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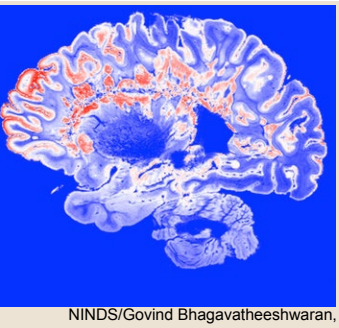

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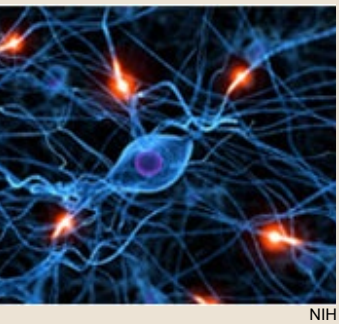

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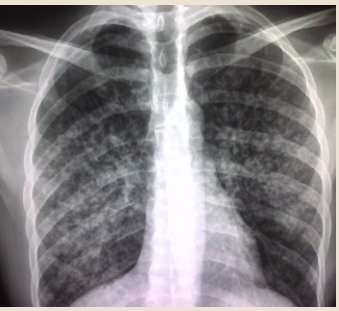


Sandra Bermúdez

Multiple Sclerosis Among Service Members of the Active and Reserve Components of the U.S. Armed Forces and Among Other Beneficiaries of the Military Health System, 2007–2016

Valerie F. Williams, MA, MS; Shauna Stahlman, PhD, MPH; Saixia Ying, PhD

During 2007–2016, a total of 2,031 active component service members received incident diagnoses of multiple sclerosis (MS), for an overall unadjusted incidence rate of 14.9 cases per 100,000 p-yrs. The average overall unadjusted rate among reserve/guard members during this surveillance period was 6.9 cases per 100,000 persons. In both components, women had a higher overall incidence of MS than men across all race/ethnicity groups. Overall rates of MS were highest among non-Hispanic black service members. Crude annual incidence rates among active component members decreased slightly during 2007–2016, while rates among reserve/guard members were relatively stable. Among active component members, the annual female-to-male incidence ratios decreased during the 10-year period (3.7:1 in 2007 to 2.5:1 in 2016). Annual numbers of incident cases of MS decreased among non–service member Military Health System beneficiaries during this period. The median age at MS case-defining diagnosis was 32 years among active component members, 37 years among reserve/guard members, and 48 years among non–service member beneficiaries. The median time intervals between initial presentation and case-defining MS-related encounter ranged from 15 days among reserve/guard component members to 20 days among active component service members. This study makes a useful contribution to the literature on temporal changes in the incidence of MS by sex and race/ethnicity.

Multiple sclerosis (MS) is an immune-mediated inflammatory demyelinating disease of the central nervous system, affecting approximately 400,000 people in the U.S. and more than 2 million people worldwide.[1,2] Common MS symptoms include numbness and tingling in limbs, visual loss, motor weakness, double vision, gait disturbance, and balance problems.[3] Disease activity is determined by clinical relapses or magnetic resonance imaging (MRI) evidence of central nervous system lesions.[3] The inflammatory demyelination and axonal injury that characterize MS result in significant clinical disability and economic burden.[4,5]

The clinical course of MS is highly variable and evolves over many years. The main MS phenotypes are relapsing and remitting (RRMS) and progressive disease.[6] A relapsing and remitting course is the predominant MS presentation (85%) and is characterized by periods of acute decline in neurologic functioning followed by partial or complete recovery.[7,8] The median age of onset for RRMS is 30 years.[7] Between 10% and 15% of the MS population are affected by primary progressive MS (PPMS), which is associated with rapid disease progression.[8] The median age of onset for PPMS is 40 years.[8] Clinically isolated syndrome (CIS) also is considered one of the MS disease courses. A CIS is an initial event of demyelination that lasts 24 hours or more and is consistent with MS but is isolated in time and may or may not be isolated in space (i.e., symptoms present at a single site/lesion in one location vs. symptoms present at multiple sites/lesions in multiple locations).[9] Individuals who experience CIS may or may not develop MS in the future.[9] Based on the 2010 revisions to the McDonald criteria for MS, the diagnosis of MS can be made when CIS is accompanied by MRI findings (prior lesions) indicating that an earlier episode of damage occurred in a different location in the central nervous system.[10] With advances in MRI technology and improved diagnostic criteria, it is likely that MS will be diagnosed more quickly, and that fewer people will be diagnosed with CIS.[11] An accurate diagnosis is critical at this time because starting treatment with a disease-modifying therapy may delay or prevent a second neurologic episode and, therefore, the conversion of CIS to clinically definite MS.[11]

The active component of the U.S. Armed Forces comprises predominantly young adults, the major at-risk population for MS.[12,13] The associated disability, cost of treatment/clinical management, and potential impact on readiness and deployability make MS of particular relevance to the U.S. military population.[4] In January 2011, the *MSMR* reported the numbers, incidence rates, trends, and correlates of MS diagnoses among active component U.S. service members during 2000–2009.[14] Since that time, one other study has reported incidence rates among a U.S. military population: Gulf War–era veterans during 1990–2007.[15] Although the Gulf War veteran study yielded incidence rates that were slightly higher than those reported in the 2011 *MSMR* article, the overall incidence patterns by sex, race/ethnicity, and

service were similar.[14,15] The current analysis updates and expands on this earlier work by including reserve/guard component members as well as other beneficiaries of the Military Health System (MHS).

METHODS

The surveillance period was 1 January 2007 through 31 December 2016. The surveillance population included active and reserve component members of the U.S. Army, Navy, Air Force, and Marine Corps who served at any time during the surveillance period. The non-military surveillance population included other beneficiaries (i.e., retired service members, family members, and other dependents of service members and retirees, and other authorized government employees and their family members) of the MHS who accessed care through either a military medical facility/provider or a civilian facility/provider (if paid for by the MHS). The data used in this analysis were obtained from the Defense Medical Surveillance System (DMSS), which maintains electronic records of all actively serving U.S. military members' and other beneficiaries' hospitalizations and ambulatory visits in U.S. military and civilian (contracted/purchased care through the MHS) medical facilities worldwide.

For surveillance purposes, incident cases of MS were identified from records of hospitalizations and ambulatory visits that included diagnostic codes (ICD-9 and ICD-10) specific for MS **(Table 1)**. An incident case of MS was defined as a service member or other beneficiary having DMSS documentation of any one of the following: 1) one hospitalization with a defining diagnosis in any diagnostic position; or 2) two outpatient medical encounters at least 1 day apart with a defining diagnosis of MS in any diagnostic position; or 3) one hospitalization or one outpatient medical encounter with any of the defining diagnoses of "other demyelinating disease of the central nervous system" in any diagnostic position, followed by one outpatient medical encounter with a defining diagnosis of MS in any diagnostic position.

The incident date was considered the date of the first hospitalization or outpatient medical encounter that included a diagnosis of MS or a case-defining diagnosis of "other demyelinating diseases of the central nervous system." An individual could be considered a case once per lifetime. Service members with case-defining MS diagnoses before the start of the surveillance period were excluded from the analysis because they were not considered at risk of incident (i.e., first ever) MS. Person-time incidence rates were calculated only for members of the active component (number of cases per 100,000 person-years [p-yrs] of service). Person-time for active component service members was censored when any of the following conditions was met: an individual was identified as an MS case; an individual left service or died; the surveillance period ended. Person-time incidence rates were not calculated for reserve/guard component members because start and end dates of active duty service periods (and corresponding TRICARE eligibility) were not available. Instead, incidence rates for reserve/guard members were calculated per 100,000 individuals who served at any time during the given calendar year. Average rates during the overall surveillance period were calculated by taking the mean of the annual rates. Individuals not at risk during the given calendar year were removed. Similarly, rates were not computed for non–service member beneficiaries because their time periods of TRICARE eligibility were not available.

The time between the initial and case-defining medical encounter was calculated for each incident case. The total number of inpatient and outpatient encounters for MS were computed for the 2016 calendar year among all MS cases and among cases diagnosed in 2016.

