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CDC/Prof. Frank Hadley Collins, Cntr. for Global Health and Infectious Diseases, Univ. of Notre Dame

CDC/Michael L. Levin, PhD

Update: Malaria, U.S. Armed Forces, 2020

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 2020, a total of 28 service members were diagnosed with or reported to have malaria. This was the lowest number of cases in any given year during the 10-year surveillance period and represents a 15.2% decrease from the 33 cases identified in 2019. The relatively low numbers of cases during 2012–2020 mainly reflect decreases in cases acquired in Afghanistan, a reduction largely due to the progressive withdrawal of U.S. forces from that country. The number of malaria cases caused by *Plasmodium falciparum* in 2020 (n=8) was the second lowest observed during the surveillance period. The percentage of 2020 cases of malaria caused by *Plasmodium vivax* (53.6%; n=15) was the highest during any given year of the surveillance period. The remaining 5 malaria cases were labeled as associated with other/unspecified types of malaria (17.9%). Malaria was diagnosed at or reported from 13 different medical facilities in the U.S., Germany, Africa, 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?

The 2020 total of 28 malaria cases among active and reserve component service members was the lowest annual count of cases during the past 10 years. The 2020 proportion of cases (53.6%) due to *P. vivax* was the highest of the 10-year period.

WHAT IS THE IMPACT ON READINESS AND FORCE HEALTH PROTECTION?

The decrease in total counts of malaria cases during the last decade reflects the reduced numbers of service members exposed to malaria in Afghanistan. The persistent threat from *P. falciparum* associated with duty in Africa underscores the importance of preventive measures effective against this most dangerous form of malaria.

Worldwide, the incidence rate of malaria is estimated to have decreased from 71.1 per 1,000 population at risk in 2010 to 57.5 in 2015 and 56.8 in 2019.[1] These decreases represent reductions of 27% and 2%, respectively, and indicate a slowing of the rate of decline since 2015.[1] This plateauing of malaria incidence rates is especially apparent in countries that accounted for high proportions of cases globally (e.g., Nigeria, the Democratic Republic of the Congo, India).[1] During 2010–2019, malaria-related deaths decreased steadily from 594,000 in 2010 to 453,000 in 2015 and 409,000 in 2019.[1]

Countries in Africa accounted for about 94% of worldwide malaria cases and malaria-related deaths in 2019.[1] Nigeria (27%), the Democratic Republic of the Congo (12%), Uganda (5%), Mozambique (4%), and Niger (3%) accounted for slightly more than half (51%) of all cases globally.[1] Most of these cases and deaths were due to mosquito-transmitted *Plasmodium falciparum* and occurred among children under 5 years of age,[1] but *Plasmodium vivax, Plasmodium ovale*, and *Plasmodium malariae* can also cause severe disease.[1–3] Globally in 2019, 2.8% of estimated malaria cases were caused by *P. vivax*; however, over four-fifths of vivax malaria cases occurred in 6 countries: India, Pakistan, Afghanistan, Ethiopia, Papua New Guinea, and Indonesia.[1] It is important to note that, while heightened malaria-control efforts have reduced the incidence of *P. falciparum* malaria in many areas, the proportion of malaria cases caused by *P. vivax* has increased in some regions where both parasites coexist (e.g., Djibouti, Pakistan, Venezuela).[3,4]

Since 1999, the *MSMR* has published regular updates on the incidence of malaria among U.S. service members.[5–7] 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).[8,9] 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.[10–19]

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 as well as 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.[11–14]

MSMR malaria updates from the past 8 years documented that the annual case counts among service members after 2011 were the lowest in more than a decade.[7,20–25] In particular, these updates showed that the numbers of cases associated with service in Afghanistan had decreased substantially in the past 8 years, presumably because of the dramatic reduction in the numbers of service members serving there. This update for 2020 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 2011 through 31 December 2020. 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 non-military 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 nonprimary diagnosis of malaria due to a specific *Plasmodium* species; 4) a hospitalization record with a nonprimary diagnosis of malaria plus a diagnosis of anemia, or thrombocytopenia and related conditions, or malaria complicating pregnancy in any diagnostic position; 5) a hospitalization record with a nonprimary diagnosis of malaria plus diagnoses of signs or symptoms consistent with malaria in each diagnostic position antecedent to malaria;[26] 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 International Classification of Diseases, 9th and 10th Revision (ICD-9 and ICD-10, respectively) 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 before diagnosis were considered acquired in those respective countries. All remaining cases were considered to have acquired malaria in unknown locations.

RESULTS

In 2020, a total of 28 service members were diagnosed with or reported to have malaria **(Table 2)**. This total was the lowest number of cases in any given year during the surveillance period and represents a 15.2% decrease from the 33 cases identified in 2019 **(Figure 1)**. The percentage of 2020 cases of malaria caused by *P. vivax*

TABLE 1. ICD-9 and ICD-10 diagnosis codes used in defining cases of malaria from the records for inpatient encounters (hospitalizations)

	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

ICD, International Classification of Diseases.

TABLE 2. Malaria cases by *Plasmodium* species and selected demographic characteristics, active and reserve components, U.S. Armed Forces, 2020

	P. vivax	*P. falciparum*	Other/ unspecified	Total	% total
Total	15	8	5	28	100.0
Component					
Active	13	5	4	22	78.6
Reserve/Guard	2	3	1	6	21.4
Service					
Army	10	4	3	17	60.7
Navy	2	0	1	3	10.7
Air Force	2	2	1	5	17.9
Marine Corps	1	2	0	3	10.7
Sex					
Male	13	7	5	25	89.3
Female	2	1	0	3	10.7
Age group (years)					
<20	1	0	0	1	3.6
20–24	5	4	0	9	32.1
25–29	3	2	1	6	21.4
30–34	1	1	4	6	21.4
35–39	4	0	0	4	14.3
40–44	0	0	0	0	0.0
45–49	0	1	0	1	3.6
50+	1	0	0	1	3.6
Race/ethnicity group					
Non-Hispanic white	13	7	2	22	78.6
Non-Hispanic black	0	1	3	4	14.3
Other/unknown	2	0	0	2	7.1

(53.6%; n=15) was the highest during any given year of the surveillance period. Of the 13 cases in 2020 not attributed to *P. vivax*, 8 (28.6%) were identified as due to *P. falciparum* and 5 were reported as associated with other/unspecified types of malaria (17.9%). The number of malaria cases caused by *P. falciparum* in 2020 was the second lowest observed during the 10-year surveillance period **(Figure 1)**. Similar to 2019, the majority of U.S. military members diagnosed with malaria in 2020 were male (89.3%), active component members (78.6%), in the Army (60.7%), and in their 20s (53.5%) **(Table 2)**.

