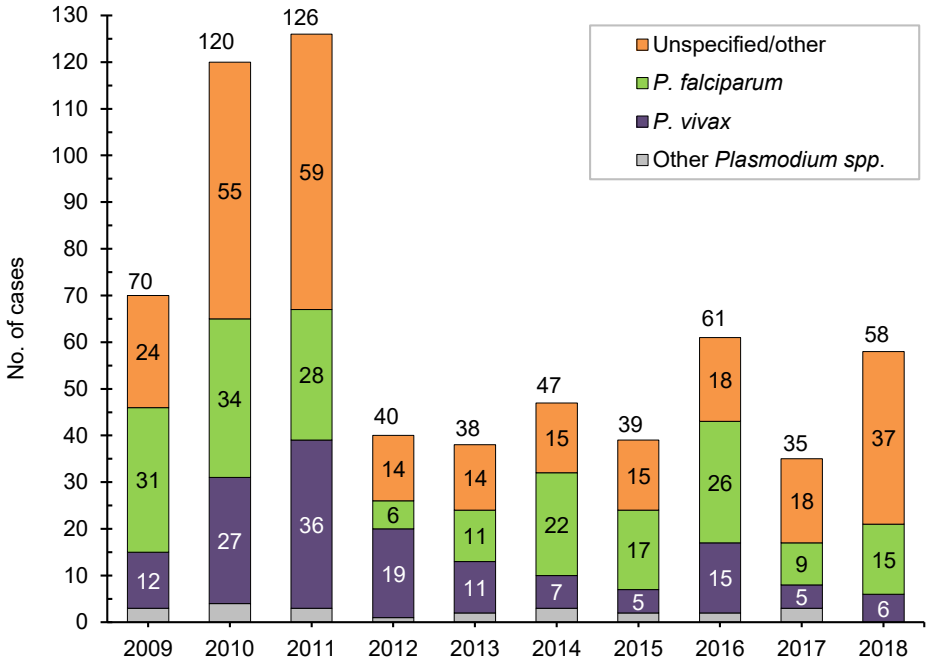
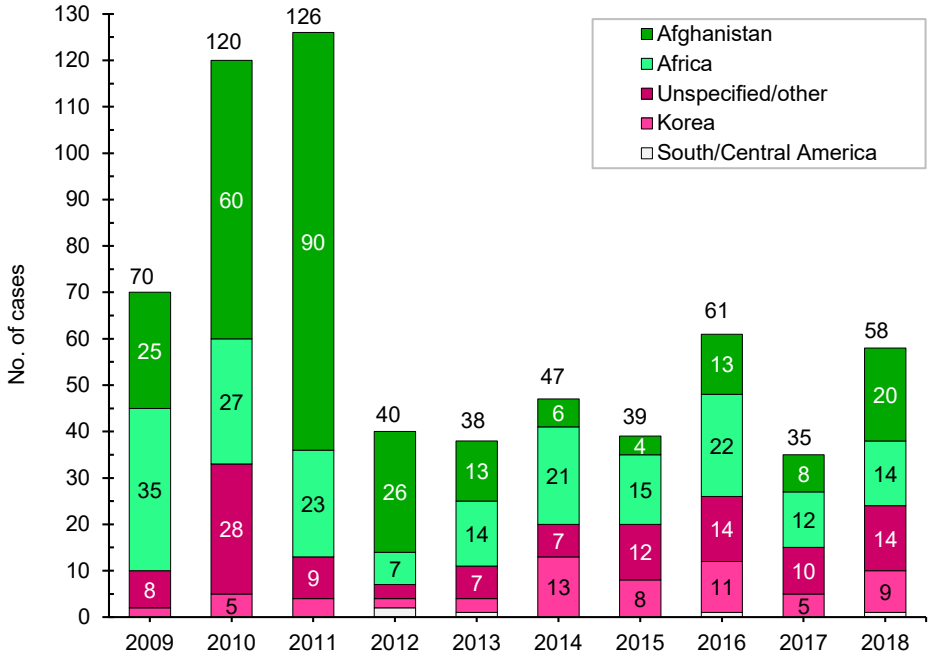


FIGURE 2. Annual numbers of cases of malaria associated with specific locations of acquisition, U.S. Armed Forces, 2009–2018



of primary concern in Africa. The planning and execution of military operations on that continent must incorporate actions to counter the threat of infection by that potentially deadly parasite wherever it is endemic. The 2014–2015 employment of U.S. service members to aid in the response to the Ebola virus outbreak in West Africa is an example of an operation where the risk of *P. falciparum* malaria was significant.[2] The finding that *P. falciparum* malaria was diagnosed in over one quarter of the cases in 2018 further underscores the need for continued emphasis on prevention of this disease, given its potential severity and risk of death.

The observations about the seasonality of diagnoses of malaria are compatible with the presumption that the risk of acquiring and developing symptoms of malaria in a temperate climatic zone of the Northern Hemisphere would be greatest during May–October. Given the typical incubation periods of malaria infection (approximately 9–14 days for *P. falciparum*, 12–18 days for *P. vivax* and *P. ovale*, and 18–40 days for *P. malariae*)[22] and the seasonal disappearance of biting mosquitoes during the winter, most malaria acquired in Korea and Afghanistan would be expected to cause symptoms during the warmer months of the year. However, it should be noted that studies of *P. vivax* malaria in Korea have found that the time between primary infection and clinical illness among different *P. vivax* strains ranges between 8 days and 8–13 months and that as many as 40–50% of infected individuals may not manifest the symptoms of their primary illness until 6–11 months after infection.[23] Klein and colleagues recently reported a cluster of 11 U.S. soldiers with *P. vivax* malaria who were likely infected at a training area located near the southern border of the demilitarized zone in 2015.[24] Nine of the malaria cases developed their first symptoms of infection 9 or more months after exposure and after their departure from Korea.[24] Transmission of malaria in tropical regions such as sub-Saharan Africa is less subject to the limitations of the seasons as in temperate climates but depends more on other factors affecting mosquito breeding such as the timing of the rainy season and altitude (below 2,000 meters).[25]

There are significant limitations to this report that should be considered when interpreting the findings. For example, the ascertainment of malaria cases is likely incomplete; some cases treated in deployed or non-U.S. military medical facilities may not have been reported or otherwise ascertained at the time of this analysis. Furthermore, it should be noted that medical data from military treatment facilities that are using MHS GENESIS are not available in DMSS, which was implemented at different sites throughout 2017. These include

TABLE 3. Number of malaria cases, by geographical locations of diagnosis or report and presumed location of acquisition, active and reserves components, U.S. Armed Forces, 2018

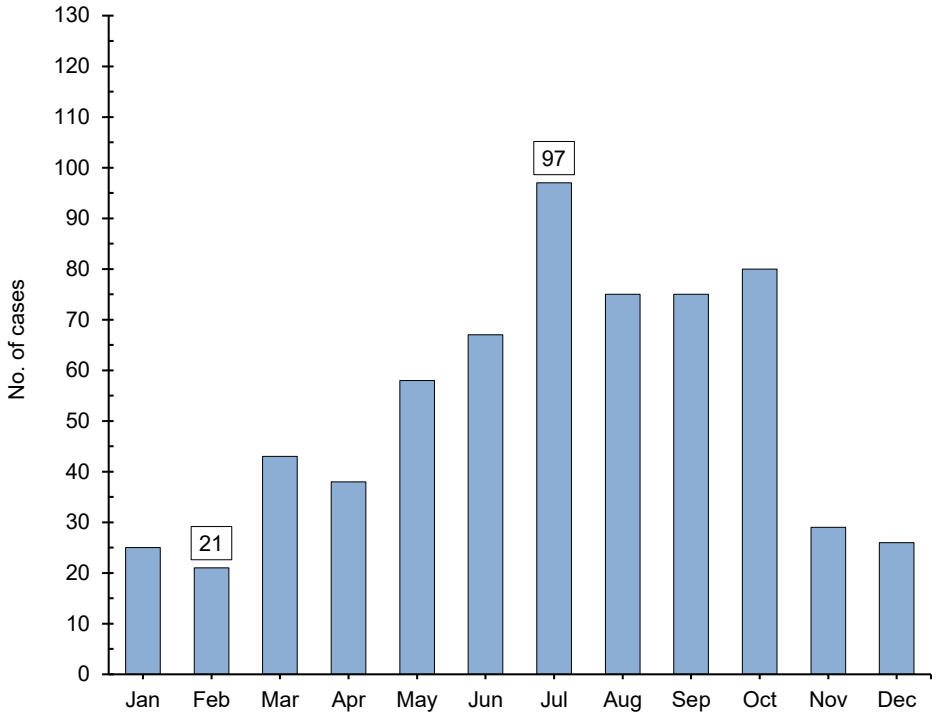
	Presumed location of infection acquisition						
Location where diagnosed or reported from	Korea	Afghanistan	Africa	South/ Central America	Other or unknown location	Total for location of diagnosis or report	% of total 2018 cases
Womack Army Medical Center, Fort Bragg, NC	0	10	1	0	0	11	19.0
Carl R. Darnall Army Medical Center, Fort Hood, TX	2	0	1	0	1	4	6.9
Camp Lacy, Bagram, Afghanistan	0	4	0	0	0	4	6.9
Location not reported	0	1	2	0	2	5	8.6
Landstuhl Regional Medical Center, Germany	0	1	2	0	0	3	5.2
Evans Army Community Hospital, Fort Carson, CO	0	1	0	0	1	2	3.4
Fort Belvoir Community Hospital, VA	0	0	1	0	1	2	3.4
Guthrie Ambulatory Health Care Clinic, Fort Drum, NY	0	0	2	0	0	2	3.4
Brian Allgood Army Community Hospital, Seoul, South Korea	2	0	0	0	0	2	3.4
Camp Casey, Tongduchon, South Korea	2	0	0	0	0	2	3.4
673rd Medical Group, Joint Base Elmendorf-Richardson, AK	0	0	0	0	1	1	1.7
Naval Medical Center, San Diego, CA	0	0	1	0	0	1	1.7
Irwin Army Community Hospital, Fort Riley, KS	0	0	0	0	1	1	1.7
Blanchfield Army Community Hospital, Fort Campbell, KY	0	0	0	0	1	1	1.7
Walter Reed National Military Medical Center, Bethesda, MD	0	0	0	0	1	1	1.7
General Leonard Wood Army Community Hospital, Fort Leonard Wood, MO	1	0	0	0	0	1	1.7
341st Medical Group, Malmstrom Clinic, MT	0	0	1	0	0	1	1.7
William Beaumont Army Medical Center, TX	0	1	0	0	0	1	1.7
59th Medical Wing, Wilford Hall Ambulatory Surgical Center, Joint Base San Antonio-Lackland, TX	0	0	1	0	0	1	1.7
75th Medical Group, Hill Air Force Base Medical Clinic, UT	0	0	0	0	1	1	1.7
Naval Medical Center, Portsmouth, VA	0	0	0	0	1	1	1.7
Troop Medical Clinic, Fort Richardson, AK	0	1	0	0	0	1	1.7
87th Medical Group, Joint Base McGuire-Dix-Lakehurst, NJ	0	0	1	0	0	1	1.7
628th Medical Group, Joint Base Charleston, SC	0	0	0	1	0	1	1.7
Army Health Clinic, Vicenza, Italy	0	0	0	0	1	1	1.7
Robinson Health Clinic, Fort Bragg, NC	0	1	0	0	0	1	1.7
Remote location within the U.S.	0	0	0	0	2	2	3.4
Expeditionary Medical Facility, Djibouti	0	0	1	0	0	1	1.7
Army Health Clinic, Camp Humphreys, Pyeongtaek, South Korea	1	0	0	0	0	1	1.7
Army Health Clinic, Yongsan, South Korea	1	0	0	0	0	1	1.7
Total	9	20	14	1	14	58	

Naval Hospital Oak Harbor, Naval Hospital Bremerton, Air Force Medical Services Fairchild, and Madigan Army Medical Center. Therefore, the medical encounter data for individuals seeking care at 1 of these facilities were not captured in this analysis.