RESULTS

Active component

During 2007–2016, a total of 2,031 active component service members received incident diagnoses of MS, for an overall crude (unadjusted) incidence rate of 14.9 cases per 100,000 p-yrs **(Table 2)**. The overall rate of MS among females (34.4 cases per 100,000 p-yrs) was three times that of males (11.5 cases per 100,00 p-yrs). The highest overall incidence rates were observed among service members diagnosed after age 30 with rates peaking among those aged 40 years or older (26.4 cases per 100,000 p-yrs) **(Table 2)**. The median age at case-defining MS diagnosis was 32 years (interquartile range [IQR]=26–38) **(data not shown)**. There were no pronounced differences in median age at diagnosis between race/ethnicity groups among incident MS cases in the active component **(data not shown)**. The overall incidence rate was

TABLE 1. ICD-9 and ICD-10 diagnostic codes used for multiple sclerosis case classification[a]

Condition	ICD-10 codes	ICD-9 codes
Multiple sclerosis	G35	340
Other demyelinating diseases of the central nervous system	G36.*, G37.*	341.0, 341.1, 341.2*, 341.8, 341.9

[a]Armed Forces Health Surveillance Branch. Surveillance Case Definitions: Multiple sclerosis. https://www.health.mil/Military-Health-Topics/Health-Readiness/Armed-Forces-Health-Surveillance-Branch/Epidemiology-and-Analysis/Surveillance-Case-Definitions

*Any digit/character, up to and including the last position

highest among non-Hispanic black service members (20.3 cases per 100,000 p-yrs) and lowest among Hispanic service members and those of other or unknown race/ethnicity (11.3 cases per 100,000 p-yrs and 11.2 cases per 100,000 p-yrs, respectively). Overall race/ethnicity-specific sex incidence ratios (female to male) ranged from 2.6:1 among non-Hispanic black service members to 3.8:1 among service members of other or unknown race/ethnicity. The overall incidence rate was higher in the Air Force than all other services (1.5 times that of the Navy and 2.2 times that of the Marine Corps) **(Table 2)**. Among military occupational groups, service members in healthcare occupations had the highest overall incidence rate (23.4 cases per 100,000 p-yrs) and those in combat-specific occupations had the lowest overall rate (9.6 cases per 100,000 p-yrs). The overall incidence rate of MS was 18.2% higher among officers compared to enlisted service members and 22.4% higher among service members who had ever been deployed to CENTCOM compared to those who had never been deployed **(Table 2)**.

During the 10-year surveillance period, crude annual incidence rates of MS decreased by 25.4%. Annual rates of MS were higher among female service members than male service members throughout the 10-year period and decreased by 43.2% during this time **(Figure 1)**. The annual rates of MS among male service members decreased by 16.6% from 2007 to 2016. These reductions resulted in a decrease in the annual sex incidence ratios (female to male) during the surveillance period (3.7:1 in 2007 to 2.5:1 in 2016). The higher annual incidence rates among non-Hispanic black service members were consistent throughout the surveillance period and decreased by 40.8% during this time **(Figure 2)**. Stratification of annual incidence rates by race/ethnicity and sex showed that rates among non-Hispanic black females were higher than rates among non-Hispanic white females in all but 4 years of the surveillance period (2010, 2011, 2013, and 2015) **(Figure 3)**. Non-Hispanic black males showed a similar pattern with annual incidence rates that were higher than rates among their non-Hispanic white counterparts in 7 of the 10 years (2007 and 2009–2014). The decrease in sex incidence ratios was apparent among non-Hispanic white (4.4:1 in 2007 to 2.2:1 in 2016) and non-Hispanic black service members (3.5:1 in 2007 to 2.6:1 in 2016). For the military services, annual rates were highest among Air Force members in all years of the surveillance period and lowest among Marine Corps members in all years except 2014 **(Figure 4)**. Throughout the surveillance period, rates among service members in healthcare occupations were consistently higher than those in the other occupational groups **(data not**

TABLE 2. Incident cases and incidence rates of multiple sclerosis, active component, U.S. Armed Forces, 2007–2016

	Total 2007–2016		
	No.	%	Rate[a]
Total	2,031	100.0	14.9
Sex			
Male	1,340	66.0	11.5
Female	691	34.0	34.4
Age at diagnosis			
<20	72	3.5	4.3
20–24	306	15.1	8.5
25–29	468	23.0	14.4
30–34	405	19.9	19.3
35–39	399	19.6	25.2
40+	381	18.8	26.4
Race/ethnicity			
Non-Hispanic white	1,230	60.6	14.8
Non-Hispanic black	448	22.1	20.3
Hispanic	192	9.5	11.3
Other/unknown	161	7.9	11.2
Male, by race/ethnicity			
Non-Hispanic white	886	43.6	12.0
Non-Hispanic black	243	12.0	14.5
Hispanic	124	6.1	8.8
Other/unknown	87	4.3	7.4
Female, by race/ethnicity			
Non-Hispanic white	344	16.9	36.9
Non-Hispanic black	205	10.1	38.4
Hispanic	68	3.3	24.1
Other/unknown	74	3.6	28.2
Service			
Army	765	37.7	14.6
Navy	428	21.1	13.3
Air Force	659	32.4	20.3
Marine Corps	179	8.8	9.3
Military grade			
Enlisted	1,636	80.6	14.4
Officer	395	19.4	17.1
Military occupation			
Combat-specific	193	9.5	9.6
Health care	276	13.6	23.4
Other	1,562	76.9	14.9
Ever deployed to CENTCOM			
No	955	47.0	13.4
Yes	1,076	53.0	16.4

[a]Rate per 100,000 person-years

shown). During 2012–2016, the annual incidence rates of service members who had ever deployed to CENTCOM were higher than for those who had never been deployed **(data not shown).**

Among active component service members, the distribution of the time interval between initial presentation and case-defining MS-related encounter was unimodal with a median of 20 days **(Figure 5, data not shown)**. Approximately four-fifths (80.5%; n=1,635) of the incident MS cases received their case-defining diagnoses between 0 and 90 days after initial presentation. The vast majority (93.3%) of cases received their case-defining diagnoses within a year of initial presentation **(Figure 5)**.

Close to two-thirds (66.0%) of the incident MS cases among active component service members met the case definition criteria of having had an MS-related (ICD-9: 340; ICD-10: G35) hospitalization or two MS-related ambulatory visits during the surveillance period **(data not shown)**. The remainder (34.0%) met the case definition criteria of having had an initial diagnosis of "other demyelinating disease of the central nervous system" (CIS) followed by a case-defining diagnosis (outpatient) of MS **(data not shown)**.

Among active component service members in 2016, approximately one-third (33.9%; n=688) of all MS cases had at least one MS-related ambulatory encounter subsequent to their case-defining encounter. These cases contributed a total of 3,347 ambulatory encounters, representing about five outpatient visits per individual. In 2016, slightly less than 2% (n=38) of all cases had one or more MS-related hospitalizations. These cases contributed a total of 418 hospital bed days, representing about 11 bed days per individual. Of the incident cases diagnosed in 2016 (n=154), the vast majority (93.5%) had at least one MS-related ambulatory encounter in the months after their case-defining diagnoses. On average, there were approximately seven MS-related outpatient visits per individual. Less than one-eighth (11.7%; n=18) of the cases diagnosed with MS in 2016 had one or more inpatient encounters during 2016. These cases contributed a total of 85 hospital bed days, representing about five bed days per individual.

FIGURE 1. Annual incidence rates of multiple sclerosis, total and by sex, active component, U.S. Armed Forces, 2007–2016