Of the 28 malaria cases in 2020, slightly more than one-fifth of the infections were considered to have been acquired in Afghanistan (21.4%, n=6); slightly more than one-sixth (17.9%, n=5) were attributed to Africa; and one-seventh (14.3%; n=4) were attributed to Korea **(Figure 2)**. The remaining cases could not be associated with a known, specific location (46.4%, n=13); no cases were considered to have been acquired in South/Central America. Of the 5 malaria infections considered acquired in Africa in 2020, 2 were linked to Djibouti; and 1 each to Benin, Niger, and Burkina Faso **(data not shown)**.

During 2020, malaria cases were diagnosed or reported from 13 different medical facilities in the U.S., Germany, Africa, and Korea **(Table 3)**. Almost three-eighths (36.4%; 8/22) of the total cases with a known location of diagnosis were reported from or diagnosed outside the U.S., which represents a slight increase from the 31.4% of malaria cases in this category in 2019. The largest number of malaria cases associated with a single medical facility during 2020 was 5 at the Landstuhl Regional Medical Center in Germany.

In 2020, the percentage of malaria cases acquired in Africa (17.9%; n=5) decreased from 2019 (45.5%) and was most similar to the percentages in 2011 (19.0%) and 2012 (17.5%) **(Figure 2)**. The percentage of Afghanistan-acquired cases (21.4%; n=6) in 2020 was lower than the percentages in 2019 (30.3%) and 2018 (33.9%). The percentage of malaria cases acquired in Korea (14.3%; n=4) in 2020 was higher than in 2019 (6.1%) and was most similar to the percentages in 2018 (15.3%) and 2017 (14.3%) **(Figure 2)**.

Between 2011 and 2020, 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 2020, 57.1% (16/28) of malaria cases among U.S. service members were diagnosed during May–October **(data not shown)**. This proportion is lower than the 74.8% (380/508) of cases diagnosed during the same 6-month intervals over the entire 10-year surveillance period. During 2011–2020, the proportions of malaria cases diagnosed or reported during May–October varied by region of acquisition: Korea (90.3%; 56/62); Afghanistan (83.4%; 161/193); Africa (63.9%; 101/158); and South/Central America (40.0%; 2/5) **(data not shown)**.

EDITORIAL COMMENT

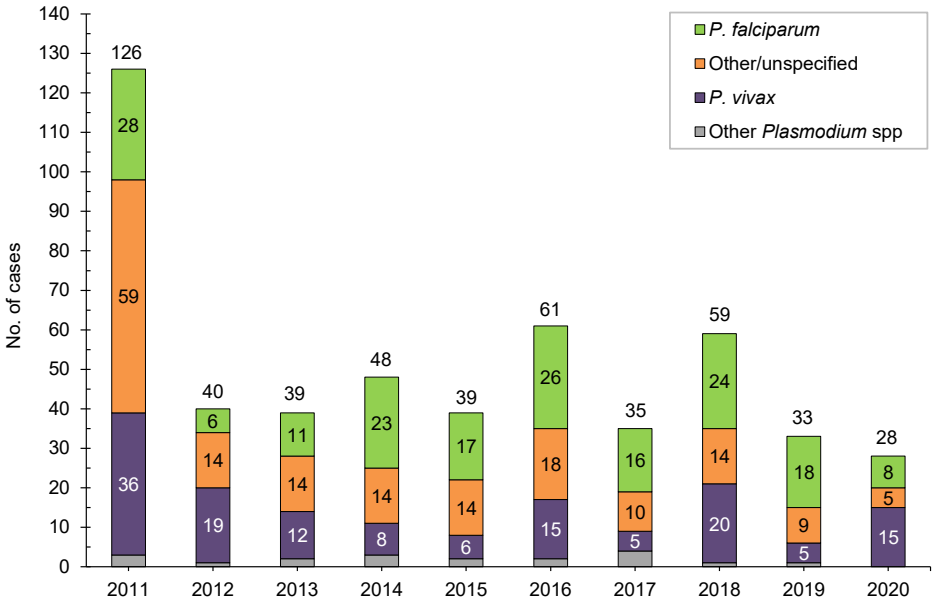
MSMR annual reports on malaria incidence among all U.S. services began in 2007. The current report documents that the number of cases during 2020 decreased from 2019 and was the lowest of any of the previous years in the 2011–2020 surveillance period. Most of the marked decline in the past 9 years is 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. The 2020 percentage of cases caused by *P. vivax* (53.6%) was the highest of any year of the surveillance period. Although the predominant species of malaria in Korea and Afghanistan has been *P. vivax*, the more dangerous *P. falciparum* species is of primary concern in Africa. The planning and execution of military operations on the African 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.[19,27] The finding that *P. falciparum* malaria was diagnosed in more than one-quarter of the cases in 2020 further underscores the need for continued emphasis on prevention of this disease, given its potential severity and risk of death. Moreover, a recent article noted the possibility of false negative results for *P. falciparum* on the rapid diagnostic tests favored by units in resource-limited or austere locations.[28] Although additional research is needed, commanders and unit leaders may need to be extra vigilant with forces that are far forward.

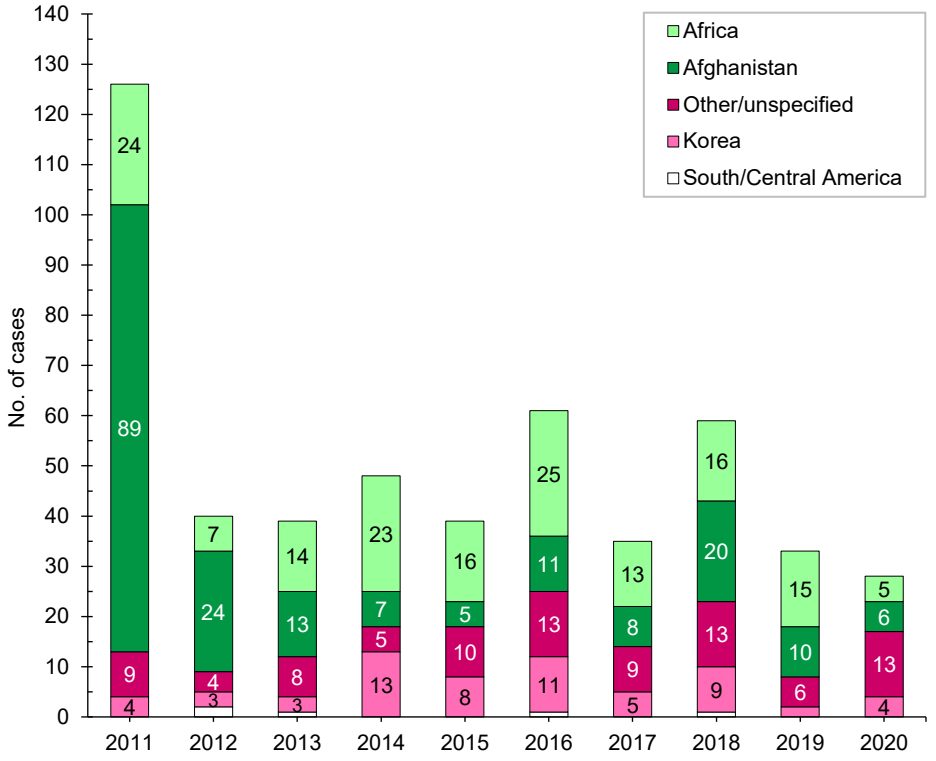
The observations about the seasonality of diagnoses of malaria are compatible with the presumption that the risk of acquiring and developing symptoms of malaria in a temperate climatic zone of the Northern Hemisphere would be greatest during May–October. Given the typical incubation periods of malaria infection (approximately 9–14 days for *P. falciparum*, 12–18 days for *P. vivax* and *P. ovale*, and 18–40 days for *P. malariae*)[26] 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.[29,30] Klein and colleagues 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.[31] Nine of the malaria cases were identified when patients first presented with symptoms of infection 9 or more months after exposure and after their departure from Korea.[31] Transmission of malaria in tropical regions