This *MSMR* report represents the first time that cases were included if they had a positive malaria antigen test plus an outpatient record with a diagnosis of malaria in any diagnostic position within 30 days of the specimen collection date. The relative accuracy of this revised case definition in estimating malaria incidence is corroborated by the results of a study in this issue of the *MSMR*.[26] It is estimated that this modification of the case definition added about 10 cases over the 10-year surveillance period on top of the 624 cases that were identified in the reportable events and hospitalizations data. Diagnoses of malaria that were documented only in outpatient settings without records of a positive malaria antigen test and that were not reported as notifiable events were not included as cases. Also, the locations of infection acquisitions were estimated from reported relevant information. Some cases had reported exposures in multiple malarious areas, and others had no relevant exposure information. Personal travel to or military activities in malaria-endemic countries were not accounted for unless specified in notifiable event reports.

As in prior years, in 2018 most malaria cases among U.S. military members were treated at medical facilities remote from

FIGURE 3. Cumulative numbers of diagnoses and reported cases of malaria, by month of clinical presentation or diagnosis, U.S. Armed Forces, January 2009–December 2018



malaria endemic areas. Providers of acute medical care to service members (in both garrison and deployed settings) should be knowledgeable of and vigilant for the early clinical manifestations of malaria among service members who are or were recently in malaria-endemic areas. Care providers should also be capable of diagnosing malaria (or have access to a clinical laboratory that is proficient in malaria diagnosis) and initiating treatment (particularly when *P. falciparum* malaria is clinically suspected).

Continued emphasis on adherence to standard malaria prevention protocols is warranted for all military members at risk of malaria. Personal protective measures against malaria include the proper wear of permethrin-treated uniforms and the use of permethrin-treated bed nets, the topical use of military-issued DEET-containing insect repellent, and compliance with prescribed chemoprophylactic drugs before, during, and after times of exposure in malarious areas. Current Department of Defense guidance about medications for prophylaxis of malaria summarizes the roles of chloroquine, atovaquone-proguanil, doxycycline, mefloquine, and primaquine.[27]

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Re-evaluation of the *MSMR* Case Definition for Incident Cases of Malaria

Francis L. O'Donnell, MD, MPH (COL, USA, Ret.); James D. Mancuso, MD, DrPH (COL, MC, USA); Shauna Stahlman, PhD, MPH

The *MSMR* has been publishing the results of surveillance studies of malaria since 1995. The standard *MSMR* case definition uses Medical Event Reports and records of hospitalizations in counting cases of malaria. This report summarizes the performance of the standard *MSMR* case definition in estimating incident cases of malaria from 2015 through 2017. Also explored was the potential surveillance value of including outpatient encounters with diagnoses of malaria or positive laboratory tests for malaria in the case definition. The study corroborated the relative accuracy of the *MSMR* case definition in estimating malaria incidence and provided the basis for updating the case definition in 2019 to include positive laboratory tests for malaria antigen within 30 days of an outpatient diagnosis.

WHAT ARE THE NEW FINDINGS?

The *MSMR* case definition provides an estimate of the incidence of malaria in the U.S. Armed Forces. This case definition was updated to include an outpatient healthcare encounter associated with a laboratory test that is positive for malaria parasite antigen.

WHAT IS THE IMPACT ON READINESS AND FORCE HEALTH PROTECTION?

Careful diagnostic evaluation, documentation of confirmed diagnoses, and submission of Medical Event Reports for malaria are crucial for surveillance of the health of the force. Targeted surveillance of special operations forces, members of the Reserve/National Guard, and those stationed in OCONUS embassies would improve DoD malaria risk estimates.

Surveillance for the occurrence of cases of malaria among members of the U.S. Armed Forces has been historically important for many reasons. During World War II, the Korean and Vietnam conflicts, and more recent combat operations in Afghanistan and Somalia, service in regions endemic for malaria was associated with a high incidence of malaria. During World War II, even service at military bases in the southeastern U.S. carried a risk for malaria. Today, the threat of malaria is most apparent for those serving in Korea, Afghanistan, and Africa, but risk also applies for many other regions where transmission still occurs. Surveillance for malaria cases is intended to generate actionable information, in other words, information useful in making policy and command decisions to carry out actions to reduce or eliminate the threat of the disease and the associated morbidity and mortality among service members. For malaria, there are many possible preventive measures, including controlling mosquito vectors (e.g., through the identification and elimination of mosquito breeding sites, as well as the use of pesticides, netting, and repellants on clothing and exposed skin) and using antimicrobial agents to kill infective *Plasmodia* through chemoprophylaxis and treatment of human malaria infections. In addition, surveillance can provide information about the efficacy of such actions and the extent to which they are being carried out.

The *MSMR* has published the results of surveillance studies of malaria cases in service members since 1995.[1] Initial studies counted mainly the Medical Event Reports (MERs) of cases of malaria submitted through the Reportable Medical Events System (RMES) for conditions deemed notifiable because of their public health importance. In 2002, the *MSMR* added diagnoses of malaria made during hospitalizations to its surveillance case definition.[2] Diagnoses from hospitalizations were counted only if they were recorded in the first diagnostic position of the record of hospitalization. In the January 2011 annual *MSMR* update on malaria cases, a more detailed case definition was used for the first time. The most noteworthy change in the new case definition was the addition of cases from some hospitalization records in which the diagnosis of malaria was not in the first diagnostic position.[3] The details of that case definition are described in the Methods section.

The January 2012 *MSMR* presented the results of an analysis of sources of variability in estimates of malaria case counts. Counts of MERs of malaria, hospitalizations with diagnoses of malaria, and outpatient encounters with diagnoses of malaria were examined. Additional factors considered were diagnoses that listed a particular species of *Plasmodium*, patient histories of travel to malarious countries, and laboratory tests ordered and found positive for malaria. The findings of that analysis prompted no changes to the *MSMR* criteria for cases of malaria.[4]

This report describes an analysis that re-examined the *MSMR* criteria for counting cases of malaria as well as other possible surveillance criteria for identifying cases among members of the U.S. Armed Forces. The goal of the analysis was to evaluate the use of current and possibly revised criteria in arriving at surveillance estimates for the

incidence of malaria. Surveillance diagnoses of malaria based upon administrative and public health records lack complete clinical information that would permit validation of apparent cases and exclusion of misdiagnoses. A potential misclassification bias in malaria surveillance data could limit the application of findings toward public health action.

This study performed an assessment of the validity of data sources used in malaria surveillance, including inpatient and outpatient records and MERs. The goal was a better understanding of the over- and under-estimation of malaria cases and how missclassification would impact confidence in the estimates of the true burden of malaria disease. Also explored in this analysis were factors that may affect the under- or over-reporting of malaria, such as service in special operations, in the reserve and National Guard, during deployment, and overseas.

METHODS

The surveillance period was 1 January 2015 through 31 December 2017. The surveillance population included all individuals who served in an active or reserve component of the U.S. Army, Navy, Air Force, or Marine Corps at any time during the surveillance period.

The *MSMR* case definition for a case of malaria used in annual updates for years 2010 through 2017 specified that a case is defined as an individual with documentation of 1 of the following: 1) an MER record of confirmed malaria, 2) a hospitalization record with a diagnosis of malaria in the first (primary) diagnostic position, 3) a hospitalization record with a non-primary diagnosis of malaria due to a specific *Plasmodium* species, 4) a hospitalization record with a non-primary diagnosis of malaria plus a diagnosis of anemia, thrombocytopenia and related conditions, or malaria complicating pregnancy in any diagnostic position, or 5) a hospitalization record with a non-primary diagnosis of malaria plus diagnoses of signs or symptoms consistent with malaria (as listed in the *Control of Communicable Diseases Manual*, 18th Edition) in each diagnostic position antecedent to malaria.[5] The relevant ICD-9 and ICD-10 codes are shown in the first table of the annual update for 2018 (pages 2–7 of this issue).[6] This analysis allowed 1 case of malaria per service member per 365-day period. When multiple records documented a single episode, the date of the earliest encounter was considered the date of clinical onset, and the most specific diagnosis was used to classify the *Plasmodium* species.

To identify additional malaria cases that did not meet the *MSMR* case definition, further review of inpatient, outpatient, RMES, and laboratory data was performed. The standardized records of the Defense Medical Surveillance System (DMSS) were searched for all records of inpatient and outpatient healthcare encounters for which a diagnosis of malaria was documented. DMSS records of MERs of notifiable cases of malaria were also captured. All MERs that reported malaria were examined whether the diagnosis was described as "confirmed" or not (e.g., unconfirmed, suspect, possible, or pending).

Malaria diagnoses that were recorded only in the records of outpatient encounters (i.e., not hospitalized or reported as a notifiable event) have not been considered case-defining in previous analyses because of concerns with poor predictive value. In this analysis, such encounters were examined to assess the possibility that true cases of malaria might be overlooked among individuals with only outpatient diagnoses of malaria. The Navy and Marine Corps Public Health Center (NMCPHC) provided records of all laboratory tests for malaria that were positive during the surveillance period. The NMCPHC identified positive and suspect cases of malaria by querying the Composite Health Care System Health Level 7 (HL7) chemistry and microbiology laboratory databases for records that contained the terms "plasmodium" or "malaria." Positive laboratory tests included microscopic identification of plasmodium on thin and thick smears and plasmodium positive antigen rapid diagnostic tests. Malaria antibody tests were excluded. Only positive test results were included. Individuals with negative laboratory test results could not be distinguished from individuals who had not been tested. Such positive tests were linked to the records of healthcare encounters (both inpatient and outpatient) and of MERs. In an attempt to validate the identification of malaria cases using the *MSMR* case definition, the clinical records of a subset of cases and non-cases were reviewed using the electronic health records in the Armed Forces Health Longitudinal Technology Application (AHLTA).

Random samples of 25 malaria cases that met the *MSMR* case definition and of 25 individuals whose records did not meet the case definition were selected. Individuals who did not meet the *MSMR* case definition included those whose only malaria diagnoses were in the records of outpatient encounters, those whose only malaria diagnosis was recorded in an unconfirmed MER, or those whose hospitalization diagnoses of malaria did not meet the case definition criteria. Cases were validated by reviewing military electronic outpatient and inpatient records, with an emphasis on laboratory confirmation, provider evaluation and assessment, and medications consistent with a malaria diagnosis. There were 4 additional patients for whom medical records did not have sufficient information because of hospitalization at non-military facilities. Those patients were contacted directly to obtain the additional records needed to confirm case status. Correction factors obtained from these samples were applied to the total population of individuals who had at least 1 outpatient encounter, 1 hospitalization, or 1 MER with a diagnosis of malaria to obtain weighted estimates of the true burden of malaria.[7] The false positive and false negative cases were closely examined for factors potentially related to misclassification, such as service in overseas deployed locations, in the National Guard or Reserve, or in special operations assignments. When applied, exact confidence intervals were used because of small sample sizes.

RESULTS

During the 3-year surveillance period, there were 1,028 instances in which a diagnosis of malaria was recorded in a record

of an MER (n=121), an inpatient encounter (n=82), or an outpatient encounter (n=825). A total of 319 unique service members accounted for these diagnoses.

Malaria cases based on the *MSMR* case definition

A total of 132 cases of malaria, among 131 unique individuals, were identified using the *MSMR* case definition. (One service member had separate diagnoses of malaria 21 months apart.) Of the 132 cases, 99 qualified as cases on the basis of a "confirmed" MER and 75 on the basis of a hospitalization that met the criteria for a case. Many cases (n=42) met the case definition criteria on the basis of both a confirmed MER and a hospitalization, but 57 cases were based upon only a confirmed MER and 33 cases were based upon only a hospitalization **(Table 1)**.