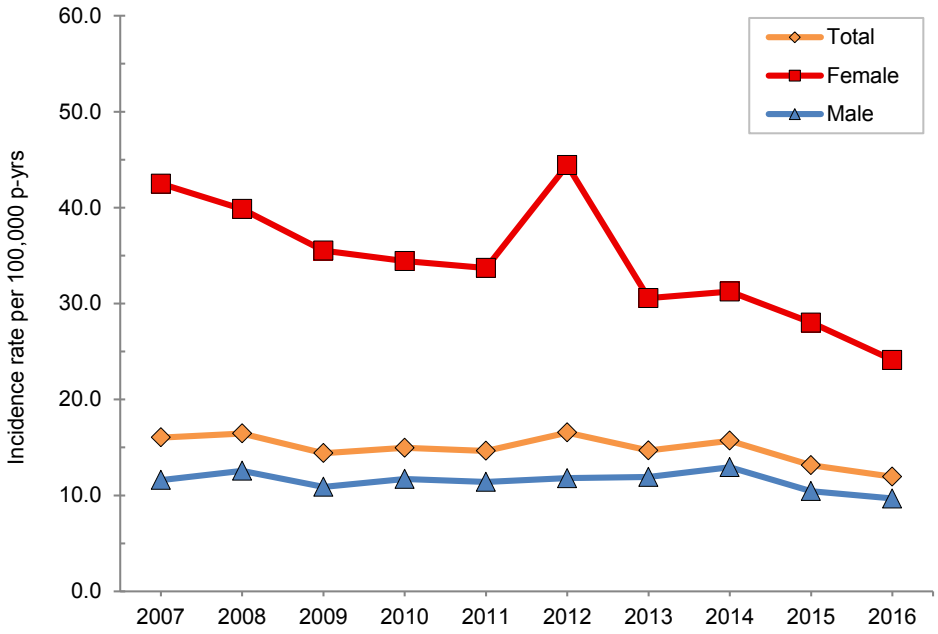
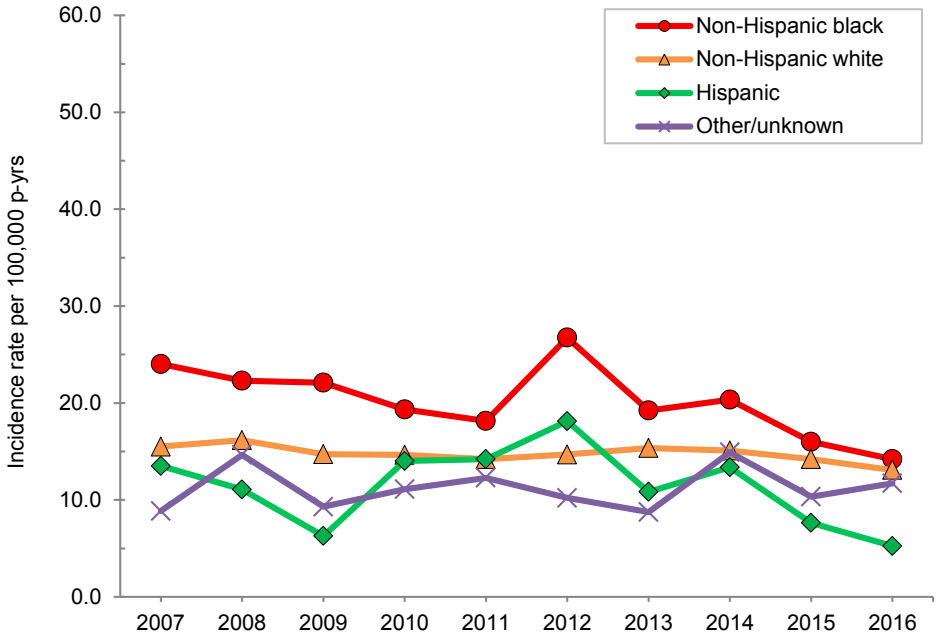


FIGURE 2. Annual incidence rates of multiple sclerosis, by race/ethnicity, active component, U.S. Armed Forces, 2007–2016



Reserve/guard component

During the 10-year surveillance period, there were 650 incident diagnoses of MS among reserve/guard component service members, for an average overall crude incidence rate of 6.9 cases per 100,000 persons **(Table 3)**. The average overall rate of MS among females (15.0 cases per 100,000 persons) was approximately three times that of males (5.1 cases per 100,000 persons). The

FIGURE 3. Annual incidence rates of multiple sclerosis, by race/ethnicity (non-Hispanic black and non-Hispanic white) and sex, active component, U.S. Armed Forces, 2007–2016

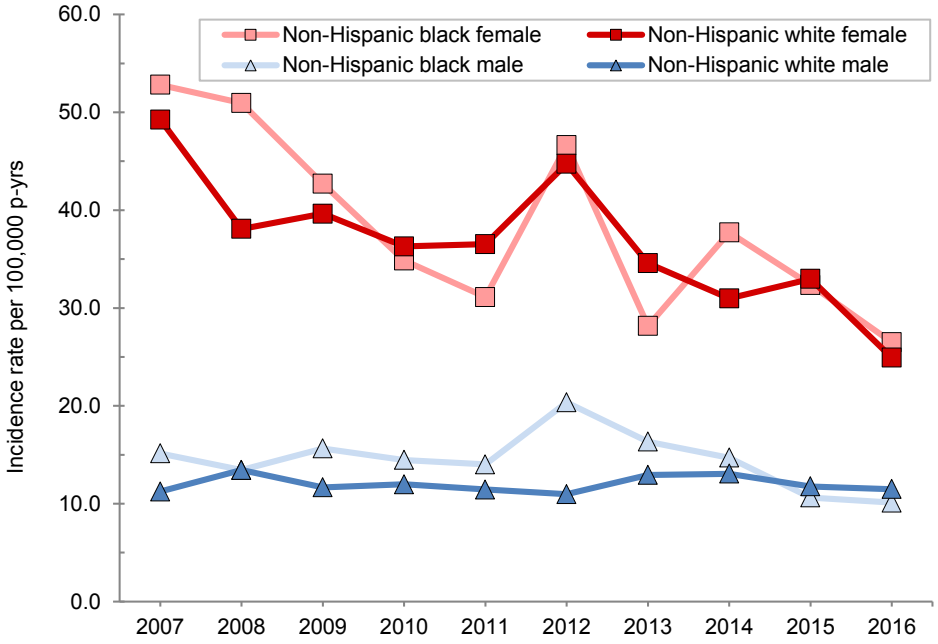
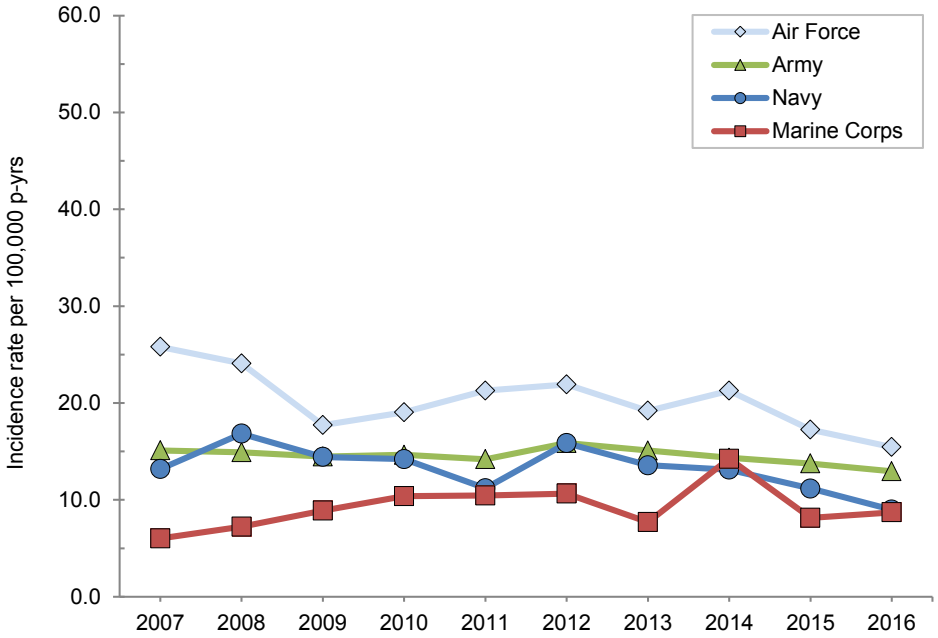


FIGURE 4. Annual incidence rates of multiple sclerosis, by service, active component, U.S. Armed Forces, 2007–2016



highest average overall incidence rates were observed among reserve/guard component members diagnosed after age 35 with rates peaking among those aged 35–39 years (11.8 cases per 100,000 persons) **(Table 3)**. The median age at case-defining MS diagnosis was 37 years (IQR=29–44) **(data not shown)**. There were no pronounced differences in median age at diagnosis between race/ethnicity groups among incident MS cases in the reserve/guard component **(data not shown)**. The average overall incidence rate of MS was highest among non-Hispanic black reserve/guard component members (9.5 cases per 100,000 persons) and lowest among Hispanic reserve/guard component members and those of other or unknown race/ethnicity (5.4 and 5.0 cases per 100,000 persons, respectively) **(Table 3)**. The average overall rate was higher among Navy and Air Force members (9.0 and 8.1 cases per 100,000 persons, respectively) than Army and Marine Corps members (6.6 and 2.8 cases per 100,000 persons, respectively). Reserve/guard members in healthcare occupations had the highest average overall incidence rate of MS (11.4 cases per 100,000 persons) and those in combat-specific occupations had the lowest overall rate (4.0 cases per 100,000 persons). The overall average incidence rate of MS was 51.2% higher among officers, compared to enlisted service members **(Table 3)**.

Among reserve/guard component members, the crude annual incidence rates of MS remained relatively stable throughout the surveillance period **(Figure 6)**. Annual rates of MS were consistently higher among females than males during the 10-year period. The annual incidence rates among females fluctuated between 12.0 (2014) and 18.4 cases per 100,000 persons (2013), while rates among males decreased by 24.5% during the period **(Figure 6)**. The annual sex incidence ratios ranged from 2.4:1 in 2014 to 4.1:1 in 2016. Small group sizes precluded stratification by race/ethnicity and other demographic and military characteristics.