FIGURE 1. Numbers of malaria cases, by *Plasmodium* species and calendar year of diagnosis or report, active and reserve components, U.S. Armed Forces, 2020



No., number.

FIGURE 2. Annual numbers of cases of malaria cases, by location of acquisition, U.S. Armed Forces, 2011–2020



No., number.

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, 2020

Location where diagnosed or reported	Korea	Afghanistan	Africa	South/ Central America	Other/ unknown location	Total	
	No.	No.	No.	No.	No.	No.	%
Landstuhl RMC, Germany	0	1	1	0	3	5	17.9
Carl R. Darnall AMC, Fort Hood, TX	2	0	0	0	2	4	14.3
Location not reported	0	0	1	0	3	4	14.3
Womack AMC, Fort Bragg, NC	0	2	0	0	0	2	7.1
Madigan AMC, Joint Base Lewis-McChord, WA	0	2	0	0	0	2	7.1
Dwight D. Eisenhower AMC, Fort Gordon, GA	1	0	0	0	0	1	3.6
Irwin ACH, Fort Riley, KS	0	0	0	0	1	1	3.6
NMC, Camp Lejeune, NC	0	0	1	0	0	1	3.6
Joint Base McGuire-Dix-Lakehurst, NJ	0	0	1	0	0	1	3.6
NBHC Little Creek, VA	0	0	0	0	1	1	3.6
Joint Base Lewis-McChord, WA	0	1	0	0	0	1	3.6
Grafenwoehr AHC, Germany	0	0	0	0	1	1	3.6
Expeditionary Medical Facility, Djibouti	0	0	1	0	0	1	3.6
AHC, Camp Humphreys, Korea	1	0	0	0	0	1	3.6
Remote location within Europe	0	0	0	0	1	1	3.6
Remote location within U.S.	0	0	0	0	1	1	3.6

RMC, Regional Medical Center; AMC, Army Medical Center; ACH, Army Community Hospital; NMC, Naval Medical Center; NBHC, Naval Branch Health Clinic; AHC, Army Health Clinic.

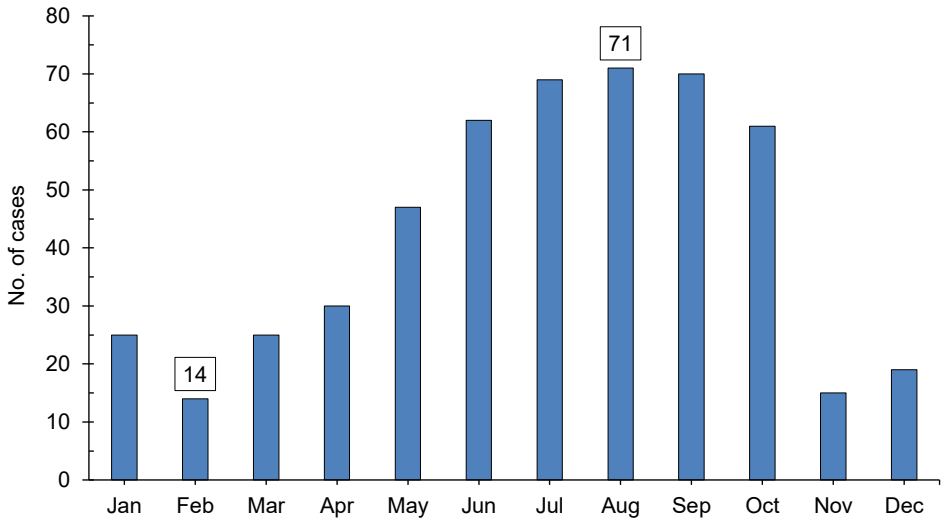
such as sub-Saharan Africa is less subject to the limitations of the seasons as in temperate climates but depends more on other factors affecting mosquito breeding such as the timing of the rainy season and altitude (below 2,000 meters).[32]

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 sites that were using the new electronic health record for the Military Health System, MHS GENESIS, between July 2017 and October 2019 are not available in the DMSS. These sites include Naval Hospital Oak Harbor, Naval Hospital Bremerton, Air Force Medical Services Fairchild, and Madigan Army Medical Center. Therefore, medical encounter data for individuals seeking care at any of these facilities from July 2017 through October 2019 were not included in the current analysis.

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 2020 most malaria cases among U.S. military members were

FIGURE 3. Cumulative numbers of diagnoses and reported cases of malaria, by month of clinical presentation or diagnosis, U.S. Armed Forces, January 2011–December 2020



No., number.

treated at medical facilities remote from 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, primaquine, and tafenoquine.[33,34]

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Historical Perspective: The Evolution of Post-exposure Prophylaxis for Vivax Malaria Since the Korean War

Victor E. Zottig, PhD (MAJ, MSC, USA); G. Dennis Shanks, MD (COL, MC, USA, Ret.)

Malaria during the Korean War

During the Korean War (1950–1953) malaria was a major infectious disease threat to infantry forces operating in Korea during the summer transmission season. *Plasmodium vivax* with a long latency period had evolved such that many soldiers were exposed to infectious mosquitoes during their service in Korea during the summer but only became aware of their infection during the next year when latent hepatic parasites (hypnozoites) reactivated to cause symptomatic relapses. Chloroquine prophylaxis taken by soldiers during their time in the malarious region adequately suppressed any parasites in the blood minimizing the impact of malaria while in the combat zone **(Figure 1)** but did not kill hypnozoites. The result was many relapse cases long after exposure to the mosquito vectors.[1] Due to 1-year tours of duty, most soldiers who contracted malaria during the Korean War were not actually symptomatic while in Korea. Thousands of cases of vivax malaria, mostly in soldiers, appeared in the U.S. beginning mid-year in 1951 **(Figure 2)**, endangering the recently acquired national malaria elimination status. Clearly, better anti-malarial medication was required.