MERs

Of the 121 MERs submitted for a diagnosis of malaria, 105 of them were characterized as "confirmed" diagnoses. Six of the 105 were duplicate reports for episodes of illness already reported via MERs, so there were 99 MER cases of malaria among 98 individuals. Of the 121 MERs submitted, 16 did not characterize the diagnosis of malaria as confirmed. However, 8 of those individuals otherwise met the *MSMR* case definition for malaria by virtue of a separate "confirmed" MER (n=4), a record of hospitalization that met the criteria for a case (n=7), or both (n=3) **(Table 1)**.

Hospitalizations

Among the 82 hospitalizations associated with recorded diagnoses of malaria, 2 did not meet any of the *MSMR* criteria for a hospitalized case of malaria. Of the remaining 80 hospitalizations, 73 had the diagnoses recorded in the first diagnostic position, but 5 of those hospitalizations were repeat hospitalizations within 365 days of a prior such hospitalization, so there were 68 cases that met the case criteria based upon the first diagnostic position. For the 7 hospitalized cases with malaria diagnoses not in the first diagnostic position, 4 met the case definition by virtue of a species-specific diagnosis for malaria, and the records of 3 cases included accompanying diagnoses indicative of malaria. A total of 75 hospitalizations met the case definition criteria for cases of malaria **(Table 1)**.

TABLE 1. Distribution of records with diagnoses of malaria according to the *MSMR* criteria for a "case" of malaria and associated positive laboratory tests for malaria

Records found that met *MSMR* criteria for a case	No. of records	+ Lab tests
A MER for malaria diagnosis described as "confirmed"	99	64
B Hospitalization with malaria diagnosis in the first diagnostic position	68	48
C Hospitalization with malaria diagnois in a secondary position but with species recorded	4	1
D Hospitalization with malaria diagnosis in a secondary position but with other qualifying diagnoses	3	0
Records found that failed to meet *MSMR* criteria for a case		
E MER for malaria diagnosis but not described as "confirmed"	16	8
F Hospitalization with malaria diagnosis in a secondary position but not meeting other criteria for a case	2	1
Cases based upon *MSMR* criteria	**No. of cases**	**+ Lab tests**
A alone	56	30
A and B	38	32
A and B and E	3	2
A and C	1	0
A and E	1	0
B alone	23	10
B and E	4	4
C alone	3	1
D alone	3	0
Records that did not meet any *MSMR* criteria for a case	**No. of records**	**+ Lab tests**
E alone	7	1
E and F	1	1
F alone	1	0
Individuals with only outpatient encounters for malaria (not cases by *MSMR* criteria)	**No. of individuals**	**+ Lab tests**
Individuals with only outpatient encounters	179	4
Those with just 1 outpatient encounter	157	1
Those with 2 outpatient encounters	10	1
Those with 3 outpatient encounters	6	2
Those with 4 to 15 outpatient encounters	6	0

Outpatient encounters with diagnoses of malaria

Of the 319 unique individuals associated with malaria diagnoses in records of inpatient or outpatient encounters or MERs, 291 service members had at least 1 outpatient encounter with a recorded diagnosis of malaria, and 28 service members had no outpatient encounters with diagnoses of malaria. Of the 132 cases that met the *MSMR* case definition for malaria (among 131 individuals), 111 cases had at least 1 outpatient encounter with a recorded diagnosis of malaria, and 21 cases had no associated outpatient malaria diagnoses. Of the 188 service members who did not meet

the *MSMR* case definition for malaria, 181 had at least 1 outpatient encounter with a recorded diagnosis of malaria and 7 had no outpatient diagnoses of malaria.

Among those 179 service members who had only outpatient diagnoses of malaria and thus did not meet the *MSMR* case definition for malaria, 22 had more than 1 such encounter and 157 had only a single outpatient encounter **(Table 1)**.

Positive laboratory tests for malaria

The NMCPHC identified 503 positive laboratory tests for malaria during the period. Those positive results were associated with 88 distinct service members, 78 of whom had records that met the *MSMR* case-defining criteria for malaria (79 cases) and 10 of whom had no such case-defining diagnosis.

Laboratory results among cases

Among the 99 cases of malaria associated with an MER of confirmed malaria, 64 had a positive laboratory test and 35 did not. Among the 75 cases of malaria associated with a hospitalization that met the *MSMR* criteria for a malaria case, 49 had a positive laboratory test and 26 did not. Among the 42 cases that met both the MER and hospitalization *MSMR* criteria for a malaria case, 34 cases had positive laboratory results and 8 did not **(Table 1)**.

Laboratory results among non-cases

Among the 9 service members who did not meet the *MSMR* criteria on the basis of a non-confirmed diagnosis of malaria in an MER (n=8), a hospitalization that did not meet the criteria (n=2), or both (n=1), 2 had positive laboratory tests (for plasmodial antigen) and 7 did not. The service member with a positive laboratory test who failed to meet both criteria was hospitalized for severe trauma; malaria was the eighth diagnosis listed in the hospitalization record. The other service member in this category was reported as a "not confirmed" case of malaria in an MER. The individual had a positive laboratory test during pre-deployment screening for blood banking purposes, but it was determined that the result was highly likely a false positive based upon lack of symptoms and having grown up in Africa. The service member was not treated for malaria.

Laboratory results among individuals who had only outpatient encounters

Of the 179 service members whose only malaria diagnoses were found in the records of outpatient encounters, 22 individuals had more than 1 outpatient encounter. Three of the 22 were found to have at least 1 positive laboratory test for *P. falciparum* antigen. One of these service members had 2 outpatient encounters 2 days apart in Germany. The first encounter listed only the diagnosis for falciparum malaria, and the second encounter included only the codes for falciparum malaria and for personal history of malaria. Chart review indicated that the service member had been evacuated from a deployment in Africa, but there were no documented hospitalizations or MERs for this individual. The other 2 service members with positive laboratory results each had 3 outpatient encounters at Fort Bliss, TX, for which the records listed falciparum malaria and unspecified malaria as diagnoses. The encounters for the 2 service members were during January to March 2015 and July to August 2015, respectively. Chart reviews indicated that, coincidentally, the initial outpatient encounters for each took place about 2 weeks after return from a visit to families in Cameroon. Again, there were no documented hospitalizations or MERs for either individual. Among the 157 service members with a single outpatient encounter, just 1 was found to have a positive laboratory test but it was not an antigen test. Clinical assessment concluded that it was probably a false positive smear test in an individual who did not have a travel history compatible with a risk of acquiring malaria.

Review of clinical records of selected cases and possible cases

In an attempt to validate the identification of malaria cases using the *MSMR* case definition, the clinical records of a subset of cases and non-cases were reviewed using the electronic records in AHLTA. Of particular interest were the findings in the records of some of the individuals who had only outpatient records of malaria diagnoses. Three of the 4 outpatient records with associated positive laboratory tests for malaria appeared to represent true cases of malaria based upon positive tests for malaria antigen, more than 1 outpatient diagnosis of malaria, and encounter records describing circumstances highly indicative of clinical malaria. The records for the fourth possible case indicated that the laboratory test was not an antigen test and the clinical assessment included information that made a diagnosis of malaria seem unlikely.

Additional clinical records were reviewed for random samples of 25 service members who met the *MSMR* case definition criteria for malaria and 25 who did not meet the case definition but who had some documentation for malaria indicated by outpatient or inpatient diagnoses, laboratory tests, or unconfirmed MERs. Two of the 25 surveillance cases of malaria could not be validated as cases by chart reviews. Three of the 25 individuals whose records did not satisfy the criteria of the *MSMR* case definition were judged to be true malaria cases on the basis of chart reviews **(Table 2)**.

In the sample, the correction factors were 92% (23/25) and 12% (3/25) **(Table 2)**. These are the proportion of *MSMR* case definition identified cases that would be assigned as cases based on chart review and the proportion of non-*MSMR* case definition identified cases that would be assigned as cases based on chart review, respectively. After applying the correction factors to the total number of malaria cases observed among those that met (n=132) and did not meet (n=188) the *MSMR* case criteria during the surveillance period, the estimated true number of cases was calculated to be 144 **(Table 3)**. This was 9% higher than the number of cases (n=132) identified when using the *MSMR* case definition.

Of the 22 individuals who were true negative cases, 13 (59%) had malaria diagnoses recorded during healthcare encounters prior to travel to malarious areas, 5 (23%) had symptoms of other pathology or were ruled out for malaria, and the clinical records of 4 (18%) had no corroborating evidence of a malaria diagnosis or of malaria treatment in outpatient or inpatient records.

TABLE 2. Comparisons of malaria diagnoses achieved through *MSMR* case definition to diagnoses confirmed with chart review

	Conclusions following chart review about presence of malaria		
Surveillance using *MSMR* case definition criteria	Malaria	Not malaria	Total
Records met the *MSMR* case definition criteria	23	2	25
Records did not meet case definition criteria	3	22	25

MSMR case correction factor: 92% (95% CI: 74–99)

MSMR non-case correction factor: 12% (95% CI: 3–31)

CI, confidence interval

TABLE 3. Validated malaria status in the U.S. Armed Forces corrected for misclassification

	Estimated malaria cases based upon results of chart review		
Surveillance using *MSMR* case definition criteria	Malaria cases (95% CI)	Not malaria (95% CI)	Total
Met case definition	121.4 (97.6–130.7)	10.6 (1.3–34.4)	132
Did not meet case definition	22.6 (4.8–58.7)	165.4 (129.3–183.2)	188
Total	144 (113.7–174.3)	176 (145.7–206.3)	320

Ratio of estimated true malaria cases (144) to those meeting *MSMR* case definition (132): 1.09 (95% CI: 0.86–1.32)

CI, confidence interval

Of the 23 true positive cases, 17 (74%) had a positive laboratory test in electronic medical records. All of the other 6 had plausible exposures to malarious areas. Two were diagnosed while deployed, 1 to Afghanistan and 1 to Djibouti, and both cases had a physician note stating that a positive test result had been obtained. One was clinically assessed as malaria and was treated presumptively before laboratory testing was performed. Two had physician notes from civilian medical facilities stating that testing had been performed and that the diagnosis was confirmed. There were 5 who contracted malaria while visiting friends and relatives overseas. One was a soldier who had been assigned to an embassy in Africa, and his records were only available through direct patient contact. The locations of presumed malaria transmission were Africa (14, including 2 exclusively in Djibouti), Korea (5), and Afghanistan (4). There were 10 documented cases of *P. falciparum*, 4 with *P. vivax*, and 9 that were unspecified. There were 7 treated with artemeter/lumefantrine, 8 with atovaquone/proguanil, 2 with chloroquine (*P. vivax* cases only), 1 with artesunate, and 5 with unspecified treatment.

Among the 2 false positive cases, there was 1 Army National Guardsman and 1 Navy Reservist. The Army soldier had already been discharged from the National Guard 3 months prior to diagnosis. Among the false negative cases, there were 2 special operations service members and 1 soldier who had recently returned from Embassy service in Africa. All 3 had sought care in civilian medical treatment facilities.