The distribution of the time interval between initial presentation and case-defining MS-related encounter among reserve/guard component members was similar in shape to that observed among active component members **(data not shown)**. The median interval was 15 days with four-fifths (80.0%; n=520) of the MS cases among service members in the reserve/guard component occurring between 0 and 90 days after initial presentation. The vast majority (93.1%) of cases received their case-defining diagnoses within a year of initial presentation **(data not shown)**.

Among reserve/guard component members, slightly less than one-quarter (23.5%) of the incident MS cases met the case definition criteria of having had an

FIGURE 5. Time interval between initial diagnosis and case-defining diagnosis among multiple sclerosis cases, active component, U.S. Armed Forces, 2007–2016

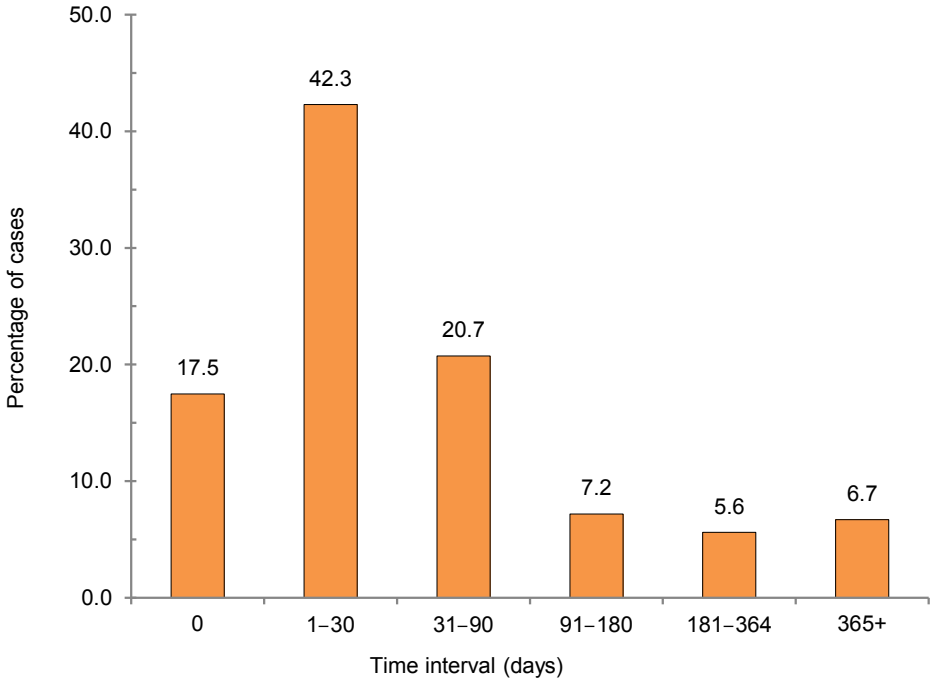
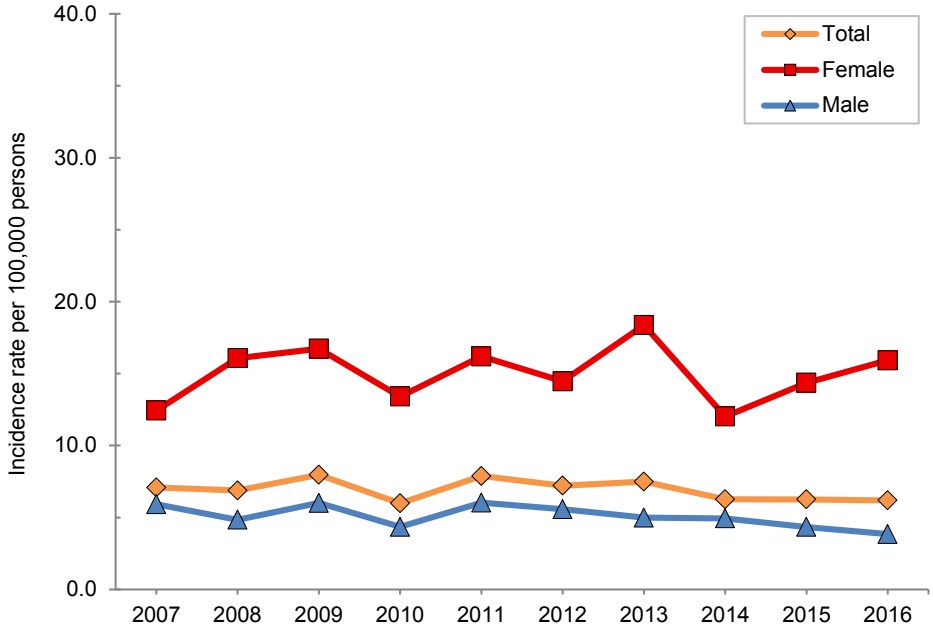


FIGURE 6. Annual incidence rates of multiple sclerosis, total and by sex, reserve/guard component, U.S. Armed Forces, 2007–2016



initial diagnosis of "other demyelinating disease of the central nervous system" (CIS) followed by an ambulatory visit with a case-defining diagnosis of MS. The remaining MS cases met the case definition criteria of having had an MS-related hospitalization or two MS-related outpatient encounters during the surveillance period **(data not shown)**.

About one-third (32.9%; n=214) of all MS cases among reserve/guard component members had at least one MS-related outpatient encounter in 2016. These cases contributed a total of 929 outpatient encounters, representing about four ambulatory visits per individual. In 2016, slightly less than 2% (n=10) of all cases had one or more MS-related hospitalizations during the surveillance period. These MS cases contributed a total of 111 hospital bed days, representing about 11 bed days per individual. Of the incident cases diagnosed in 2016 (n=56), the vast majority (83.9%) had at least one MS-related ambulatory encounter in the months after their case-defining diagnoses. On average, there were about five MS-related ambulatory visits per individual. About 10% (n=6) of the cases diagnosed with MS in 2016 had one or more inpatient encounters during 2016. These cases contributed a total of 65 hospital bed days, representing about 11 bed days per individual **(data not shown)**.

Other beneficiaries of the MHS

During 2007–2016, there were 20,849 incident diagnoses of MS among non–service member beneficiaries of the MHS. The majority of incident MS diagnoses were among females (79.9%) and those aged 40 years or older (67.9%). Limited availability of information on race/ethnicity for this population precluded stratification by this demographic characteristic. The median age at MS case-defining diagnosis was 48 years (IQR=35–60) **(data not shown)**. Between 2007 and 2016, annual numbers of incident cases of MS decreased among non–service member MHS beneficiaries **(Figure 7)**. The annual numbers of female MS cases were consistently higher than the annual numbers of male cases throughout this period.

Among non–service member beneficiaries, the distribution of the time intervals between initial presentation and case-defining MS-related encounter was similar to those observed for incident MS cases among active component and reserve/guard component service members **(data not shown)**. The median interval was 19 days with three-quarters (75.6%; n=15,764) of the MS cases among non–service

TABLE 3. Incident cases and incidence rates of multiple sclerosis, reserve/guard component, U.S. Armed Forces, 2007–2016

	Total 2007–2016		
	No.	%	Rate[a]
Total	650	100.0	6.9
Sex			
Male	390	60.0	5.1
Female	260	40.0	15.0
Age at diagnosis			
<20	7	1.1	0.7
20–24	55	8.5	3.1
25–29	103	15.8	5.4
30–34	97	14.9	7.5
35–39	127	19.5	11.8
40+	261	40.2	11.1
Race/ethnicity			
Non-Hispanic white	428	65.8	6.8
Non-Hispanic black	136	20.9	9.5
Hispanic	51	7.8	5.4
Other/unknown	35	5.4	5.0
Male, by race/ethnicity			
Non-Hispanic white	278	42.8	5.2
Non-Hispanic black	57	8.8	5.8
Hispanic	35	5.4	4.6
Other/unknown	20	3.1	3.6
Female, by race/ethnicity			
Non-Hispanic white	150	23.1	15.9
Non-Hispanic black	79	12.2	17.8
Hispanic	16	2.5	8.7
Other/unknown	15	2.3	9.6
Service			
Army	417	64.2	6.6
Navy	66	10.2	9.0
Air Force	154	23.7	8.1
Marine Corps	13	2.0	2.8
Military grade			
Enlisted	517	79.5	6.4
Officer	133	20.5	9.7
Military occupation			
Combat-specific	48	7.4	4.0
Health care	83	12.8	11.4
Other	519	79.8	7.0
Ever deployed to CENTCOM			
Never deployed	345	53.1	6.5
Ever deployed	305	46.9	7.5

[a]Average annual rate per 100,000 persons

member beneficiaries occurring between 0 and 90 days. The vast majority (90.8%) of cases received their case-defining diagnoses within a year of their initial presentation **(data not shown)**.