An 8-aminoquinoline, pamaquine, was the original synthetic antimalarial drug but it was judged by the U.S. Army to be too toxic for use because of its association with hemolysis in African American soldiers, many of whom were glucose-6-phosphate dehydrogenase (G6PD) deficient.[2] A series of pamaquine analogues were tested by a reactivated antimalarial drug development program which had been initiated during World War II. Using prison volunteers purposely infected with rapidly relapsing vivax malaria strains from the Southwest Pacific, clinical investigators in Illinois rapidly identified a better tolerated 8-aminoquinoline known as primaquine.[3,4] Once primaquine had been proven to kill hypnozoites in the liver, it was moved to field trials on troopships of returning Korean War veterans. By 1952, all troop transports had dedicated teams of medics whose function was to see that a 2-week course of primaquine (15 mg daily) was administered to every returning veteran. Within 2 years of implementing this strategy for post-exposure malaria prophylaxis, late vivax relapses in the U.S. had largely ceased due to the administration of primaquine to hundreds of thousands of soldiers.[5] Chloroquine and primaquine remained the main antimalarial prophylaxis drugs even into the Vietnam conflict (1965–1972).

Tafenoquine

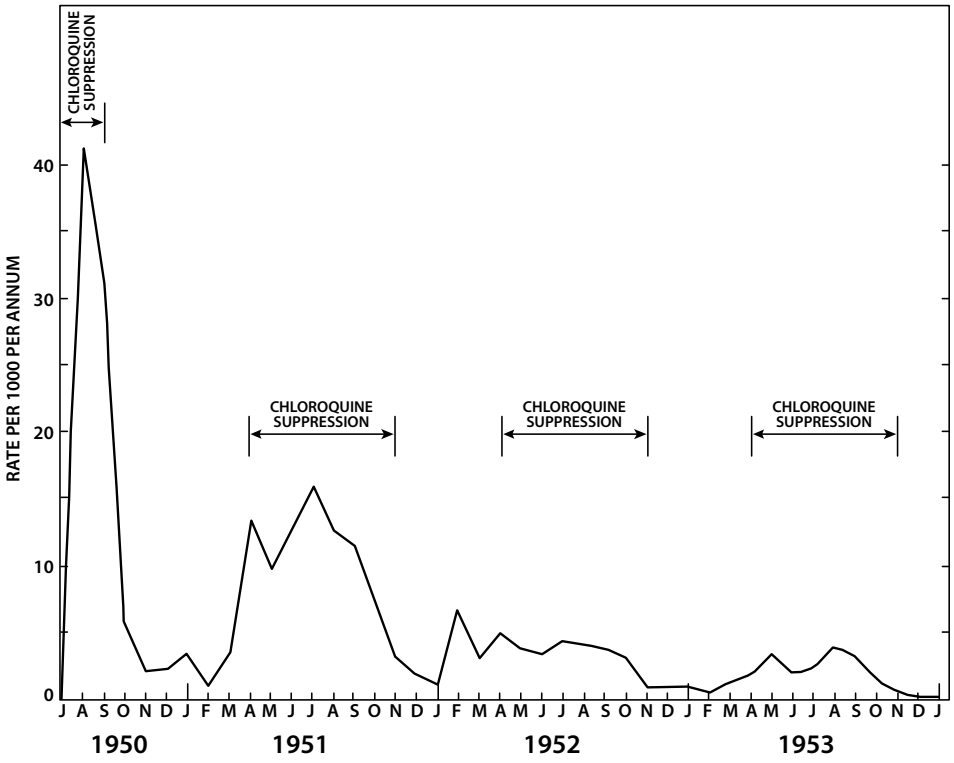
The emergence of drug-resistant malaria strains during the Vietnam conflict reinvigorated the drug development efforts by the U.S. Department of Defense (DoD) to combat this growing threat. During this effort, scientists from the Walter Reed Army Institute of Research, Division of Experimental Therapeutics (WRAIR/ET), screened thousands of potential new anti-relapse drug candidates to improve on the current standard of care, primaquine.[6] During this testing one compound, called WR238605, or tafenoquine, demonstrated desirable properties that appeared superior to those of other pre-clinical candidates and primaquine, and became a lead candidate. Field trials for tafenoquine began in 1998.

After completing extensive pre-clinical and early clinical work, WRAIR/ET transitioned tafenoquine to the U.S. Army Medical Materiel Development Activity (USAMMDA). USAMMDA continued development of tafenoquine in collaboration with WRAIR/ET, its overseas laboratories, and through commercial partnerships, ultimately establishing a cooperative research and development agreement with 60 Degrees Pharmaceutical, LLC (60 Degrees). The partnership culminated in the U.S. Food and Drug Administration (FDA) approval of tafenoquine, (trade name Arakoda) in 2018 as an antimalarial indicated for the prophylaxis of malaria for continuous dosing up to six months in patients aged 18 years and older.[7] Also in 2018, the FDA approved the use of tafenoquine (trade name Krintafel) for anti-relapse therapy of *P. vivax* in patients aged 16 years and older.[8]

Over the last decade, the DoD has seen relativity few cases of malaria, typically between 30 to 60 cases annually.[9] Although cases of *Plasmodium falciparum* malaria acquired in Africa have become more common than cases caused by other species, the numbers of cases associated with service in South Korea and Afghanistan (almost exclusively *P. vivax*) have accounted for about 25% of the recent annual totals. The low case numbers are likely attributable to the reduced presence of U.S. Armed Forces in Afghanistan and Iraq in recent years, force health protection (FHP) measures to counter the threat from the mosquito vectors, such as permethrin treated uniforms and bed nets, and command discipline to ensure service members take their chemoprophylaxis and wear uniforms properly. Tafenoquine will likely have a significant role in reducing the number of malaria cases further by increasing compliance, where weekly dosing could be preferred over daily dosing.[10]

The promise of tafenoquine is based upon several characteristics. First, tafenoquine is effective against all species and life cycle stages of the malaria parasites that infect humans; at this time, there is no known tafenoquine resistance among the 5 *Plasmodium* species that affect humans. Second, the drug is FDA-approved for up to 6 months of malaria prophylaxis while living or traveling in a malaria region. Third, the effective half-life of the drug in humans is at least 2 weeks. As a result, the frequency of maintenance doses is just weekly. This dosing schedule enhances the likelihood of good compliance, particularly in settings where supervised or observed dosing is desirable, such as in military units. The drug's long half-life provides sufficiently high drug levels to allow for what

FIGURE 1. Malaria in U.S. Army personnel in Korea, by month, July 1950–January 1954



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is called "compliance forgiveness." If a service member misses a weekly dose, there is enough drug remaining in the body to provide protective efficacy until the following scheduled dose. Although it is not recommended to miss a weekly dose, the label instructions specify that, when a weekly dose is omitted, the individual should not take a make-up dose but should simply resume the prophylaxis at the time of the next scheduled dose. Results of clinical trials have suggested that monthly dosing could be a possibility in the future.[7,11] Fourth, not only is tafenoquine effective for anti-relapse therapy (post-exposure prophylaxis) against the hypnozoites of *P. vivax* and *Plasmodium ovale*, but such therapy requires just a single dose of tafenoquine. This single dose requirement contrasts with the conventional dose schedule of primaquine which must be taken daily for 14 days, a well-known impediment to high levels of patient compliance.[12] Moreover, if the weekly prophylaxis while in the malarious area consisted of tafenoquine, no additional anti-relapse therapy would be required.