EDITORIAL COMMENT

The analysis indicated that the use of MERs and hospitalization records were reasonable approaches to estimating the incidence of cases of malaria among service members. Diagnoses of malaria documented in MERs or in records of hospitalizations were the result of careful evaluations of incident illnesses. This report shows that after accounting for misclassification, the estimated number of true malaria cases between 2015 and 2017 was 144 (95% CI: 126–162), which was very close to the *MSMR* case definition estimate of 132. Most of the correctly classified non-cases were associated with pre-travel outpatient visits during which malaria prophylaxis was given. Among the small number of misclassified true cases of malaria, all had a history of service either in special operations, an overseas embassy, or the National Guard or Reserve component. All of the false negatives had been hospitalized at a civilian medical treatment facility. Of particular interest was the observation that, although outpatient encounters with recorded diagnoses of malaria alone did not add greatly to the total numbers of cases, the association of such outpatient encounters with contemporaneous positive laboratory tests for malaria did appear to identify a few additional cases of malaria during the surveillance period. For this reason, the *MSMR* case definition has been modified to add a category of case defined by a positive laboratory test for malaria antigen in an individual who had a record of an outpatient diagnosis of malaria within 30 days of the specimen collection date.

The submission through the Disease Reporting System Internet (DRSi) of an MER of a reportable condition such as malaria is dependent upon the investigation by local public health authorities of possible cases occurring within their area of responsibility.[8] In the case of malaria, preparation of an MER would require not only knowledge of a specific individual with an illness whose signs and symptoms are compatible with malaria, but also knowledge of the results of laboratory tests that confirm the diagnosis. Collection of such information presumes that the public health official has gathered such information from medical staff caring for the individual, the laboratory, and the ailing individual (for information about relevant travel and deployment history and use of chemoprophylaxis). Given the need for such information to justify the submission of an MER, it is reasonable to presume that an MER reporting a confirmed case of malaria represents credible surveillance information.

Because of the above description of the information that would warrant the

submission of an MER of confirmed malaria through DRSi, it would seem reasonable that there should be additional documentation in the Military Health System (MHS) electronic databases of 1 or more of the following for each MER confirmed case: a hospitalization record that lists a diagnosis of malaria, a record of an outpatient encounter that lists a malaria diagnosis, a positive laboratory test for malaria; or pharmacy documentation of treatment with anti-malarial medications. Such additional documentation would be most expected for cases that were diagnosed at fixed military medical facilities where local surveillance by public health personnel would collect the information needed to justify an MER of confirmed malaria.

For diagnoses of malaria reported by an MER from non-fixed military medical facilities, such as those in deployment settings, where the documentation of health care encounters and of laboratory test results may be less than complete, documentation in electronic databases may not adequately reflect all cases of malaria. Lack of confirmatory information may not only reduce the frequency with which local public health personnel can confirm true cases of malaria, but may also handicap the ability of centralized surveillance agencies like the Armed Forces Health Surveillance Branch (AFHSB) to ascertain cases.

Most, if not all, hospitalizations associated with a diagnosis of malaria met the detailed criteria of the *MSMR* case definition. Because hospitalization records in the DMSS contain discharge diagnoses, there is an underlying presumption that these diagnoses were recorded after initial diagnostic uncertainties had been resolved. Although tentative diagnoses of malaria may be considered by healthcare providers at the time of admission to hospital, the diagnosis is unlikely to appear in the list of final diagnoses unless the evaluation of the patient's illness and the patient's response to treatment for malaria are compatible with that diagnosis.

Another factor affecting the completeness of documentation of malaria cases is the provision of purchased health care to service members in civilian treatment facilities. Although the MHS receives documentation of such care that includes diagnoses such as malaria, the results of laboratory testing and the documentation of malaria treatment are often not available. Moreover, civilian healthcare providers do not prepare or submit MERs for reportable conditions such as malaria. For service members who are diagnosed and treated for malaria in the civilian healthcare setting, the preparation and transmission of an MER depends upon the initiative of the local military public health authorities. Moreover, service members treated for malaria by civilians in an outpatient setting might never be recognized as cases without efforts by military public health officials to collect the results of the relevant laboratory testing as the basis for submitting an MER of a confirmed case.

The use of records of outpatient encounters alone to define cases of malaria has not been adopted in the AFHSB case definition of malaria because of a variety of considerations. First, provisional or tentative diagnoses of malaria are often entered into outpatient records while the results of laboratory tests for malaria are pending. One previous analysis found that documentation of malaria laboratory test performance was infrequent for those with only outpatient diagnoses of malaria and that none of the laboratory tests performed was positive for malaria.[4] Second, miscoding of diagnoses of malaria may occur in conjunction with healthcare encounters for prescribing malaria chemoprophylaxis or provision of malaria prevention counseling. Lastly, inadvertent, erroneous use of malaria codes in encounter records may occur. Prior analysis has found a very low likelihood that a patient with only an outpatient diagnosis of malaria actually has malaria.[4]

The review of a subset of clinical records for individuals who did and did not meet the *MSMR* criteria for malaria cases was informative. As described above, outpatient diagnoses of malaria in association with positive tests for malaria antigen found in laboratory data did not meet the criteria for the existing *MSMR* case definition but were assessed as true malaria cases by chart review. For this reason, the *MSMR* has decided to add this group to the case definition. However, the small proportion of additional malaria cases (12%) found among the randomly selected individuals who did not meet the *MSMR* case definition (most of whom were found in outpatient data only) does not appear to justify further change to the case definition. While their inclusion would slightly increase the identification of malaria cases, it would also result in the inclusion of a large number of false positive cases.

The *MSMR* case definition used in this and previous issues of the *MSMR* closely matched the estimate of the true burden of malaria in the U.S. military obtained from chart review.[6] The lower estimates used by the Centers for Disease Control and Prevention in their surveillance reports reflect a strict case definition requiring lab confirmation by blood smear or polymerase chain reaction, which likely underestimates the true disease burden.[9]

The main limitation of this report is the absence of a true "gold standard" for malaria case status. The chart review adds additional information, getting closer to such a standard, but some of the records may have been incomplete, leading to persistent misclassification. Such missclassification is likely to lead to an underestimate of malaria since the likelihood of misclassification is greater in the cases not meeting the case definition because of incomplete records. However, this study demonstrates that the magnitude of this residual error is likely to be small.

This study suggests that the U.S. military should have confidence that the *MSMR* estimates are close to the true burden of malaria disease and that the impact and trends identified by surveillance are accurate. However, it also suggests that selected populations, including special operations, Reserve/National Guard, and those stationed in overseas embassies, should be targeted for increased active surveillance. Moreover, better capture of inpatient hospitalizations at civilian medical facilities is needed to ensure quality of care for the service member, communication of health issues to military providers, and proper surveillance by military public health authorities. Finally, Reportable Medical Events surveillance should be strengthened in order to provide the timeliness, accuracy, and precision needed to inform force health protection policy.

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Update: Incidence of Glaucoma Diagnoses, Active Component, U.S. Armed Forces, 2013–2017

Leslie Clark, PhD, MS; Steven Taubman, PhD; Shauna Stahlman, PhD, MPH

Glaucoma is an eye disease that involves progressive optic nerve damage and vision loss, leading to blindness if undetected or untreated. This report describes an analysis using the Defense Medical Surveillance System to identify all active component service members with an incident diagnosis of glaucoma during the period between 2013 and 2017. The analysis identified 37,718 incident cases of glaucoma and an overall incidence rate of 5.9 cases per 1,000 person-years (p-yrs). The majority of cases (97.6%) were diagnosed at an early stage as borderline glaucoma; of these borderline cases, 2.2% progressed to open-angle glaucoma during the study period. No incident cases of absolute glaucoma, or total blindness, were identified. Rates of glaucoma were higher among non-Hispanic black (11.0 per 1,000 p-yrs), Asian/Pacific Islander (9.5), and Hispanic (6.9) service members, compared with non-Hispanic white (4.0) service members. Rates among female service members (6.6 per 1,000 p-yrs) were higher than those among male service members (5.8). Between 2013 and 2017, incidence rates of glaucoma diagnoses increased by 75.4% among all service members.

WHAT ARE THE NEW FINDINGS?

The vast majority of glaucoma diagnoses in active component service members (97.6%) represent early stage disease (borderline or suspect glaucoma). Over the surveillance period, incidence rates of glaucoma diagnoses increased by 75.4% overall; the greatest increase occurred in service members <20 years of age, which may reflect improved detection among younger service members.

WHAT IS THE IMPACT ON READINESS AND FORCE HEALTH PROTECTION?

There is no cure for glaucoma, and vision loss caused by glaucoma does not return with treatment; treatment only stops or reduces the rate of new vision loss. Glaucoma prevention efforts should continue to focus on early detection through periodic and comprehensive eye examinations performed by an eye care professional (optometrist or ophthalmologist).

Glaucoma refers to a group of eye diseases that can damage the optic nerve and can result in vision loss and blindness. This condition is often, but not always, associated with elevated intraocular pressure (IOP), also called ocular hypertension. Elevated IOP can be the result of excessive production of aqueous humor, reduced flow of fluid out of the eye, or both. Aqueous humor is a transparent fluid that fills the anterior and posterior chambers of the eye and that flows passively out of the eye. Elevated pressure not relieved by treatment is believed to result in optic nerve damage in most affected individuals.[1] Usually, damage to the optic nerve and loss of visual field are gradual and painless; however, there is a form of the disease called acute angle closure in which the trabecular meshwork becomes blocked, leading to a rapid rise in IOP and eye pain. This urgent condition requires immediate treatment.[2]

A finding of elevated IOP alone is insufficient to diagnose glaucoma, but it is 1 of the findings that can be used to classify a patient with glaucoma suspect or borderline glaucoma. The American Academy of Ophthalmology defines glaucoma suspect as having 1 of the following findings in at least 1 eye: consistently elevated IOP, optic nerve deterioration or nerve fiber layer defect suggestive of glaucoma, or a visual field abnormality consistent with glaucoma. A diagnosis of primary open angle glaucoma (POAG) is supported when 2 or more of these findings are present, especially in the presence of other established risk factors.[3,4] POAG is the most common form of glaucoma. In this form, the drainage area between the cornea and the iris, which forms an angle, is open but aqueous fluid flow is inadequate. In angle-closure glaucoma, the angle is reduced or blocked by the iris. Other less common forms of the disease include steroid-induced glaucoma and disease associated with developmental anomalies and systemic syndromes. There are also congenital forms of the disease that are diagnosed at birth or in early childhood.[1] The end stage of the disease, termed absolute glaucoma, is total blindness.

Risk factors for the development of glaucoma include elevated IOP, being 60 years of age or older, being of black, Asian, or Hispanic race/ethnicity, and having a family history of glaucoma.[5,6] Comorbid conditions associated with increased risk for glaucoma include hypertension, diabetes, uveitis, eye injuries, and eye conditions requiring extended corticosteroid use.[6]

Among U.S. adults, glaucoma ranks among the top 3 most common causes of

blindness.[7] Estimates of glaucoma prevalence in the U.S. vary widely based on study population and whether estimates include those considered borderline or glaucoma suspect. Using data from the 2005–2008 National Health and Nutrition Examination Survey (NHANES), Gupta et al. estimated that the overall prevalence of glaucoma in U.S. civilians 40 years of age or older is 2.1%, which represents approximately 2.9 million cases.[8]

Glaucoma is considered a disqualifying condition for enlistment in the military.[9] Glaucoma that is diagnosed while in service but deemed resistant to treatment or that affects the visual field will be evaluated by a medical evaluation board for possible separation from service.[9] A prior *MSMR* analysis identified more than 117,000 incident cases of glaucoma in active component service members between 1998–2013 but noted that incidence rates had declined for those service members 44 years of age or older during the surveillance period.[10] In addition, 94.5% of cases were borderline or glaucoma suspect cases.[10] The current analysis updates the prior *MSMR* report using data from 2013–2017.