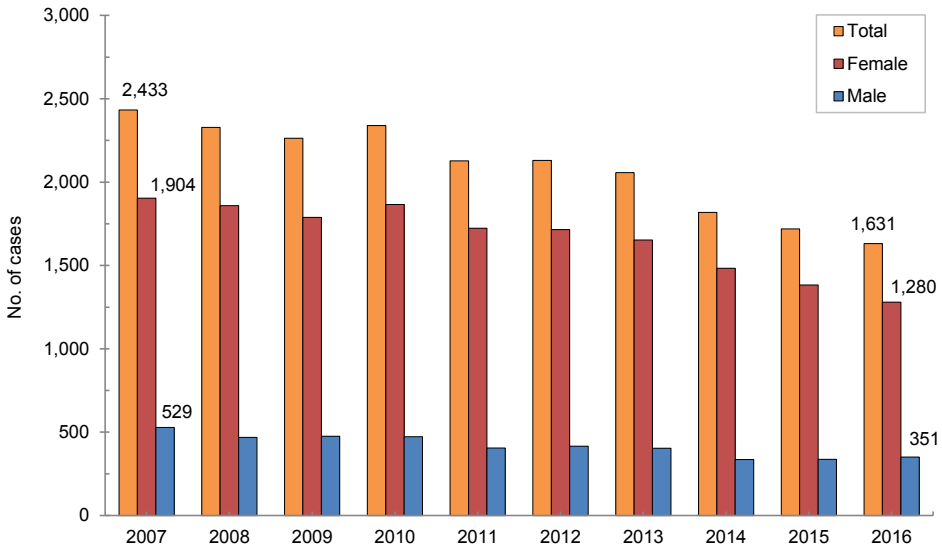
Among non–service member beneficiaries of the MHS, 11.3% of the incident MS cases met the case definition criteria of having had an initial diagnosis of "other demyelinating disease of the central nervous system" (CIS) followed by an ambulatory visit with a case-defining diagnosis of MS. The remaining MS cases met the case definition criteria of having had an MS-related hospitalization or two MS-related outpatient encounters during the surveillance period **(data not shown)**.

Three-quarters (75.4%; n=15,721) of all MS cases among non–service member MHS beneficiaries had at least one MS-related outpatient encounter in 2016. These cases contributed a total of 87,784 ambulatory visits, representing about six MS-related outpatient encounters per individual. In 2016, less than 4% (n=744) of all cases had one or more MS-related hospitalizations. These MS cases contributed a total of 19,689 hospital bed days, representing about 26 bed days per individual. Of the incident cases diagnosed in 2016 (n=1,631), three-quarters (75.2%) had at least one MS-related ambulatory encounter in the months after their case-defining diagnosis. On average, there were about five MS-related outpatient visits per individual. Approximately 8% (n=129) of the cases diagnosed with MS in 2016 had one or more inpatient encounters during this year. These cases contributed a total of 2,444 hospital bed days, representing about 19 bed days per individual.

EDITORIAL COMMENT

This report documents a crude overall incidence rate of MS of 14.9 cases per 100,000 p-yrs among active component U.S. service members. Using an MS case definition similar to that employed in the current study, the 2011 *MSMR* analysis yielded a crude overall incidence rate among active component U.S. service members of 12.9 cases per 100,000 p-yrs during 2000–2009.[14] An average annual age-specific (17–50 years) MS incidence rate of 9.6 cases per 100,000 p-yrs has been reported among a Gulf War–era (1990–2007) U.S. military veteran population.[15] Differences in case-defining diagnostic criteria likely account, at least in part, for the difference in these overall incidence estimates. For example, MS cases included in the study of a Gulf War–era U.S. military-veteran population were identified first by diagnostic codes and then verified using standardized clinical criteria (e.g., McDonald criteria).[10,15,16] Because the MS cases in the current and the

FIGURE 7. Counts of multiple sclerosis cases among non–service member beneficiaries of the Military Health System, total and by sex, 2007–2016



2011 *MSMR* analyses were defined exclusively by diagnostic codes and not verified using clinical records, the resulting rates are undoubtedly inflated.

There are few U.S. civilian population studies of MS incidence with which to compare the current results. At the time of this report, only one U.S. study that focused on an ethnically diverse population during a comparable time period was available in the published literature. Carried out in Southern California during 2008–2010, this population-based retrospective cohort study reported a crude overall MS incidence rate of 5.0 per 100,000 p-yrs.[17] Diagnostic codes were used to identify potential cases and diagnoses were confirmed by MS specialists' review of medical records, MRI scans, and diagnostic test results using the revised McDonald criteria.[17] Contemporary MS incidence estimates are available for various regions of Canada and range from 7.9 per 100,000 population (unadjusted rate) in British Columbia to 11.4 per 100,000 population (age- and sex-adjusted rate) in Manitoba.[18,19] Differences between estimates of MS incidence from studies of military populations and those from various general populations should be interpreted with caution for several reasons. In addition to differences in case-defining diagnostic criteria, there are potential differences across the studies in terms of methods used to compute estimates, demographic characteristics (e.g., age, gender, race/ethnicity) of populations, and the reliability of recorded diagnoses. Specifically, age- and/or sex-adjusted incidence estimates are not directly comparable to the crude (unadjusted) estimates. Regarding demographic characteristics, the U.S. military is predominantly composed of young and middle-aged adults, whereas general populations include all age groups (some, such as the very young and the very old, with very low risk of first/incident clinical presentations of MS).[20] In addition, the readily available access to health care in the military (unrestricted access to health care at no cost for active component service members) also may account for the increased incidence rates of MS observed in military populations.

The current analysis yielded a crude average overall rate of 6.9 cases per 100,000 persons among reserve/guard component members. To our knowledge, this is the first time that MS incidence has been reported for this component of the U.S. military.

Several of the demographic patterns of overall MS incidence rates during the surveillance period are similar to those reported in the earlier *MSMR* analysis.[14] As in the 2011 report, women had a higher overall incidence of MS than men across all race/ethnicity groups and overall rates of MS were highest among non-Hispanic black service members.[14] In the current study, these patterns were apparent among both active component service members and reserve/guard members and are consistent with existing North American literature on MS incidence by sex[14,15,17-19] and race/ethnicity.[14,15,17] As in the earlier *MSMR* analysis, the higher overall incidence of MS among non-Hispanic blacks was found among females, and to a lesser degree, among males.[14] Among active component service members, overall incidence rates were highest in the Air Force and lowest in the Marine Corps. Rates were also lowest among Marine Corps members in the Gulf War–era MS cohort.[15] Differences in rates among the services observed in the current study may reflect differences in demographic characteristics. For example, the active component of the Air Force has a higher proportion of females and may have an age distribution that differs from the other services.[21] Because female sex and older age are risk factors for MS, these differences may account, at least in part, for the elevated crude incidence rates observed among active component Air Force members. For members of the reserve/guard component, overall MS incidence rates were highest among those in the Navy or the Air Force and lowest among those in the Marine Corps. Overall incidence rates of MS were highest among active and reserve/guard members in healthcare occupations. This finding warrants further analysis to examine adjusted (e.g., by age and sex) incidence rates among service members within this occupational category.

Crude annual incidence rates among active component service members decreased by 25.4% during 2007–2016, while rates among reserve/guard component members were relatively stable over the course of the surveillance period. The decrease in annual incidence rates observed among active component members is largely a reflection of the decrease in annual rates among females during the surveillance period (43.2%); rates among males decreased by 16.6% during

the period. These reductions resulted in a decrease in the annual sex incidence ratios (female to male) during the 10-year period. Reductions in annual sex incidence ratios also have been observed in two recent Canadian studies.[18,19] In a recent study using a primary care database representative of the UK population, Mackenzie et al. reported a consistent downward trend in MS incidence rates among both sexes.[22] One possible explanation for the downward trend in MS incidence is a reduction in false-positive diagnoses through the use of improved diagnostic techniques and criteria. However, this potential explanation does not account for the difference in the rate of change in incidence by sex observed in the current study.

Among non–service member MHS beneficiaries, annual numbers of incident cases of MS decreased during the surveillance period; the annual numbers of female MS cases were consistently higher than those of male cases. It is important to note that the sex distribution of this population of non–service member beneficiaries is much more balanced (closer to 50% female) than the two service member populations in this analysis.[23] Given this difference in the sex distribution and the higher prevalence and incidence of MS among women in general, the markedly higher numbers of female MS cases observed among non–service member beneficiaries is not unexpected.