In December 2019, the Defense Health Agency (DHA) published an update to Deployment Health Procedures, procedural instruction (PI) 6490.03 approving tafenoquine as a second-line malaria prophylaxis countermeasure for FHP.[13] This update is the first step in the introduction of tafenoquine to the warfighter. Combatant Commands, such as U.S. Africa Command (AFRICOM) and U.S. Indo-Pacific Command (INDOPACOM) have applied the DHA PI updates and incorporated tafenoquine as a new malaria prophylaxis option in their internal policies. As the drug is administered in the broader military and civilian population and 60 Degrees completes the FDA post-marketing commitments, more information on, and familiarization with, the properties of the drug will be realized and it is expected that DoD's guidance will evolve to integrate the new information.

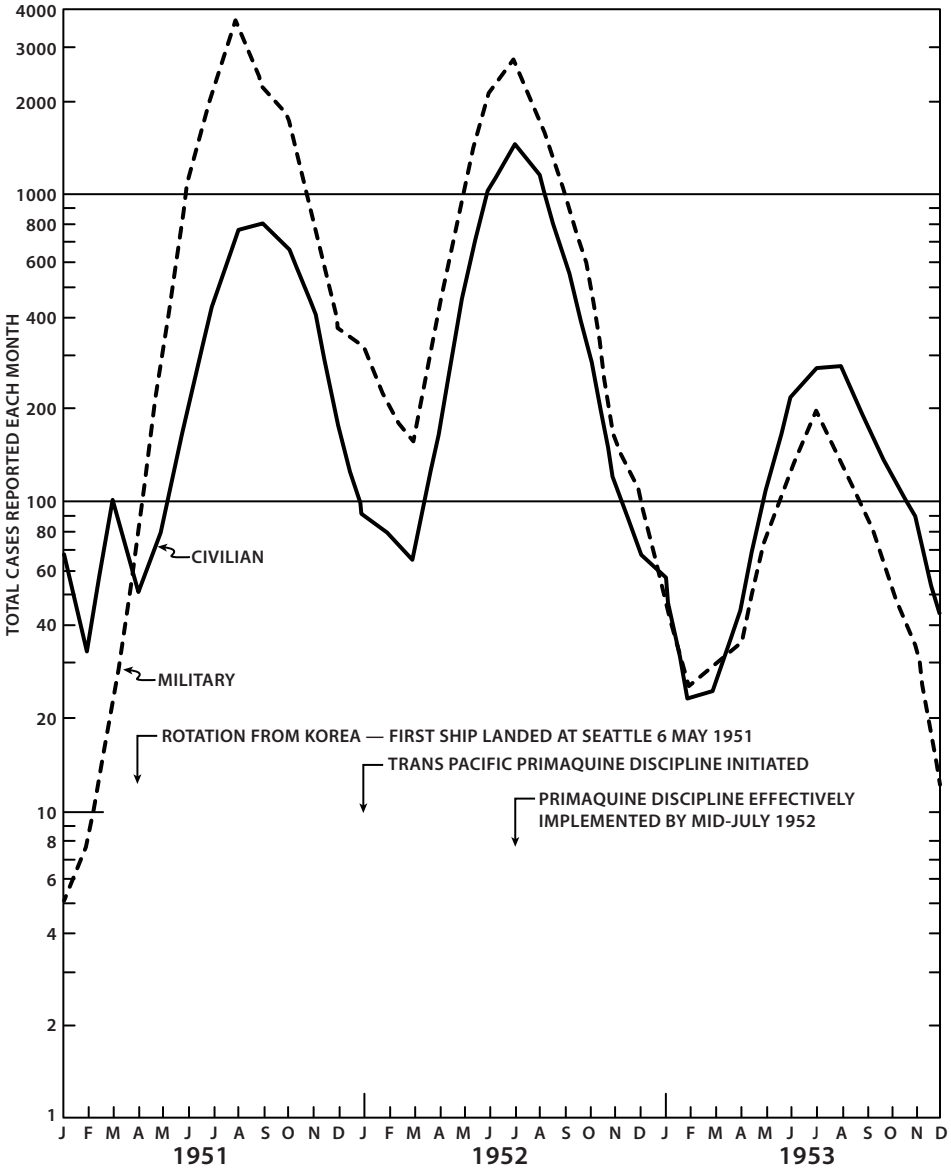
As noted in PI 6490.03, there are additional factors to consider when contemplating the use of tafenoquine.[13] First, tafenoquine (as well as primaquine) should not be prescribed for persons who have G6PD deficiency because of the risk of drug-induced hemolytic anemia. Current DoD policy provides for the routine screening of all service members for G6PD deficiency and for documentation of the results in the service members' individual health records. Second, current FDA approval of tafenoquine for chemoprophylaxis specifies a duration of use of no more than 6 months; however, there are ongoing post-marketing studies to extend the duration of use to 12 months.[14]

EDITORIAL COMMENT

Malaria relapses are an adaptation of the parasite to survive between transmission seasons through latency in the liver followed by reactivation months to even a year after infection. Many U.S. Army veterans who served in the Southwest Pacific during the World War II reported greater than 20 separate malaria episodes triggered by relapses from the liver despite taking chemo-suppressive medications. Pamaquine was too toxic for use but its better tolerated cousin primaquine largely solved the problem of post-deployment relapses during the Korean War. Efficacious medications are only part of the equation needed for force health protection. Better tolerated drugs that could be given infrequently enough (e.g., weekly as opposed to daily) so as to facilitate supervised administration of the medication (directly observed therapy) are also desirable.

Despite a very long developmental history, tafenoquine is now available to replace primaquine as a better tolerated medication to treat soldiers infected with relapsing malaria.[14] In addition, the very long (2-week) half-life of tafenoquine allows it to be given weekly (200mg in adults) for reliable chemoprophylaxis following a 3-day loading dose regimen consisting of 200 mg per day for a total of 600 mg. It seems likely, based on work in the Royal Thai Army, that tafenoquine monthly regimens may eventually be devised which would further increase compliance and thus effectiveness.[11] Anti-relapse therapy consists of a single dose of 300 mg of tafenoquine taken after departure from the area of malaria risk. Further work at WRAIR/ET is being conducted with the aim of finding a regimen or combination that can be safely given to G6PD-deficient individuals, but currently tafenoquine is limited to those known to have adequate G6PD activity

FIGURE 2. Malaria morbidity in the U.S, by month, 1951–1953



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by laboratory measurement. Tafenoquine is effective against all malaria species and life cycle stages of the malaria parasite that infect humans, has no known malaria resistance, and provides a convenient dosing regimen, all of which will likely result in vastly improved compliance and effectiveness in the prevention of malaria in U.S. service members. Whether tafenoquine will have a major role in public health efforts to eliminate malaria globally remains to be seen, but tafenoquine is certainly a major advance in FHP against malaria for soldiers deployed to endemic areas.