METHODS

The Defense Medical Surveillance System (DMSS) was used to identify all active component service personnel (Army, Navy, Air Force, and Marines) whose healthcare records contained a diagnosis of glaucoma during 1 January 2013 through 31 December 2017. The DMSS contains administrative records for all medical encounters of military service members who are hospitalized or receive ambulatory care at military treatment facilities or through civilian purchased care if paid for by the Military Health System. A case of glaucoma was defined as having 1) at least 1 inpatient encounter with a diagnosis of glaucoma in any diagnostic position, 2) at least 1 outpatient encounter from an optometry or ophthalmology clinic (Medical Expense and Reporting System code beginning with 'BBD', or 'BHC') with a diagnosis of glaucoma in any diagnostic position, or 3) at least 2 outpatient or in-theater (Theater Medical Data Store) medical encounters within 180 days with a diagnosis of glaucoma in any diagnostic position.

The incidence date was defined as the earliest medical encounter that qualified the service member as a case. An individual was counted as an incident case only once during the study period, and person-time for service members with glaucoma was censored at the time of the incident diagnosis. Service members with incident diagnoses prior to 2013 or with an incident diagnosis while in the reserve or guard components were excluded. Denominators for incidence rates of glaucoma were calculated based on the total active component person-time in years for each year in the study period. The ICD-9 and ICD-10 codes used to define glaucoma, including classification of glaucoma type, are provided in **Table 1**.

Disease progression was analyzed by evaluating changes in glaucoma type over time for each service member. A glaucoma case was estimated to have progressed if the incident diagnosis was for borderline, congenital, or unspecified glaucoma and was followed by a medical encounter with a diagnosis that was more specific or severe than the initial diagnosis (e.g., open-angle, angle-closure, or absolute).

In addition to estimating the incidence of glaucoma, the overall burden of glaucoma was measured by counting the number of medical encounters with a primary diagnosis of glaucoma. Risk factors for glaucoma were also identified. These conditions were defined by having at least 1 diagnosis in any diagnostic position of diabetes, family history of glaucoma, or uveitis **(Table 2)** occurring on or prior to the incident diagnosis of glaucoma.

The average time from incident diagnosis to separation from military service was measured overall and by incident glaucoma type. This analysis was performed on a sub-group of service members who left service between 2013 and 2017 and included incident cases of glaucoma that were diagnosed prior to 2013.

RESULTS

During the 5-year surveillance period, a total of 37,718 incident cases of glaucoma were identified. This represents an overall incidence rate of 5.9 per 1,000 person-years (p-yrs) **(Table 3)**. The rate of incident glaucoma diagnoses among female service members (6.6 per 1,000 p-yrs) was 14% higher than that of male service members (5.8 per 1,000 p-yrs). The rate was highest among non-Hispanic black service members (11.0 per 1,000 p-yrs) and it was more than double the rate among non-Hispanic white service members (4.0 per 1,000 p-yrs). Rates among both Asian/Pacific Islander (9.5 per 1,000 p-yrs) and Hispanic (6.9 per 1,000 p-yrs) service members were also elevated in comparison with non-Hispanic white service members.

TABLE 1. Diagnostic and procedure codes used for glaucoma classification

Diagnosis classification	ICD-9[a]	ICD-10[a]
Congenital/childhood glaucoma	743.2*, 365.14	Q15.0
Borderline glaucoma (glaucoma suspect)	365.0*	H40.0*
Glaucoma unspecified	365, 365.9, 365.7*	H40.9
Open-angle glaucoma	365.1*	H40.1*
Angle-closure glaucoma	365.2*	H40.2*
Corticosteroid-induced glaucoma	365.3*	H40.6*
Glaucoma associated with anomalies and syndromes	365.4*, 365.5*, 365.6* (excluding 365.65), 365.8*	H40.89, H42, H40.5*, H40.8*, H40.4*
Glaucoma associated with trauma	365.65	H40.3*
Absolute glaucoma	360.42	H44.51*

[a]An asterisk (*) indicates that any subsequent digit/character is included

TABLE 2. ICD-9-CM codes used for predisposing conditions

Predisposing condition	ICD-9[a]	ICD-10[a]
Diabetes	250.*	E10*, E11*
Uveitis	360.11, 364.3	H44.13*, H20.9*
Family history of glaucoma	V19.11	Z83.511

[a]An asterisk (*) indicates that any subsequent digit/character is included

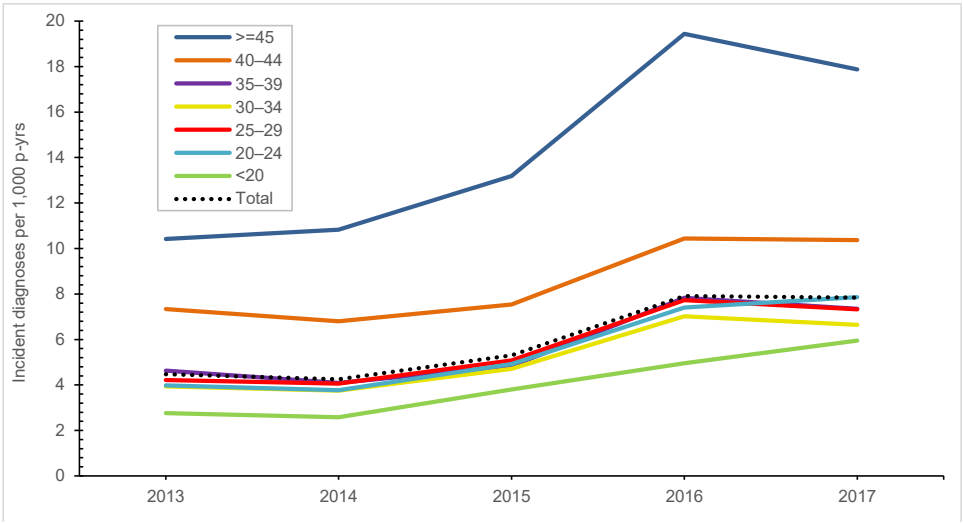
The incidence rate of glaucoma diagnosis increased with increasing age **(Table 3)**. Between 2013 and 2017, incidence rates of glaucoma diagnoses increased by 75.4% among all service members **(Figure)**. When viewed over time, rates among service members increased over the surveillance period in all age groups **(Figure)**. The rate in 2017 among service members aged 45 years or older was 17.9 per 1,000 p-yrs. This represents an increase of 71.5% from 2013. The 2017 rate demonstrated an 8% decline from the 2016 rate, which, at 19.4 cases per 1,000 p-yrs, was the highest rate during the surveillance period. Glaucoma diagnosis rates among service members younger than 20 years of age increased 115% over the study period. **(Figure)**

Overall, the incidence rate of glaucoma diagnosis was highest among Army personnel (7.0 per 1,000 p-yrs) and lowest among Marines (3.3 per 1,000 p-yrs) **(Table 3)**. Junior officers (5.5 per 1,000 p-yrs) had the lowest rates by grade, followed by junior enlisted (5.8 per 1,000 p-yrs) and senior enlisted (5.9 per 1,000 p-yrs) personnel. Senior officers had the highest rates of glaucoma diagnoses compared to their junior and enlisted counterparts. When stratified by occupational category, service members whose primary occupational code categorized them in healthcare or communications/intelligence occupations had higher rates of glaucoma diagnoses than those working in other occupations.

Diagnosis categories and disease progression

When the incident diagnoses were grouped by disease type, 97.6% of the cases were classified as borderline glaucoma or glaucoma suspect **(Table 4)**. The next largest category was POAG, which represented 1.2% of the cases. Less than 1 percent of the incident cases were coded as any other type of glaucoma. Of those service members with an initial diagnosis of borderline glaucoma, 2.2% later received a diagnosis of POAG or other more severe glaucoma diagnoses.

FIGURE. Incidence rates of glaucoma, by age (years) at diagnosis, active component, U.S. Armed Forces, 2013–2017



Burden

Among 37,718 diagnosed cases, there were 32,553 such medical encounters. An individual could become a diagnosed case without receiving a glaucoma diagnosis in the primary diagnostic position; however, to be counted in the burden analysis, a glaucoma diagnosis was required to be in the primary diagnostic position which accounts for the difference in the number of diagnosed cases versus the number of medical encounters ascertained in the burden analysis. **Table 5** shows the number and percentage of medical encounters when categorized by the glaucoma diagnosis made in the primary diagnostic position. Even though borderline glaucoma represented 97.6% of the incident cases, this diagnosis represented only 84.6% of total medical encounters with a glaucoma diagnosis in the first diagnostic position. The 1.2% of service members with an incident diagnosis of POAG or who progressed to POAG utilized 10.2% of total medical encounters.

Comorbidities

Overall, 1.6% of those with a glaucoma diagnosis had also been diagnosed with diabetes, while less than 1% (0.3%) of glaucoma cases had a family history of glaucoma documented via diagnosis prior to their glaucoma diagnosis. Pre-existing uveitis was more common among those with glaucoma associated with anomalies and other disorders (22.1%) and in those with unspecified glaucoma (4.0%), while overall, 1.1% of all incident glaucoma cases had a pre-existing uveitis diagnosis **(data not shown)**.

Career impact

The median time to separation or death among service members diagnosed with glaucoma did not vary much

TABLE 3. Incident counts and rates of glaucoma by demographic and military characteristics, active component, U.S. Armed Forces, 2013–2017

	No.	Rate[a]
Total	37,718	5.9
Sex		
Male	31,274	5.8
Female	6,444	6.6
Race/ethnicity		
Non-Hispanic white	15,116	4.0
Non-Hispanic black	11,058	11.0
Hispanic	6,218	6.9
Asian/Pacific Islander	2,315	9.5
American Indian/Alaska Native	307	4.7
Other/unknown	2,704	6.8
Age group (years)		
<20	1,805	4.1
20–24	11,400	5.6
25–29	8,556	5.6
30–34	5,306	5.2
35–39	4,032	5.7
40–44	3,378	8.4
45+	3,241	14.3
Service		
Army	16,651	7.0
Navy	9,188	5.9
Marine Corps	3,054	3.3
Air Force	8,825	5.8
Grade		
Junior enlisted (E1-E4)	16,431	5.8
Senior enlisted (E5-E9)	14,411	5.9
Junior officer (O1-O3; W01-W03)	3,806	5.5
Senior officer (O4-O10; W04-W05)	3,070	7.6
Occupation		
Combat-specific[b]	4,326	4.7
Motor transport	1,139	6.1
Pilot/air crew	1,011	4.2
Repair/engineering	10,661	5.7
Communications/intelligence	9,215	6.7
Health care	4,615	8.2
Other	6,751	5.6

[a]Rate per 1,000 person-years
[b]Infantry/artillery/combat engineering/armor

TABLE 4. Counts and percentages of incident diagnoses of glaucoma by diagnosis category, active component, U.S. Armed Forces, 2013–2017

	Incident diagnosis category		Progressed	
Diagnosis classification	No.	% of total	No.	%
Congenital/childhood glaucoma	2	0.0	0	0.0
Borderline glaucoma/glaucoma suspect	36,811	97.6	818	2.2
Glaucoma-unspecified	199	0.5	57	28.6
Primary open-angle glaucoma	450	1.2		
Angle-closure glaucoma	43	0.1		
Corticosteroid-induced glaucoma	91	0.2		
Glaucoma associated with anomalies, disorders	86	0.2		
Glaucoma associated with trauma	36	0.1		
Absolute glaucoma	0	0.0		
All types	37,718	100.0		

TABLE 5. Number of glaucoma-related encounters among service members diagnosed with glaucoma, active component, U.S. Armed Forces, 2013–2017

Diagnosis (first diagnostic position)	Medical encounters[a]	
	No.	% of total
Congenital/childhood glaucoma	6	0.02
Borderline glaucoma	27,553	84.64
Glaucoma-unspecified	641	1.97
Open-angle glaucoma	3,322	10.20
Angle-closure glaucoma	203	0.62
Corticosteroid-induced glaucoma	185	0.57
Glaucoma associated with anomalies, disorders	437	1.34
Glaucoma associated with trauma	202	0.62
Absolute glaucoma	4	0.01
All types	32,553	100.00

[a]Burden counts reflect the number of medical encounters with a primary diagnosis of glaucoma

when analyzed by the incident diagnosis. On average, the shortest amount of time served following the initial diagnosis with any type of glaucoma occurred among those initially diagnosed with corticosteroid-induced glaucoma (3.3 years), followed by those diagnosed with glaucoma associated with trauma (3.8 years) **(data not shown)**. The longest amount of time served following initial diagnosis occurred among those initially diagnosed with POAG (8.3 years). On average, service members served for 4.5 years following any initial glaucoma diagnosis **(data not shown)**.