The median age at MS case-defining diagnosis was 32 years among members of the active component, 37 years among reserve/guard members, and 48 years among non–service member beneficiaries. This statistic was not presented in 2011 *MSMR* article but a mean age at diagnosis of 33.3 years (SD=7.9 years) was reported among service members with active duty during the Gulf War era.[15] There were no pronounced differences in median age at diagnosis between race/ethnicity groups among incident MS cases in the active component or the reserve/guard component. However, the median age at diagnosis among reserve/guard component members with MS was 5 years higher than that for active component members with MS. The median age at MS case-defining diagnosis among non–service member beneficiaries is most comparable with the median age of 42 years reported from a population-based cohort in Southern California.[17]

The median time intervals between initial presentation and case-defining MS-related encounter ranged from 15 days among reserve/guard component members to 20 days among active component service members. There were no pronounced differences between the three study populations in terms of the proportion of the incident MS cases who received their case-defining diagnoses between 0 and 90 days after initial presentation (range=76% to 81%). The 2011 *MSMR* analysis reported that a little over half (54%) of the MS cases had an interval of between 0 and 90 days.[14] This proportion is markedly lower than those observed in the current study. This difference likely reflects, at least in part, the effects of improved diagnostic techniques and criteria introduced over the past decade.

The proportion of MS cases with an initial diagnosis of CIS ("other demyelinating disease of the central nervous system") varied by group. Slightly more than one-third (34.0%) of the MS cases among active component members had an initial diagnosis of CIS, compared to 23.5% of cases among reserve/guard members and 11.3% cases among non–service member beneficiaries. Some CIS-related encounters among MS cases in the reserve/guard component may have occurred in the civilian healthcare system. Records for such encounters would not have been available for analysis, which may, in part, account for the lower proportion of reserve/guard MS cases with an initial CIS diagnosis compared to MS cases in the active component.

The results of this study should be interpreted with consideration of several important limitations. As previously mentioned, because the cases of MS were defined exclusively by diagnostic codes and not verified by professional clinical review, the numbers of cases of MS presented here are likely inflated. Wallin et al. found that only about half of patients with ICD-9 codes for MS within the medical record system of academically affiliated Veterans Affairs Medical Centers actually had a correct MS diagnosis after rigorous clinical review using the McDonald criteria.[15,16] Conversely, other factors could have led to MS incidence being underestimated. For instance, cases could have been missed if service members sought care from sources other than the MHS or purchased care providers, or if affected individuals terminated their military service after a single outpatient encounter with an MS diagnosis. In addition, incidence rates could not be computed for non–service member beneficiaries because their time periods of TRICARE eligibility were not available. Finally, because the summary of MS-related inpatient and outpatient encounters were computed for the 2016 calendar year, most MS cases diagnosed in 2016 did not have full 12-month follow-up periods.

Also, there are limitations to the generalizability of the findings because of the characteristics of the surveillance populations. For example, active component service members have unrestricted access to health care at no cost as well as open access to specialists; as such, this may limit the validity of comparisons to civilian populations, for whom limited access to, and inability to pay for, care may restrict hospitalization and use of outpatient services. Thus, generalizations of the observed results should be limited to similar groups during a similar time period.

As one of the few published U.S. studies of MS incidence among a demographically diverse population, this study makes a useful contribution to the literature on temporal changes in the incidence of MS by sex and race/ethnicity. Observed differences in incidence rates of MS by occupational category and service warrant further analysis to examine adjusted (e.g., by age, sex, race/ethnicity) incidence rates among service members within these categories. Findings also suggest a need for sensitivity analyses to assess the robustness of the apparent decrease in MS incidence observed in this study, particularly among females. Results indicating that non-Hispanic blacks have higher incidence of MS than non-Hispanic whites are consistent with recent literature and highlight the importance of studying a racially and ethnically diverse population as findings may lead to important insights into the etiology and prognosis of MS.[14,15,17,24]

MS has the potential to impose a significant operational and healthcare

burden on the military. Compared with direct all-cause medical costs for other chronic conditions reported in the literature, MS ranked second behind congestive heart failure.[4] Estimated costs of MS increase when comorbidities are taken into account. Comorbidities are common among individuals with chronic diseases, including MS.[24] Relative to the general population, people with MS have an increased risk of comorbidities such as cardiovascular disease (e.g., hypertension, stroke), psychiatric disorders (e.g., depression, anxiety), and autoimmune conditions (e.g., thyroiditis, systemic lupus).[26-30] Recent research indicates that comorbidity is associated with diagnostic delays, disability progression, and progression of lesion burden (as evidenced by magnetic resonance imaging).[30-35] Such findings highlight the importance of enhanced medical surveillance of the MS population to allow for targeted earlier interventions that may improve quality of life and reduce the impact of comorbidities on the functional status of those with MS.

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Challenges with Diagnosing and Investigating Suspected Active Tuberculosis Disease in Military Trainees

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Between 1 January 2010 and 31 December 2016, a total of 14 U.S. and international military personnel in training at Joint Base San Antonio–Lackland, TX, were hospitalized due to suspected pulmonary tuberculosis (TB); of these, five personnel were diagnosed with active TB disease. Only one TB case had pulmonary symptoms, but these symptoms were not suggestive of TB. The incidence rate in the training population was 1.89 per 100,000 population (95% CI: 0.81, 4.42), with a higher rate when restricted to international military students attending the Defense Language Institute English Language Center. No instances of TB transmission were identified. The variety of atypical presentations and their resulting diagnostic and public health challenges prompted this retrospective review of all hospitalized cases. This case series highlights both the importance of a high index of clinical suspicion when TB is being considered in close congregate settings as well as the risk of overreliance on acid-fast bacilli staining and nucleic acid amplification testing for ruling out active pulmonary disease in young, otherwise healthy trainees. Practical solutions are suggested.

The incidence rates of active tuberculosis (TB) disease in the general U.S. population[1] and the U.S. military[2] have declined over the past two decades, with foreign birth remaining one of the strongest correlates of risk. The disparity between foreign-born and U.S.-born persons, and its implications for prevention and elimination, are particularly important at Joint Base San Antonio (JBSA)–Lackland, TX. As one of the largest military installations in the U.S., JBSA-Lackland hosts three training platforms with trainees who include large numbers of foreign-born students: 1) the Defense Language Institute English Language Center (DLIELC), which conducts English language training for international military and civilian personnel from more than 110 countries; 2) the Inter-American Air Forces Academy (IAAFA), which provides military and technical education to Air Force members representing more than 20 Latin American and Caribbean countries; and 3) Basic Military Training (BMT), which provides the initial entry training for all enlisted members of the U.S. Air Force, among whom 1%–2% are born overseas.

Current TB testing programs vary by training platform. International military students are required to have a screening chest x-ray as part of their medical examination before arrival to evaluate for active disease. If abnormalities are found on arrival, further evaluation is performed by sputum smear tests and culture. IAAFA-projected aviators are also screened for active TB with a chest x-ray during their flight physical, conducted at variable times during training. New U.S. Air Force recruits are universally tested during BMT in-processing week for latent TB. U.S.-born recruits who report no history of a positive tuberculin skin test (TST) are screened with a single TST; all others are screened with an interferon gamma release assay (IGRA)—previously either the QuantiFERON®-TB or QuantiFERON®-TB Gold, and currently, as of January 2017, the T-SPOT® TB.

Regardless of birthplace, persons with pulmonary TB may present with a variety of clinical features. Atypical and asymptomatic presentations can pose diagnostic challenges, resulting in potentially serious treatment delays,[3,4] belated contact investigations, and increased transmission risk. Because of close-quarter living arrangements[5] and a degree of stress-induced immunosuppression,[6] the TB transmission risk may be greater in military training environments. Recently, there have been several atypical and asymptomatic presentations of active TB, as well as suspected cases that were eventually found not to have TB, among the population of trainees at JBSA-Lackland. This report summarizes the retrospective case series to review the challenges and lessons learned from these atypical presentations.

METHODS

All trainees at JBSA-Lackland who are suspected to have active TB disease, whether identified through screening or clinical symptoms, are admitted to the San Antonio Military Medical Center for evaluation. Admission is based on a reviewing physician's clinical suspicion; in review, this is typically based on risk factors such as positive TST or IGRA and

abnormal radiographic imaging. By using the trainee health hospitalization registry and cross-referencing against consult records of the San Antonio Military Medical Center Infectious Disease Service, a case list was generated for all JBSA-Lackland trainees hospitalized for TB diagnostic evaluation between 1 January 2010 and 31 December 2016.