Author affiliations: U.S. Army Medical Materiel Development Activity (MAJ Zottig); Australian Defence Force Malaria and Infectious Diseases Institute, Enoggera, QLD, Australia (Dr. Shanks).

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Surveillance for Vector-borne Diseases Among Active and Reserve Component Service Members, U.S. Armed Forces, 2016–2020

Francis L. O'Donnell, MD, MPH (COL, USA, Ret.); Michael Fan, PhD; Shauna Stahlman, PhD, MPH

This report summarizes data from electronic reports of reportable medical events (RMEs) to examine the incidence of vector-borne infectious diseases among members of the U.S. Armed Forces during a recent 5-year period. Case reports of such diseases were characterized as confirmed, probable, or suspected by the senders of the RME reports. Records of inpatient and outpatient care were not searched to find additional cases. Lyme disease and malaria were the most common diagnoses among confirmed cases. The next most common diagnoses were Zika virus infection, Rocky Mountain spotted fever, and dengue. Those 5 diseases were responsible for 94% of all confirmed vector-borne diseases reported as RMEs. Among the 1,068 RMEs for vector-borne diseases (confirmed, probable, and suspected), there were only 105 such cases that could be linked to a record of hospitalization for the same diagnosis.

WHAT ARE THE NEW FINDINGS?

In the last decade, the most common vector-borne diseases among U.S. Armed Forces tended to be Lyme disease, malaria, Rocky Mountain spotted fever, dengue, and leishmaniasis. During 2014–2016, the pandemics of chikungunya and Zika virus transiently inserted those diseases into the top 5. The declining incidences of malaria and leishmaniasis during 2016–2020 are likely due to reduced numbers of service members assigned to endemic regions of the world.

WHAT IS THE IMPACT ON READINESS AND FORCE HEALTH PROTECTION?

The current findings reemphasize that the threat to service members from vector-borne diseases will vary according to the prevalent endemic diseases of specific geographic locations, the availability of protective vaccines, and the implementation of individual and group preventive measures.

The U.S. Armed Forces and the Department of Defense (DoD) have traditionally dedicated considerable effort to the prevention and treatment of vector-borne diseases that may adversely affect the ability of military service members to train for and execute their operational mission. A continuing element of that effort has been the performance of surveillance of vector-borne illnesses to guide preventive actions. The pages of the *MSMR* reflect over 25 years of surveillance studies to inform military leaders and preventive medicine/public health assets about the incidence of vector-borne diseases and appropriate steps to counter the associated threat. The February 2018 issue of the *MSMR* contained the results of the most recent, broad surveillance study of the most concerning vector-borne diseases.[1] This article presents an updated review of this subject, utilizing a modified methodology for capturing the occurrence of cases.

METHODS

The surveillance period was 1 January 2016 through 31 December 2020. The surveillance population included all active and reserve component service members in the Army, Navy, Air Force, or Marine Corps who served at any time during the surveillance period. It is DoD policy that cases of certain specified medical conditions and events of public health importance shall be reported electronically through military health channels for surveillance purposes.[2] Conditions covered by this policy are referred to as reportable medical events (RMEs). The content of such electronic reports is stored in the databases of the Defense Medical Surveillance System (DMSS), which was used to ascertain cases for this analysis. The vector-borne diseases that are the focus of this report are listed in **Table 1**. Almost all vector-borne diseases of concern for military service members are designated as RMEs.

For this analysis, a "confirmed", "probable", or "suspected" case was defined as an individual identified through an RME report of a vector-borne disease that was described as "confirmed", "probable", or "suspect" by having met specified laboratory or epidemiologic criteria.[2] An individual could be counted once per lifetime for each type of vector-borne disease. For example, an individual could be counted once for malaria and once for leishmaniasis during the surveillance period. Individuals diagnosed as a case prior to the start of the surveillance period were excluded. Confirmed cases were prioritized over probable and suspected cases, respectively.

A case was considered to be hospitalized if they had an inpatient admission within 30 days before or after the date of onset reported in the RME. In addition, the inpatient record had to include a diagnosis for the vector-borne disease as listed in **Table 1** in any of the diagnostic positions. The total number of cases hospitalized, as well as the percentage hospitalized and number of bed days were summarized for each vector-borne disease.

RESULTS

During the 5-year surveillance period, the electronic records of RMEs identified 709 confirmed cases of vector-borne

TABLE 1. Reportable vector-borne diseases, with ICD-10 diagnostic codes, type of infectious agent, type of vectors, geographic distribution, and availability of FDA-approved vaccine

Vector-borne disease	ICD-10	Agent	Vector(s)	Geographic distribution	U.S. FDA-approved vaccine?
Arboviral diseases, neuroinvasive and non-neuroinvasive	A83.*–A84.*, A85.2, A93.0, A93.2–A93.8, A94	Virus			
Eastern equine encephalitis	A83.2	Virus	Mosquito	Americas	
Australian (Murray Valley) encephalitis, Oropouche virus	A83.4, A93.0	Virus	Mosquito; midge	Australia, New Guinea; South America, Panama	
California virus encephalitis	A83.5	Virus	Mosquito	United States	
Japanese encephalitis	A83.0	Virus	Mosquito	Asia, Pacific Islands, Australia	Yes
Tick-borne encephalitis	A84.0–A84.1, A84.9	Virus	Tick	Europe	
Western equine encephalitis	A83.1	Virus	Mosquito	Americas	
St. Louis encephalitis	A83.3	Virus	Mosquito	Americas	
West Nile virus	A92.3*	Virus	Mosquito	Global except Southeast Asia, South America, Australia	
Chikungunya	A92.0	Virus	Mosquito	Africa, Southeast Asia, Philippines, Americas	
Rift Valley fever	A92.4	Virus	Mosquito	Africa, Arabia	
Zika virus infection	A92.5	Virus	Mosquito	Africa, Southeast Asia, Americas	
Hemorrhagic fevers	A98.0–A98.2	Virus			
Crimean-Congo HF	A98.0	Virus	Tick	Africa, Central Asia, Europe, Middle East	
Omsk HF	A98.1	Virus	Tick	Russian Federation	
Kyasanur Forest disease	A98.2	Virus	Tick	India	
Dengue	A90, A91	Virus	Mosquito	Throughout tropical regions of world	Yes
Ehrlichiosis/anaplasmosis	A77.4*	*Rickettsia* spp	Tick	North America, Asia, Europe	
Filariasis	B72, B73.*, B74.*	Helminth	Mosquito	South America, Central America, Africa, Asia, Pacific islands	
Leishmaniasis	B55.*	Protozoan	Sandfly	Asia, Africa, Middle East, South America, Central America, Mediterranean	
Lyme disease	A69.2*	Bacterium	Tick	North America, Europe, China, Japan	
Malaria	B50.*–B54.*	Protozoan	Mosquito	Africa, Asia, Pacific islands, Tropical regions of Americas	
Plague	A20.*	Bacterium	Flea	Almost worldwide	Yes
Relapsing fever	A68.*	Bacterium	Tick, louse	Americas, Asia, Europe, Africa	
Rocky Mountain spotted fever	A77.0–A77.3, A77.8–A77.9	*Rickettsia* spp	Tick	United States, South and Central America	
Trypanosomiasis	B56.*–B57.**	Protozoan	Tsetse fly, reduvid bug	Africa, Central America, South America	
Tularemia	A21.*	Bacterium	Tick, deerfly, mosquito	North America, Europe, Russia, China, Japan	
Typhus	A75.*	*Rickettsia* spp	Louse, flea, mite	Central America, South America, Africa, Asia	
Yellow fever	A95.*	Virus	Mosquito	Africa, South America, Central America	Yes