EDITORIAL COMMENT

The results of this analysis indicate that most service members (97.6%) initially diagnosed with glaucoma are in the early stages of the disease (borderline or suspect glaucoma). This finding is similar to the previous *MSMR* analysis in which 94.5% of incident glaucoma diagnoses fell into this category.[10] These diagnoses of borderline glaucoma/glaucoma suspect may reflect cases with transient elevation in IOP, which may never result in nerve damage. Most types of glaucoma progress slowly and can

be managed well with medication to reduce aqueous fluid production or increase fluid outflow. Eventually, some cases may require surgery to enable better fluid drainage.[1,2] Among service members whose disease progressed beyond the borderline diagnosis, prior to separation from service or the end of the study period, the most common form of glaucoma was POAG.

The incidence rates of glaucoma diagnoses increased with age and among all age groups over the study period. The greatest increase over time in rates occurred among the youngest age groups. These findings may reflect improved detection of borderline glaucoma among younger service members. The striking increase in incidence rates in younger service members likely reflects increased ascertainment, possibly due to more frequent measurement of intraocular pressure in this population. Incidence rates by service were lowest among Marines, which likely reflects the younger age distribution of this service. Rates by occupational category at incident diagnosis were highest among healthcare workers, possibly due to increased healthcare-seeking behaviors in this group.

As seen in civilian populations, incidence of glaucoma was higher among non-Hispanic black, Asian/Pacific Islander, and Hispanic service members compared with non-Hispanic white or American Indian/Alaska Native service members.

Not surprisingly, the majority of medical encounters for glaucoma (85%) had a primary diagnosis indicating borderline or glaucoma suspect. Because the majority of incident cases in this analysis were classified as borderline glaucoma or glaucoma suspect, this finding is not unexpected. Notably, this finding differs from the previous *MSMR* analysis of glaucoma burden because of differences in the methodology used to assess the burden of disease. The 2014 *MSMR* analysis included any medical encounters with any diagnosis of glaucoma in any diagnostic position in assessing the burden of disease for glaucoma cases.[10] In addition, the prior burden analysis attributed glaucoma medical encounters to the most severe glaucoma diagnosis a case had received. In other words, if the most severe diagnosis a case had received was for POAG, burden medical encounters would be attributed to POAG, even when the medical encounter itself may have had a less severe diagnosis (e.g. borderline or glaucoma suspect) listed in the primary diagnostic position. In contrast, the current burden analysis classified medical encounters by the glaucoma diagnosis listed in the primary diagnostic position of the medical encounter, which is consistent with the standard *MSMR* burden methodology used in its annual burden analysis.[11] The net result of this difference in methodology is that fewer medical encounters overall were included in the burden analysis and a greater proportion of encounters were classified as borderline or glaucoma suspect. These findings should be interpreted in light of this methodological difference.

Most types of glaucoma cause no symptoms until damage to the optic nerve and visual field loss is substantial. For this reason, the National Eye Institute of the National Institutes of Health recommends that individuals with risk factors for glaucoma should receive regular comprehensive dilated eye exams. Those with increased risk include anyone with a family history of glaucoma, those with diabetes, African Americans older than 40 years of age, and individuals 60 years of age or older.[12]

One limitation of this analysis is that an unknown number of the incident diagnoses of borderline glaucoma may reflect a transient elevation of IOP, which, while properly identified during the medical encounter, may never progress to glaucoma, which requires damage to the optic nerve. Therefore, the incidence rates of glaucoma reported here are likely overestimates of the population truly at risk for advanced disease. It is also possible that many service members diagnosed with borderline glaucoma did not receive a subsequent diagnosis with a more advanced form of the disease during the period covered by this analysis because of the slow nature of the progression of the disease and the fact that many separate from service before the disease becomes problematic.

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Outbreak of Acute Respiratory Illness Associated with Adenovirus Type 4 at the U.S. Naval Academy, 2016

Amy E Rogers, MD, MPH (LCDR, MC, USN); Xiaoyan Lu, MS; Marie E. Killerby, VetMB, MPH; Elizabeth Campbell, BS, RN; Linda Gallus, MBA (CDR, MSC, USN); Edwin Kamau, PhD, MS (MAJ, MSC, USA); Irma B. Froh; Gosia Nowak, MSc, MPH; Dean D. Erdman, DrPH; Senthilkumar K. Sakthivel, PhD; Susan I. Gerber, MD; Eileen Schneider, MD, MPH; John T. Watson, MD; Lucas A. Johnson, MD, MTM&H (LCDR, MC, USN)

Human adenoviruses (HAdVs) are known to cause respiratory illness outbreaks at basic military training (BMT) sites. HAdV type-4 and -7 vaccines are routinely administered at enlisted BMT sites, but not at military academies. During August–September 2016, U.S. Naval Academy clinical staff noted an increase in students presenting with acute respiratory illness (ARI). An investigation was conducted to determine the extent and cause of the outbreak. During 22 August–11 September 2016, 652 clinic visits for ARI were identified using electronic health records. HAdV-4 was confirmed by real-time polymerase chain reaction assay in 18 out of 33 patient specimens collected and 1 additional HAdV case was detected from hospital records. Two HAdV-4 positive patients were treated for pneumonia including 1 hospitalized patient. Molecular analysis of 4 HAdV-4 isolates identified genome type 4a1, which is considered vaccine-preventable. Understanding the impact of HAdV in congregate settings other than enlisted BMT sites is necessary to inform discussions regarding future HAdV vaccine strategy.

WHAT ARE THE NEW FINDINGS?

In late summer 2016, the U.S. Naval Academy noted an increase in acute respiratory illness and conducted an investigation. Laboratory analysis confirmed adenovirus (HAdV-4) in 19 ill patients, and genetic sequencing confirmed a single strain of HAdV-4. This report provides new evidence of the impact of adenovirus at a federal military service academy.

WHAT IS THE IMPACT ON READINESS AND FORCE HEALTH PROTECTION?

Human adenoviruses (HAdVs) are known to cause respiratory illness outbreaks at basic military training (BMT) sites. HAdV type-4 and -7 vaccines are administered at enlisted BMT sites. Understanding the impact of HAdV in officer accession/training settings is necessary to inform discussions regarding HAdV vaccine strategy, reduce morbidity of respiratory illness in this population, and positively impact training throughout.

Human adenoviruses (HAdVs) are non-enveloped double-stranded DNA viruses and are common causes of upper and lower respiratory tract illness.[1] The multiple types of adenoviruses are associated with a spectrum of clinical presentations ranging from mild illness to severe disease and pneumonia.[1,2] HAdV types 4 (HAdV-4) and 7 (HAdV-7) have been associated with outbreaks of acute respiratory illness (ARI) among new recruits at U.S. enlisted basic military training (BMT) sites since the 1950s.[2-6] Because of evidence of multiple HAdV-4 and HAdV-7 outbreaks in enlisted BMT populations, routine vaccination against HAdV-4 and HAdV-7 at enlisted BMT sites was implemented in 1971 and resulted in a 50%–60% reduction in ARI.[7]

During a period of vaccine non-availability between 1999 and late 2011, rates of HAdV-related illness and hospitalizations increased dramatically at enlisted BMT sites, but rates rapidly declined following reintroduction of the vaccine in late 2011.[5,8] The cessation of the HAdV-4 and HAdV-7 vaccination resulted in outbreaks of HAdV associated ARI with attack rates as high as 5%–10% per week.[9-15] The HAdV-4 and HAdV-7 vaccine is a live oral vaccine approved for use in military populations 17–50 years of age.[16] This vaccine is recommended by the Department of Defense (DoD) for enlisted BMT recruits and is not currently recommended for routine administration in other populations, including federal service academies, such as the U.S. Naval Academy (USNA).[17] Occasionally, HAdV outbreaks have been reported in settings other than enlisted BMT sites, including colleges, inpatient and long-term care settings, and communities,[18–23] but the extent and frequency of such outbreaks in the U.S. are not well described. Additionally, ARIs have previously been described as a frequent cause of morbidity at the USNA,[24-25] and 1 study has implicated HAdV.[25]

Beginning in late August 2016, staff at the USNA Brigade Medical Clinic (BMC) noted an increase in the number of students presenting with ARI including fever above 100.5°F with pharyngitis. An investigation was performed to further characterize the etiology and magnitude of this ARI outbreak.

METHODS

Population and setting

The USNA is a 4-year coeducational federal service academy in Annapolis, MD. The student body is composed of approximately 4,400 students, with 1,100 students per class year; 25% of students are female. The USNA is both a military and academic training environment with living conditions comparable to civilian undergraduate institutions; all students reside in dormitory-style housing (maximum 4 persons per room), dine and socialize predominantly with members of their company (groups of approximately 150 students comprising students from all 4 class levels), and attend undergraduate courses with classmates of their year group. Students obtain non-emergency medical care at the BMC located within the dormitory facility. Dormitory-style housing at USNA with 2–4 persons per room differs substantially from Navy/Marine Corps BMT sites, where recruits are housed in open bay barracks housing 20 or more persons per room.

First-year students at USNA typically arrive on campus in early July to begin daily military training and strenuous physical conditioning prior to the start of the academic year in late August. Second-to-fourth-year USNA students return to campus in mid-August and host joint activities for all 4 year groups immediately prior to the resumption of the academic year. In 2016, first-year students reported on 1 July, and second-to-fourth-year students returned to campus on 18 August. Academic courses began on 22 August 2016.

ARI surveillance

Retrospective BMC medical visit data were obtained from the Military Health Data Repository System (MDR). The MDR is a centralized data repository that captures, archives, validates, integrates, and distributes healthcare data from the DoD worldwide network of over 260 facilities.[26] Records of clinical encounters encompassing the final 2 weeks of first-year student military training through the first 5 weeks of the academic term (8 August–25 September 2016) and the equivalent 7-week periods for the 2012–2015 academic years were reviewed to ascertain BMC visit numbers and rates. The combined mean of the 2012–2015 ARI visits and rates were used as the baseline. ARI visits and rates from 2016 were compared to the baseline for the equivalent 7-week period. Both initial visits and follow-up visits were included in the calculation of baseline rates. For the purposes of this investigation, an outbreak was defined as rates or visits for ARI that were more than 1.96 standard deviations above the baseline.

ARI was defined using a previously published standardized case definition that employed ICD-9 and ICD-10 diagnosis codes **(Table 1)**.[8] To better capture the impact of illness on clinical resources, patient visits (rather than affected students) were examined; students could be diagnosed with ARI more than once during the study timeframe. Demographic variables obtained for the 2016 patients included age, sex, company, and class year. For the period from 2012–2015, only data on ARI were accessed.