For each case, a chart review was conducted to collect the following information: age, sex, country of birth, and state of birth, if U.S.-born; history of Bacillus Calmette–Guérin (BCG) vaccination; type and duration of symptoms, if any; results of TST, IGRA, chest x-ray, and chest computed tomography (CT); results of testing of sputum or other body fluid by acid-fast bacilli (AFB) staining, culture, and GeneXpert, an automated nucleic acid amplification test used to detect *Mycobacterium tuberculosis* DNA; and final diagnosis. For those with culture-positive TB, the results of drug resistance testing for first-line anti-TB drugs were obtained through either the electronic health record or regional health department. For foreign-born trainees without any BCG documentation in the record, receipt of the vaccination was presumed on the basis of country-specific standard policy, as outlined in the BCG World Atlas (www.bcgatlas.org). For the cases of confirmed pulmonary TB, the public health contact investigations were reviewed.

To allow for better comparison to other populations in the literature, TB incidence rates were calculated per 100,000 population with 95% CI for all trainees and for each training platform.

RESULTS

A total of 14 trainees were hospitalized for TB evaluation during the 7-year study period. One case of active pulmonary TB in a DLIELC student was previously reported[7] and was included as trainee E. This case was included in the incidence rate calculation. All were male, aged 19–29 years. Half (four of eight) of the BMT trainees and all (six of six) of the DLIELC trainees were born overseas. A slight majority (eight of 14) were asymptomatic at the time of hospital admission, and TST and IGRA results were highly variable **(Table 1)**. All trainees had abnormalities on their chest x-ray, chest CT, or both with predominantly upper lobe involvement and a minority demonstrating cavitation **(Table 2)**.

TABLE 1. Descriptions and diagnoses of trainees hospitalized for suspected active tuberculosis, Joint Base San Antonio–Lackland, TX, 2010–2016 (N=14)

Trainee	Year	Age	Status	Birthplace	BCG	TST	IGRA	Symptoms	Diagnosis
A	2012	21	BMT	U.S. (Texas)	No	29 mm	Positive (>10 IU/mL)[b]	Cough, congestion x2 days	Pulmonary TB
B	2012	27	BMT	Ghana	Yes	N/A	Positive (>10 IU/mL)[b]	None	Culture-negative TB
C	2015	19	DLI	Saudi Arabia	Yes	15 mm	Positive (7.26)[b]	None	Pulmonary TB
D	2016	23	DLI	Cameroon	Presumed[a]	Reactive	*Not available*	Testicular pain x5 months	Pulmonary and genitourinary TB
E[e]	2010	28	DLI	Afghanistan	Presumed[a]	N/A	Positive (quantitative not reported)[b]	None	Pulmonary TB
F	2010	28	BMT	Peru	Presumed[a]	18 mm	*Not available*	Fever, chills, cough x2 weeks	Latent TB infection
G	2010	19	BMT	U.S. (Arizona)	No	0 mm	Negative (quantitative not reported)[b]	Pleuritic chest pain x1 week	Nocardiosis
H	2010	20	BMT	Philippines	Yes	24 mm	Positive (quantitative not reported)[b]	None	Pneumonia
I	2012	22	DLI	Afghanistan	Presumed[a]	N/A	*Not available*	Cough x8 days; hemoptysis x1 week	Pneumonia
J	2015	29	DLI	Afghanistan	Presumed[a]	N/A	Positive (quantitative not reported)[b]	None	Latent TB infection
K	2015	22	DLI	Saudi Arabia	Presumed[a]	0 mm	Indeterminate[c]	Cough, congestion x8 days	Pneumonia
L	2016	21	BMT	U.S. (Ohio)	No	Reactive	Negative (0.00)[b]	None	Histoplasmosis
M	2016	19	BMT	Philippines	Yes	N/A	Positive (0.39)[b]	None	History of treated TB
N	2016	19	BMT	U.S. (Texas)	No	27 mm	Positive (>50, 37)[d]	None	*Mycobacterium simiae*

BCG, Bacillus Calmette–Guérin; BMT, Basic Military Training; DLI, Defense Language Institute; GU, genitourinary; IGRA, interferon gamma release assay; TB, tuberculosis; TST, tuberculin skin test

[a]Presumed vaccination based on country-specific standard policy outlined in BCG World Atlas (www.bcgatlas.org)

[b]QuantiFERON®-TB minus Nil (patient's background) expressed as international units/mL (IU/mL)

[c]Indeterminate due to mitogen low response for the QuantiFERON®-TB Gold

[d](Panel A minus Nil control, Panel B minus Nil control)

[e]Previously published case, included in the incidence rate calculations

TABLE 2. Imaging results of trainees hospitalized for suspected active tuberculosis, Joint Base San Antonio–Lackland, TX, 2010–2016 (N=14)

Trainee	Chest x-ray	Chest computed tomography
A	R apical opacities	R lung apex nodular opacities (largest 8 mm) with cluster GGO
B	RUL focal opacities	RUL focal opacification and coalescing lung nodules
C	RUL nodular opacities	RUL mass-like cavitary consolidation with TIB distribution, hilar lymphadenopathy
D	Unremarkable	R lung apex scarring, 13 mm juxtaesophageal lymph node with rim enhancement
E[a]	RUL and RLL consolidation	RUL nodules with calcification and hilar lymphadenopathy
F	RML possible cystic cavity (4.5 x 3.6 cm)	Unremarkable
G	LUL thin walled cavity (11 mm)	LUL cavity with surrounding consolidation (4.3 x 3.2 cm) with TIB distribution and GGO
H	Cardiac apex focal opacities	RLL, RML, and RUL apex patchy multifocal infiltrates
I	RUL focal consolidations	Not performed
J	RUL nodular opacities	RUL calcified nodularity with associated bronchiectasis
K	RUL and LLL consolidations	RUL and LLL consolidations with air bronchograms
L	LUL nonspecific lesion (2 cm)	LUL cavitary nodule (2 cm) with small adjacent airspace opacity
M	L apical nodular opacities	LUL and L apical calcified and non-calcified nodules with TIB distribution
N	Enlarged azygos shadow (1.3 cm)	RUL subplural nodular opacities (largest 16 mm) with TIB distribution and RLL GGO

GGO, ground glass opacity; LLL, left lower lobe; LUL, left upper lode; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; TIB, tree-in-bud

[a]Previously published case, included in the incidence rate calculations

Five of the trainees were eventually diagnosed with active TB disease: trainees A, C, and E with culture-positive pulmonary TB; trainee B with culture-negative pulmonary TB; and trainee D with culture-positive pulmonary TB and concurrent genitourinary TB. The remaining nine trainees received the alternative diagnoses of pneumonia (n=3), latent TB infection (n=2), prior treated pulmonary TB (n=1), non-TB mycobacterium infection (n=1), histoplasmosis (n=1), and nocardiosis (n=1) **(Table 1)**.

The majority (three of five) of trainees with TB originated from the DLIELC, and four were born overseas (Ghana, Saudi Arabia, Cameroon, and Afghanistan). Most trainees with TB presented with no symptoms (three of five). Only trainee A reported respiratory symptoms, and these were most consistent with an afebrile upper respiratory infection. Trainees B, C, and E were admitted due to high clinical suspicion of TB based on screening tests and imaging, while trainee D was hospitalized with scrotal pain potentially attributable to TB. Trainees A, B, and C had repeated sputa, including induced sputa, that were AFB smear and GeneXpert negative, and diagnoses were made based on recovery of *M. tuberculosis* from culture, except for trainee B, who was diagnosed with culture-negative TB due to history and radiological features. Trainee D initially had three negative AFB smears and GeneXpert assays; after AFB smear and GeneXpert of a testicular abscess tested positive, a fourth sputum sample was obtained, which was smear and GeneXpert positive. Trainee E underwent a bronchoscopy to obtain samples that were AFB smear and GeneXpert negative, but the diagnosis was made on the basis of culture recovery of *M. tuberculosis*. All isolates from culture-positive cases were pan-susceptible to first-line medications **(Table 3)**.

During this period, the incidence rate of active TB in the JBSA training population (including the previously published case) was 1.89 per 100,000 population (95% CI: 0.81, 4.42). The rates were 13.1 (95% CI: 3.71, 35.7) and 0.83 (0.14, 2.73) in the DLIELC and BMT training platforms, respectively. Contact investigations did not reveal any secondary cases indicating transmission, but there were difficulties in conducting these investigations and identifying any potential transmission. The delay in diagnosis was particularly problematic in the DLIELC population because many trainees already completed their training and had left JBSA-Lackland. The delayed diagnosis also prevented the establishment of baseline LTBI rates for comparison after the conversion period. The DLIELC was additionally complicated in that there was a heterogeneous population of trainees from different countries, each with a different baseline latent TB rate making it difficult to establish when concentric TB testing should be expanded.