ICD, International Classification of Diseases; FDA, Food and Drug Administration.

diseases, 196 probable cases, and 163 suspected cases among service members of the active and reserve components **(Table 2)**. Active component service members comprised 86% of confirmed cases, 84% of probable cases, and 83% of suspected cases. There were no RMEs for any of the diagnoses of hemorrhagic fevers, filariasis, plague, relapsing fever, or yellow fever. The category "Arboviral diseases, neuroinvasive and non-neuroinvasive" included 3 cases of confirmed West Nile virus infection, 1 case of confirmed tick born encephalitis (TBE), and 4 unspecified types, for a total of 8 confirmed cases in that category. Only the 14 diagnostic categories displayed in **Table 2** had any RMEs during the 5-year period.

Of the total of 709 confirmed cases, 668 (94%) were associated with RME diagnoses of Lyme disease (n=311), malaria (n=172), Zika virus infection (n=80), Rocky Mountain spotted fever (RMSF) (n=54), and dengue fever (n=51). The other diagnoses that were reported as confirmed cases were much less commonly documented **(Table 2)**.

The distribution of diagnoses among probable RME cases was different from that of confirmed cases. It was noteworthy that Lyme disease was the diagnosis for 53 (27%) of the 196 probable cases, but RMSF accounted for 116 (59%) of the total probable cases. None of the other diagnoses was reported more than 5 times as probable cases during the 5 year surveillance period **(Table 2).**

Among the suspected cases, the most common RMEs were for Lyme disease (n=74), RMSF (n=54), and Zika virus infection (n=14). Together those three diagnoses were the subject of 87% of suspected cases of RMEs **(Table 2).** For the results described below, the emphasis will be on confirmed cases.

Lyme disease

Lyme disease accounted for 43.8% of all confirmed RME cases and was the most common of the vector-borne diseases reported during 2016–2020. The annual numbers of confirmed cases were greatest in 2016 and lowest in 2018, when the number of Lyme disease cases was actually lower than the count of malaria cases **(Figure 1).** The numbers of probable and suspected cases of Lyme disease (n=127) were actually lower than the counts for RMSF (n=170) during the surveillance period **(Table 2)**.

Malaria

Diagnoses of malaria (n=172) contributed 24.2% of all confirmed RME cases of vector-borne diseases during the 5 year surveillance period. The highest count was in 2018 (n=51) but the most recent two years had the lowest counts of the period (n=26 and 20, respectively) **(Figure 1)**. There were only 12 cases of malaria in RME reports of probable and suspected cases **(Table 2)**.

Zika virus infection

Confirmed cases of Zika virus infection numbered 80 during the period

TABLE 2. Numbers of confirmed, probable, and suspected cases of vector-borne diseases, active and reserve components, U.S. Armed Forces, 2016–2020

	Confirmed cases[a]			Probable cases[a]			Suspected cases[a]			Total[a]
	AC	RC	AC + RC	AC	RC	AC + RC	AC	RC	AC + RC	
Lyme disease	271	40	311	48	5	53	66	8	74	438
Malaria	149	23	172	3	0	3	9	0	9	184
Zika virus infection	64	16	80	2	0	2	12	2	14	96
Rocky Mountain spotted fever	46	8	54	97	19	116	40	14	54	224
Dengue	45	6	51	1	4	5	3	1	4	60
Leishmaniasis	16	0	16	1	1	2	0	0	0	18
Arboviral diseases, neuroinvasive and non-neuroinvasive	8	0	8	2	1	3	1	0	1	12
Tick-borne encephalitis	(1)	0	(1)	(1)	0	(1)	0	0	0	(2)
West Nile virus infection	(3)	0	(3)	0	0	0	(1)	0	(1)	(4)
Trypanosomiasis	5	0	5	1	0	1	0	0	0	6
Chikungunya	4	1	5	1	1	2	0	1	1	8
Ehrlichiosis/anaplasmosis	3	0	3	5	0	5	3	2	5	13
Typhus	1	2	3	2	0	2	0	0	0	5
Tularemia	1	0	1	1	1	2	1	0	1	4
Total	613	96	709	164	32	196	135	28	163	1,068

[a]Numbers in parentheses are included in the totals for the broad category of "arboviral diseases, neuroinvasive and non-neuroinvasive".
AC, active component; RC, reserve component.

(Table 2). However, 73 of those cases were reported in 2016, with the remainder reported in 2017 (n=4), 2019 (n=2), and 2020 (n=1) **(data not shown).** Zika virus was introduced into the Americas in 2015 and the case counts in the U.S. as well as in the U.S. Armed Forces peaked in 2016.[3] Of the 16 service member cases reported as probable or suspected, 12 were reported in 2016 **(data not shown).**

Rocky Mountain spotted fever

Confirmed cases of RMSF (n=54), unlike all other diagnoses that are reportable, were outnumbered by reports of probable (n=116) and suspected (n=54) cases of RMSF **(Table 2).** This phenomenon is likely the result of the necessity to confirm the diagnosis of RMSF (and related rickettsial diseases) via the performance of acute and convalescent serological studies or other more sophisticated tests such as a PCR test for DNA, immunohistochemistry of a biopsy specimen, or a positive culture. The current RME guidelines include RMSF in the broader category of Spotted Fever Rickettsiosis, which includes conditions with similar clinical presentations that may be distinguished only with the testing procedures mentioned above.