Laboratory investigations

All laboratory testing obtained was ordered by treating providers based upon clinical suspicion, recommended diagnostic protocols, and BMC clinic standard operating procedures.[23] When performed, nasopharyngeal (NP) swabs were tested for influenza by Sofia Influenza A+B

TABLE 1. ICD-9 and ICD-10 diagnosis codes for each of the 3 categories of acute respiratory illness (ARI)[a]

Acute upper respiratory infections	ICD-9[b]	ICD-10[b]
Acute nasopharyngitis [common cold]	460	J00
Acute pharyngitis	462	J02.9, J02.8
Acute tonsillitis	463	J03.9, J03.8
Acute laryngitis and tracheitis	464	J04
Acute laryngitis	464.0*	J04.0
Acute tracheitis	464.1*	J04.1*
Acute laryngotracheitis	464.2*	J04.2
Acute epiglottitis	464.3*	J05.1*
Croup	464.4*	J05.0
Supraglottitis, unspecified	464.5*	J04.3*
Acute upper respiratory infections of multiple or unspecified sites	465	J06
Acute laryngopharyngitis	465.0	J06.0
Other multiple sites	465.8	J06.9
Unspecified site	465.9	J06.9
Acute bronchitis and bronchiolitis		
Acute bronchitis	466.0	J20.9
Acute bronchiolitis	466.1	J21.9
Acute bronchiolitis due to other infectious organisms	466.19	J21.8
Pneumonia		
Pneumonia due to adenovirus	480.0	J12.0
Viral pneumonia, unspecified	480.9	J12.9
Bronchopneumonia, organism unspecified	485*	J18.0
Pneumonia, organism unspecified	486*	J18.9
Viral Illness		
Viral Illness	79.99	B34.9

[a]Table layout and ICD-9 codes taken from O'Donnell and Taubman, 2015[8]

[b]An asterisk (*) indicates that any subsequent digit/character is included

Fluorescent Immunoassay (FIA) (Quidel Corp., San Diego, CA). Oropharyngeal swabs (OP) were tested for Group A streptococci (GAS) by Sofia Strep A FIA (Quidel Corp).

Submission of clinical specimens for viral culture laboratory testing was based on the clinical suspicion of individual providers because early testing did not indicate that influenza or GAS were likely causative agents. Viral culture laboratory testing was initially performed at Walter Reed National Military Medical Center (WRNMMC) and then HAdV-4 positive specimens were transferred to the U.S. Centers for Disease Control and Prevention (CDC) for serotyping. Providers obtained increased numbers of samples commensurate with the initial increase in ARI cases and then later reduced the frequency of testing of patients after HAdV was identified on 9 September 2016 and was determined to be a likely cause of the increased ARI visits.

WRNMMC utilized R-Mix shell vial and D3 Ultra DFA Respiratory Virus Screening and ID Kit (Diagnostic HYBRIDS, Inc., Athens, OH) following manufacturer's recommendation with slight modifications. Briefly, specimens were inoculated onto cell monolayer in the R-Mix shell vials and stained for the presence of viral antigens using a pool of monoclonal antibodies directed against influenza A, influenza B, parainfluenza type 1, parainfluenza type 2, parainfluenza type 3, adenovirus, and respiratory syncytial virus. If virus-specific fluorescence was noted by screening, virus identification was performed using individual monoclonal antibodies staining.

At the CDC, HAdV-4 positive specimens were tested by a generic pan-HAdV real-time polymerase chain reaction (pan-rPCR) assay to confirm HAdV detection and typed by PCR and sequencing of hexon gene hypervariable regions 1-6 (HVR1-6)[28] and HAdV type-specific rPCR assays.[29] Specimens were also tested at the CDC for other respiratory pathogens by FTD Respiratory Pathogens 21 (FTD-21) real-time reverse transcription PCR (RT-PCR) (Fast-track diagnostics Ltd., Sliema, Malta), which tests for influenza A; influenza A (H1N1) swl; influenza B; rhinovirus; coronavirus NL63, 229E, OC43, HKU1; parainfluenza 1, 2, 3, 4; human metapneumovirus A/B; bocavirus; respiratory syncytial virus A/B; adenovirus; enterovirus; parechovirus; and *Mycoplasma pneumoniae*. For specimens that tested positive for both rhinovirus and enterovirus by FTD-21 rRT-PCR, RT-PCR and sequencing of partial VP4/VP2 region were performed to distinguish rhinovirus and enterovirus detection.[30]

CDC selected HAdV-positive specimens with sufficient volume and relatively low cycle threshold values representing patients infected at the beginning, middle, and end of the outbreak for genomic sequencing to identify similarities, and specimens were inoculated into A549 cells. For genomic sequencing, DNA libraries of the isolates were constructed using Nextera XT DNA Library Prep Kit (Illumina Inc., San Diego, CA) and paired-end sequencing was performed on the MiSeq using 500-cycle Miseq Reagent Kit V2 (Illumina Inc.). De novo assemblies were achieved using CLC Genomics Workbench v8.5.1 (CLCbio, Seoul, South Korea). Phylogenetic trees of nearly full genome sequences obtained in this study and selected from GenBank® were constructed using the neighbor-joining method implemented in MEGA7.[31,32] In silico restriction enzyme analysis of the HAdV-4 genomes was performed using Geneious v8.1.6 (Biomatters Ltd. Auckland, New Zealand), and genome types were determined using established guidelines and reference fragment patterns.[33,34]

Case identification and clinical presentation

A confirmed HAdV case was any USNA student evaluated and diagnosed with ARI by clinical staff with symptom onset occurring during 22 August–23 September 2016 and a positive result for HAdV by culture/immunofluorescence assay (IFA) or rPCR of a NP or OP swab. Individual BMC electronic medical records were reviewed for all students who had a NP or OP swab submitted for HAdV testing during 22 August–23 September 2016. In addition, hospital admissions records for all students admitted during 1 August–30 September 2016 were reviewed to account for admissions to medical facilities outside of the BMC. Navy Environmental Preventive Medicine Unit 2 clinical staff reviewed electronic health record data using a standardized questionnaire to obtain patient demographics, date of symptom onset, recent illnesses, symptom presentation, medical history, ill contacts, recent hospitalization, treatment, and radiologic findings. Medical record review and surveillance data were analyzed using Stata software, version 13.0 (StataCorp, College Station, TX) and SAS/STAT software, version 9.4 (2014, SAS Institute Inc., Cary NC). Categorical variables were reported as percentages in each category.

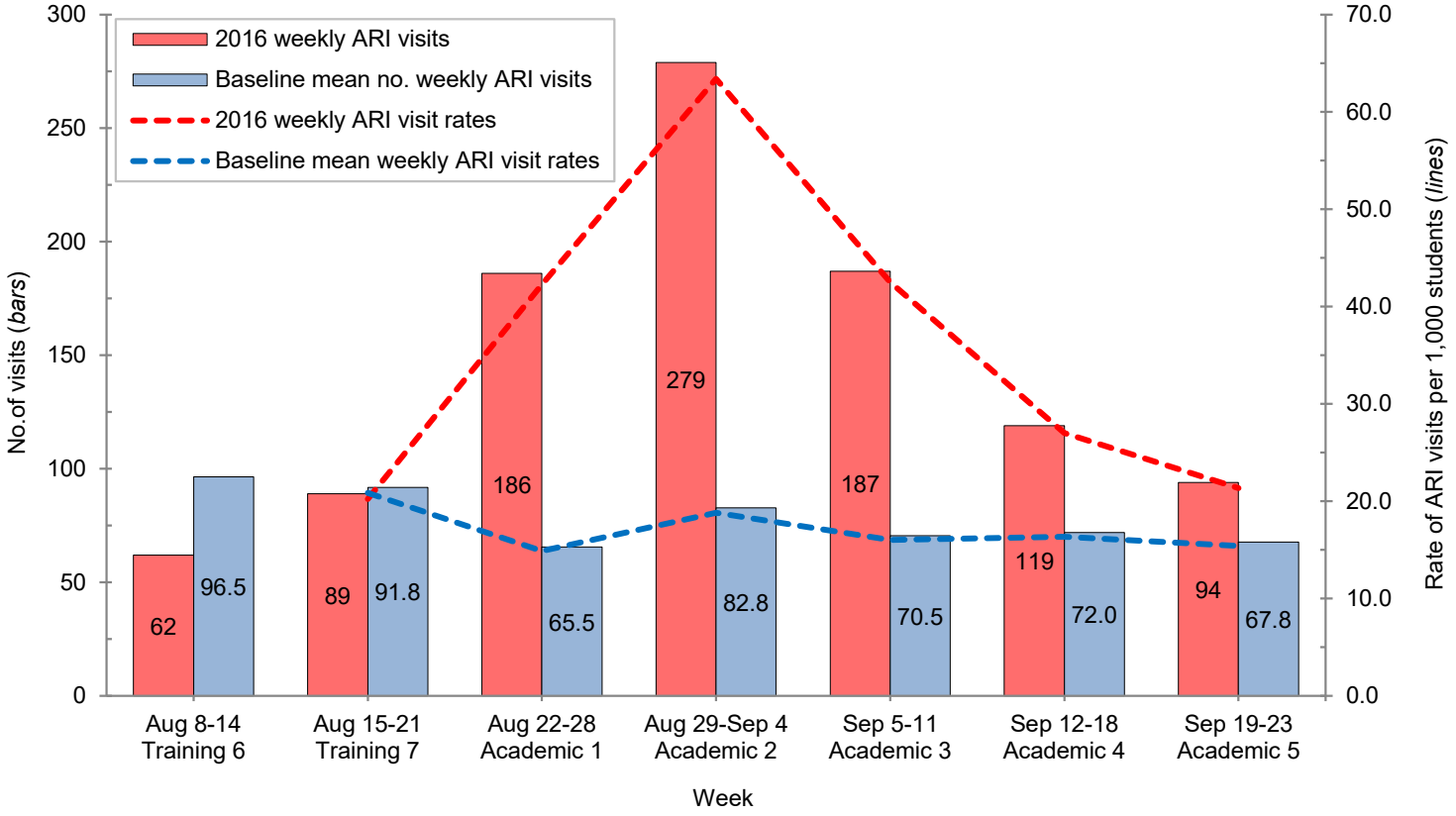
RESULTS

ARI surveillance

During 8 August–23 September 2016, 1,016 outpatient medical visits from 828 unique students (over 20% of the USNA student body) resulted in ARI diagnoses. During 22 August–11 September 2016, 652 outpatient medical visits (representing 547 unique students) resulted in ARI diagnoses, a value more than 3 standard deviations greater than the baseline value. Compared to baseline visits, an excess of 433 student ARI visits occurred during this 3 week period **(data not shown)**. Additionally, the 2016 ARI rate during the same 3-week period was 49 ARI cases per 1,000 students per week, a nearly 3-fold increase compared to the baseline rate **(data not shown)**.

During the first academic week (22 August–28 August 2016), 79% (131/165) of students presenting with illness were first-year students **(data not shown)**. Overall, 61.8% of all ARI-related visits in week 1 were for students 18 years or younger. During the second academic week (29 August–4 September 2016), the rate of ARI among all students (first-to-fourth-year students) peaked and was more than 3 times the baseline rate **(Figure 1)**. In the third academic week (5 September–11 September 2016), 75.4% (141/187) of all ARI-related visits were among students 19 years or older **(data not shown)**. Rates of ARI were similar between companies. Between 30.5% and 34.4% of the ARI patients who presented to clinic per week were female **(data not shown)**.

FIGURE 1. Diagnoses of acute respiratory illness (ARI), August–September 2016, U.S. Naval Academy



Laboratory investigation

During 22 August–23 September 2016, clinical lab samples from ARI cases included 156 rapid GAS tests (2.6% positive) and 28 rapid influenza tests (0% positive) **(data not shown)**. Lab samples for 33 patients were sent for viral testing, including for HAdV testing.