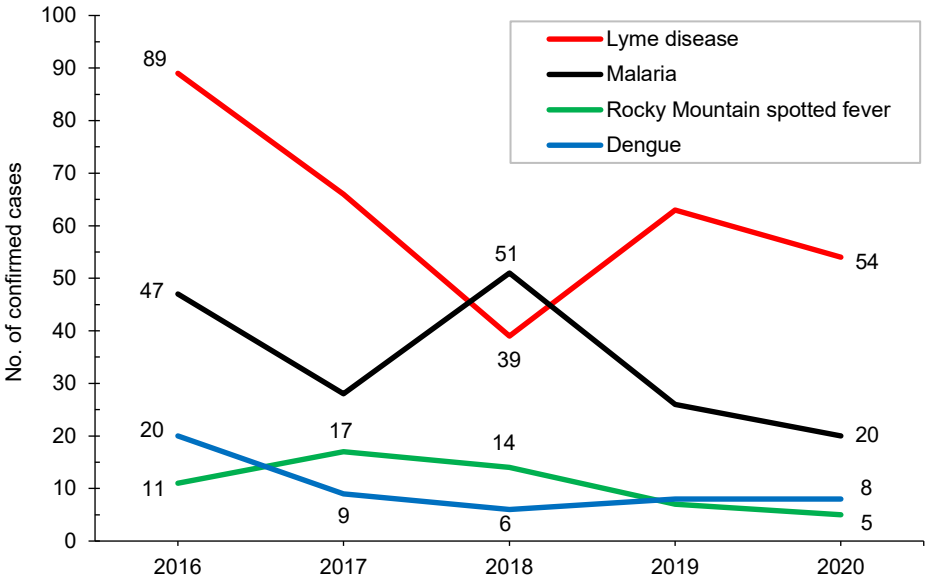
Dengue

Of the total of 60 cases of dengue reported via RME, 51 were described as confirmed **(Table 2).** At least 18 of those confirmed cases were reported by an overseas treatment facility and an additional 14 cases were linked to an overseas travel location. The most commonly cited of those locations were Djibouti (n=7) and the Philippines (n=5). There were relatively few RME cases of dengue that were classified as probable (n=5) or suspected (n=4) **(data not shown).**

Leishmaniasis

There were 16 confirmed cases of leishmaniasis reported during the period but only 2 of them were reported in 2019 and none in 2020 **(Table 2, data not shown).** Of the 6 cases for which the reports mention a location where the service member may have acquired the infection, 5 specify either Iraq, Afghanistan, or Syria and 1 mentions Palau **(data not shown).** Probable cases numbered 2 and there were no suspected cases.

FIGURE. Annual counts of confirmed cases of most common RMEs, active and reserve components, U.S. Armed Forces, 2016–2020



RME, reportable medical event; No., number.

TABLE 3. Frequency of hospitalizations of service members with RMEs for vector-borne diseases and associated number of hospital bed days, active and reserve components, U.S. Armed Forces, 2016–2020

Diagnoses	Total RME reports[a]	Total associated hospitalizations[a]	% of RME reports with associated hospitalization[a]	Hospital bed days[a]
	No.	No.	No.	No.
Malaria	184	80	43.5	308
Lyme disease	438	11	2.5	71
Dengue	60	7	11.7	35
Arboviral diseases, neuroinvasive and non-neuroinvasive	12	4	33.3	19
Tick-borne encephalitis	(2)	(1)	50.0	(1)
Rocky Mountain spotted fever	224	1	0.4	7
Typhus	5	1	20.0	1
Total	923	104		441

[a]Numbers in parentheses are included in the totals for the broad category of "arboviral diseases, neuroinvasive and non-neuroinvasive".
RME, reportable medical event.

Arboviral diseases, neuroinvasive and non-neuroinvasive

The 3 confirmed cases and 1 suspected case of West Nile virus infection were diagnosed in the continental U.S. and the single confirmed and probable cases of tick-borne encephalitis were diagnosed in Germany **(data not shown).** Among the total of 12 cases that were reported in this broad category, 7 were associated with Germany and 5 with the U.S. **(data not shown).**

Other

The remaining 5 diagnostic categories of RMEs were associated with a total of 17 confirmed cases, 12 probable cases, and 7 suspected cases over the 5-year surveillance period **(Table 2)**. The most recent confirmed cases of chikungunya were 2 that were diagnosed in 2019 and they were associated with recent travel to the Philippines and Djibouti, respectively **(data not shown)**.

Hospitalizations

During the 5-year surveillance period, there were 1,068 RME reports submitted for confirmed, probable, and suspected cases. Associated with the service members who were the subjects of those reports, there were 105 instances of hospitalization for which the records of inpatient care specified the diagnosis of the reportable condition. Such hospitalizations reflected only 6 different reportable diagnoses **(Table 3)**. Of the 184 reported cases of malaria, 43.5% were associated with hospitalizations (n=80) for which a malaria diagnosis was recorded. For Lyme disease, the 11 hospitalizations represented 2.5% of all RME diagnoses of that condition; for dengue, the 7 hospitalizations were associated with 11.7% of all RME diagnoses; for arboviral diseases, there were 4 hospitalizations representing 33.3% of all cases that were reported. Finally, there were single hospitalizations for RMSF and typhus that represented 0.4% and 20% of RMEs for those respective diagnoses **(Table 3)**.

EDITORIAL COMMENT

The identities of the most common vector-borne diseases in this analysis were similar to those documented in previous studies. For example, *MSMR* reports covering the years 1995–1999 and 2010–2016 noted that the most common diseases included Lyme disease, malaria, RMSF, dengue fever, and leishmaniasis, just as was the case for 2016–2020.[1,4] The only exceptions to the lists of most common diseases were due to the pandemic occurrences of chikungunya and Zika virus infections starting in 2013.[3,5]

The methods employed in this surveillance study differed significantly from the two studies previously mentioned. The counts for 2016–2020 were based solely on RMEs electronically submitted by public health/preventive medicine specialists who evaluated the available information for each case in order to render an evaluation as to whether or not the diagnosis was confirmed, probable, or suspected. The previous studies utilized DMSS records of hospitalizations and/or outpatient encounters to identify cases. It is most noteworthy that using only the documentation of outpatient diagnoses to qualify as a "suspected" case, as was one of the criteria in 2010–2016, is a highly sensitive, but very non-specific means of identifying cases. The employment of just RMEs to identify and count cases of vector-borne diseases increases the probability they are true cases of the diseases of interest. However, the omission of inpatient and outpatient diagnoses of these diseases likely yields an underestimate of the true incidence of some of the conditions.

The analysis of hospitalizations among RME cases revealed that most reportable vector-borne diseases were not associated with a hospitalization within 30 days before or after the reported date of illness onset. The correlation between hospitalization and diagnosis of a reportable disease is mainly a reflection of the severity of illness. The diseases of interest in this study have a broad spectrum of clinical severity and, in particular, if a given disease can be readily treated with a highly effective antimicrobial agent, then rates of hospitalization may be quite low.

The reader is referred to the February 2018 *MSMR* article on this subject for further discussion of the topics of Lyme disease incidence in the U.S., the years of peak incidence of chikungunya and Zika virus infections, the declining incidence of leishmaniasis associated with reduced presence of service members in the Middle East, and the pitfalls of using outpatient diagnoses for surveillance.[1]

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