HAdV was detected by pan-rPCR in 26 of 46 (56.5%) specimens (NP: 17/33, 51.5%; OP: 9/13, 69.2%) representing 18 of the 33 patients (54.5%). Pan-rPCR detected HAdV from all culture/IFA positive samples (total: n=19 specimens, 16 patients) and from an additional 7 specimens representing 2 additional patients (total: n=26 specimens, 18 patients) who were culture/IFA negative **(data not shown)**. Hexon HVR1–6 sequencing and HAdV-type specific rPCR identified all HAdV positive samples as HAdV-4. Genome sequences (GenBank accession number MG030483-MG030486) obtained from 4 HAdV-4 isolates were identical with each other and showed 94.3% (accession number EF3710058.2) to 99.8% (accession numbers AY599835.1, AY599837.1 and KF006344.1) nucleotide sequence similarity to other representative HAdV-4 genomes available in GenBank. Phylogenetic analysis of all sequences revealed 2 major clades, each comprising genomes exhibiting 4a-like and 4p-like restriction profiles, respectively **(Figure 2)**. USNA sequences clustered within the 4a-like clade. Restriction profiles obtained with the USNA sequences by in silico analysis using enzymes BamHI, DraI, EcoRI, EcoRV, XhoI, and SmaI identified them as genome type 4a1.

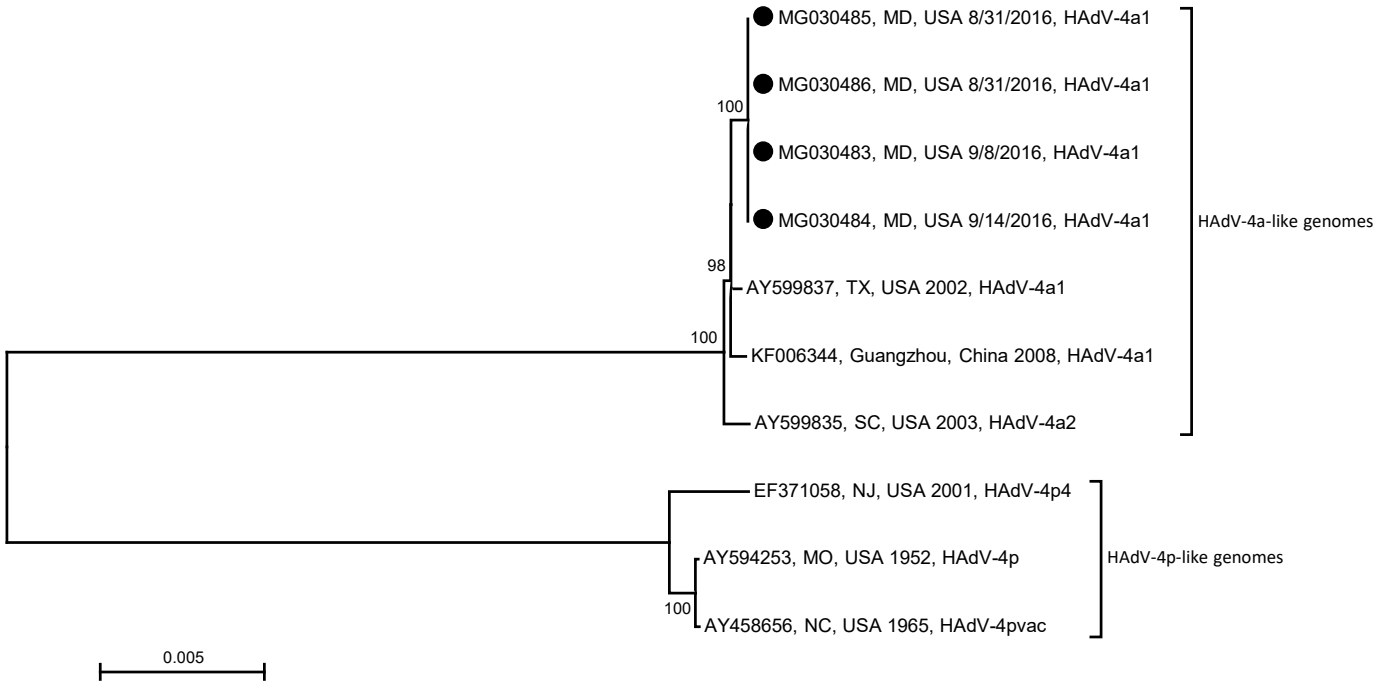
Rhinovirus was co-detected from 1 HAdV-4 positive patient and was also detected from 4 HAdV-4 negative patients by FTD-21 rRT-PCR **(data not shown)**. Enterovirus D68 (EV-D68) was also detected from 2 HAdV-4 negative patients by sequencing analysis. No other respiratory pathogens were identified on either rRT-PCR or culture/IFA. Nine patients were negative for all pathogens tested **(data not shown)**.

Case identification and clinical presentation

Eighteen HAdV-4 positive cases were identified among 33 students seen at the BMC as outpatients who had specimens submitted for viral testing. Among the 33 students with specimens collected, the median number of days from symptom onset to specimen collection was 3.0 (range 1–13 days). Among 27 charts reviewed for students hospitalized from 1 August–30 September 2016, a single additional student was hospitalized for ARI and also tested positive for HAdV by PCR; no typing was performed on the specimen from the hospitalized student.

Among the 19 laboratory-confirmed cases with symptom information available, the vast majority presented clinically with 1 or more of the following: chills, reported history of fever, symptoms persisting for ≥2 days prior to presentation, sore throat, headache, sinus congestion, and cough **(Table 2)**. Nine of the 19 HAdV positive patients had documented fever (temperature >100.5°F) determined by chart review,

FIGURE 2. Neighbor-joining tree of HAdV-4 full genome sequences obtained from the U.S. Naval Academy[a] outbreak and representative genome types available from GenBank[31]



[a]Black circles denote the 4 adenovirus isolates from patients in the U.S. Naval Academy outbreak.

Note: Bootstrap support values (1,000 replicates) were plotted at selected internal branch nodes. Scale bar corresponds to nucleotide change per site.

with a mean temperature of 102.5°F (range: 101.7–103.0°F) **(Table 2)**. The mean number of days of sick-in-quarters (time excused from all classes and activities) was 2.6 days (range 1–5 days). There were no cases with documentation of chronic underlying illness (including asthma, heart condition, respiratory illness, diabetes, obesity, or use of a prescription medication). Two patients were diagnosed with pneumonia by chest radiograph including the single hospitalized case; chest radiographs were not obtained in 17 of the 19 cases **(data not shown)**. No patient was placed on antivirals empirically for influenza and all patients presented with >95% oxygen saturation on room air **(data not shown)**.

Control measures

In response to the increase in ARI cases, campus-wide control measures were implemented on 31 August 2016, including 1) hand hygiene and cover-your-cough educational outreach messaging, 2) hand sanitizer station availability throughout campus, 3) strict implementation of mask use for symptomatic patients visiting the clinic, and 4) social distancing measures through sick-in-quarters restrictions for symptomatic individuals.

EDITORIAL COMMENT

This investigation describes a large outbreak of respiratory illness associated with HAdV-4 that occurred among students at the USNA during August–September 2016. Relative to baseline, the outbreak was estimated to have contributed to over 400 excess outpatient clinic visits during this period. The clinical syndrome included high fever, chills, sore throat, headache, and cough, which frequently led to absences from scheduled activities but rarely included pneumonia or resulted in hospitalization. HAdV-4 is an important cause of ARI and conjunctivitis worldwide.[35-38] Although HAdV-4 has been infrequently documented to be associated with acute respiratory illness among U.S. civilians,[18,39,40] it was the predominant cause of ARI among U.S. enlisted BMT recruits before reintroduction of routine vaccination in late 2011.[39,40]

The 2016 outbreak occurred in a residential college-style setting among students from diverse geographic areas who reside in dormitories (2–4 persons per dorm room) and attend mass gatherings. HAdVs are noted to persist in the environment (e.g., in lockers, on bedposts, and on pillow cases) for substantial periods of time[41] and to have a high degree of communicability.[9] The 2016 outbreak highlights the role of HAdV as a potential cause of ARI among students residing in dormitories in college-like settings. However, it is notable that attendees of federal service academies are exposed to unique physical and military training requirements as compared with civilian undergraduate institutions.

In enlisted BMT settings, HAdV-4 infection has been linked with severe respiratory illness, with a high impact on loss of training, hospitalized days, and clinical resources.[8-14] In this outbreak, cases reported a mean absence of 2.6 days following their initial visit, excluding possible

TABLE 2. Characteristics of laboratory confirmed HAdV positive cases (n=19), U.S. Naval Academy, August 29–September 23, 2016

Characteristics	Mean	Range
Age (years)	19.2	(18.0-22.0)
Documented fever (>100.5°F; n=9)	102.5	(101.7-103.0)
Mean days sick in quarters	2.6	(1-5)
	n	%
Sex		
Female	3	15.8
Class year		
First year	12	63.2
Second year	1	5.3
Third year	6	31.6
Fourth year	0	0.0
Clinical course		
Hospitalized	1	5.3
Chest radiograph-confirmed pneumonia	2	10.5
Treatment with antibiotics	3	15.8
Presenting symptoms		
Chills	18	94.7
Report of fever	17	89.5
>48 hours of symptoms[a]	17	89.5
Sore throat	16	84.2
Headache	15	78.9
Sinus congestion	13	68.4
Cough	13	68.4
Body aches	12	63.2
Fatigue	9	47.4
Tachycardia[b]	5	26.3
Diarrhea	2	10.5

[a]>48 hours of symptoms prior to presentation
[b]Tachycardia defined as heart rate >100 beats per minute

follow-up visits that may have resulted in additional days of absence. Although military enlisted recruits are routinely administered the HAdV-4 and HAdV-7 vaccines, military academy students are not routinely vaccinated with the HAdV vaccine. This outbreak was associated with HAdV-4a, a type for which the existing HAdV vaccine would have potentially offered protection, as vaccination with HAdV-4p is thought to protect against symptomatic infections with HAdV-4a-like viruses.[42]

Li and Waddel[28] first described finding 2 major genomic clusters of HAdV-4, designated here as 4p-like and 4a-like, based on restriction profile analysis, which were later confirmed and refined by whole genome sequencing.[43,44] Whereas HAdV-4p-like genomes were the most prevalent in the U.S. during the late 1960s to early 1980s, HAdV-4a-like genomes came to dominate detections among military populations in later years.[29] HAdV-4 strains associated with the 2016 outbreak were identified as HAdV-4a1, with sequences similar to strains circulating among U.S. military enlisted recruits in 2002 (GenBank accession number AY599837.1) and 2003 (GenBank accession number AY599835.1) and in China (GenBank accession number KF006344.1).

The investigation described here is subject to several limitations. Although HAdV-4 was identified in 18 of 33 patients with available specimens, it was not possible to quantify the proportion of the more than 400 excess ARI clinical encounters potentially associated with HAdV-4, as specimens were only collected based on the clinical suspicion of individual providers. Other respiratory viruses that likely contributed to ARI cases, including rhinovirus and EV-D68, were identified. Moreover, it is not known whether individuals with available specimens differed from individuals presenting with ARI who did not have specimens collected. Finally, risk factors for illness among identified cases were not ascertained and environmental sampling was not feasible during this investigation.

The epidemiology and burden of respiratory illness due to HAdV-4 in residential college settings and federal service academies requires further characterization. These results indicate the need for additional documentation of the impact of HAdV-4 in these settings to inform discussions of parameters for extending vaccine use beyond enlisted BMT settings. Providers and public health practitioners should consider HAdV as a potential contributor to ARI outbreaks, including those in residential campus settings.

Author Affiliations: Navy Environmental and Preventive Medicine Unit TWO (LCDR Rogers, LCDR Johnson); Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (Ms. Lu, Ms. Killerby, Dr. Erdman, Dr. Gerber, Dr. Schneider, Dr. Watson); Naval Health Clinic, Annapolis, MD (Ms. Campbell, CDR Gallus); Walter Reed National Military Medical Center (Dr. Kamau, Ms. Froh); Navy and Marine Corps Public Health Center (Ms. Nowak); Battelle contracting agency to Respiratory Viruses Branch, Centers for Disease Control and Prevention (Dr. Sakthievel)

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