EDITORIAL COMMENT

Among 14 trainees at JBSA-Lackland admitted for TB evaluation during the 7-year surveillance period, five were diagnosed with pulmonary TB disease. These cases were notable for their atypical presentations. All lacked the classic signs of prolonged fever, hemoptysis, anorexia, and unexplained weight loss, reaffirming that TB is challenging to diagnose based on clinical symptoms and can even present without symptoms. The microbiologic

TABLE 3. Diagnostic microbiologic evaluation of trainees diagnosed with active tuberculosis (N=5), Joint Base San Antonio–Lackland, TX, 2010–2016

Trainee	AFB source	AFB smear (positive/tested)	GeneXpert (positive MTB/tested)	AFB culture (positive MTB/tested)	Drug resistance
A	Sputum	0/3	0/3	3/3	None (INH, RIF, EMB, PZA)
B	Sputum	0/6	0/1	0/6	
	Bronchoscopy	0/1	0/0	0/1	
C	Sputum	0/4	0/3	3/4	None (INH, RIF, EMB, PZA, STM)
D	First sputum	0/3	0/3	2/3	
	Testicular abscess	1/1	1/1	1/1	
	Second sputum	1/1	1/1	1/1	None (INH, RIF, EMB, PZA)
E[a]	Bronchoscopy	0/2	0/2	1/2	None (INH, RIF, EMB, PZA)

AFB, acid-fast bacilli; MTB, *Mycobacterium tuberculosis*; INH, isoniazid; RIF, rifampin; EMB, ethambutol; PZA, pyrazinamide; STM, streptomycin

[a]Previously published case, included in the incidence rate calculations

diagnosis was particularly challenging because AFB smear and GeneXpert results for all sputum samples were negative—except the fourth sample from trainee D, which was obtained only after the diagnosis of genitourinary TB was established. The diagnoses of pulmonary TB, and the ensuing contact investigations, were delayed until cultures returned as positive, up to 6 weeks after admission.[8] The lack of symptoms and low mycobacterial burden may have been due to either early disease or host suppression of mycobacteria in this cohort of otherwise healthy young males.[9]

This case series raises concern about the increasing reliance on molecular tests for rapid diagnosis of active TB, especially in patients with minimal to no pulmonary symptoms. Although nucleic acid amplification tests have excellent overall accuracy for the detection of *M. tuberculosis* DNA from sputum samples,[10,11] their sensitivity decreases precipitously, to as low as 68%, when AFB smears are negative.[11] Bayesian approaches based on multiple rapid tests may not be ideal in situations when more aggressive TB exclusion is desired, such as high volume military and educational settings.

Because these TB cases were largely AFB smear negative, and patients were mostly asymptomatic and had no cavitary lesions on plain radiographs, the risk for mycobacterial transmission was low.[12,13] However, in close congregate and mass training settings, even a low transmission risk poses outbreak potential. Because of this risk, using guidance from the Centers for Disease Control and Prevention, local public health officials gathered contact information on all 14 cases and conducted contact investigations for those eventually diagnosed as pulmonary TB. Investigations of the DLIELC cases proved challenging due to language barriers, politico-cultural sensitivities, and the transience and heterogeneity of the population. The heterogeneous trainee population was particularly problematic for establishing a baseline latent TB infection rate, which is required for concentric testing.[14,15] By extrapolating data from Saudi Arabian healthcare worker studies[16,17] and other published incidence rates, a generous baseline of 30% positive screening tests was established. In both the DLIELC and BMT cases, the time lag between negative smears and positive cultures further complicated the investigations, as many potentially exposed persons had been moved to their next assignments or returned to their home countries. Some individuals who had permanently left the installation were unable to be contacted, highlighting the need to collect accurate, long-term personal contact information (e.g., cell phone and personal email).

In close congregate settings, it is crucial to maintain a high clinical suspicion and not prematurely dismiss cases of pulmonary TB. Clinicians should notify public health personnel as soon as pulmonary TB is being considered, rather than waiting to report once the diagnosis is officially established. Public health investigators and military training leadership have learned that it is essential to begin the preliminary stages of a contact investigation, and to establish a close working relationship with the clinicians overseeing the case, as soon as possible. This is especially prudent when the patient and exposed persons may be traveling internationally, because that factor increases the resources necessary to conduct the investigation.

In light of these lessons learned, JBSA-Lackland has developed a new policy whereby BMT trainees hospitalized with suspected pulmonary TB, who are discharged without a diagnosis explaining their imaging results (i.e., no TB or alternative diagnosis), may be placed on convalescent leave until at least three cultures are negative at the 6-week mark.[8] This recommendation is made on a case-by-case basis by a multidisciplinary team, including clinical and public health personnel, and presented to the training commander for a final decision. Because convalescent leave is not an option for students at the DLIELC, cases are discussed with training leadership and the country sponsor. If a student must be returned to training before active TB is formally ruled out, treatment for active TB can be considered, even in the absence of culture growth.[18]

Although active TB disease remains rare in the training population at JBSA-Lackland, a high degree of clinical suspicion should be maintained when trainees present with suspected TB, particularly for those born overseas. Often these cases have no pulmonary symptoms or have atypical presentations and clinical suspicion should persist even if initial AFB smears and nucleic acid amplification testing are negative. Healthcare providers and public health personnel must communicate early and frequently to understand the nuances of the clinical workup and its implications for contact investigations.

Disclaimer: The views expressed are those of the authors and do not reflect the official views or policy of the Department of Defense and its components.

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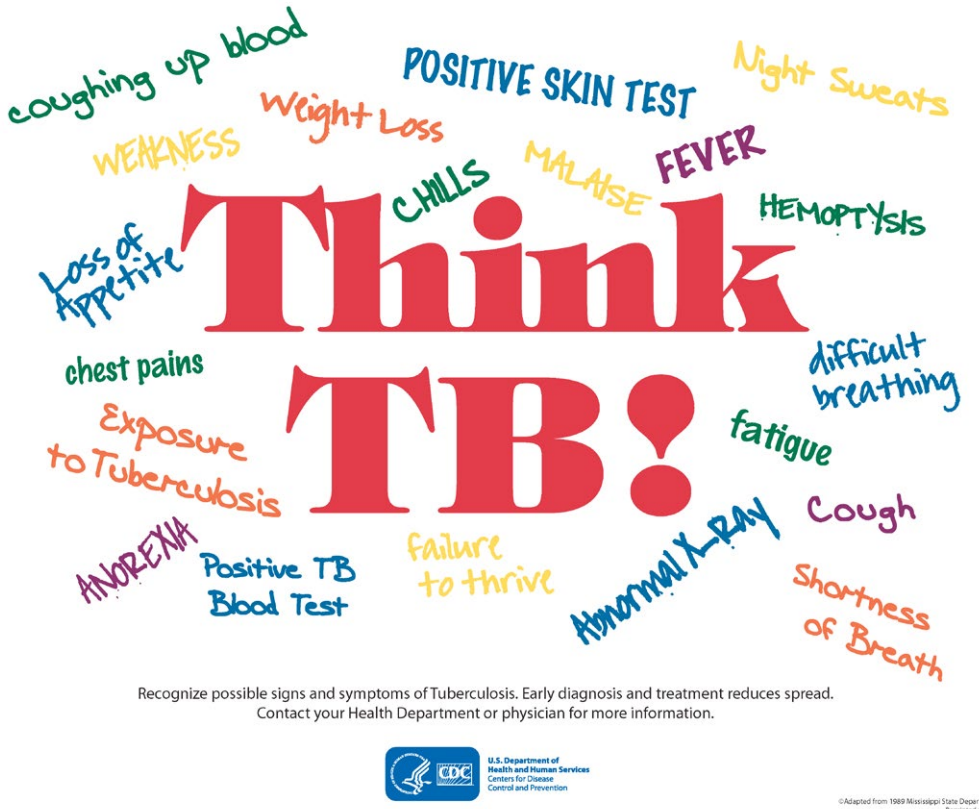

Brief Report

Mid-Season Influenza Vaccine Effectiveness Estimates for the 2016–2017 Influenza Season

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The Department of Defense (DoD) conducts year-round influenza surveillance for military healthcare beneficiaries and select civilian populations. Data from routine respiratory surveillance are used to estimate midseason influenza vaccine effectiveness (VE) and findings are shared annually at the Food and Drug Administration's advisory committee meeting on U.S. influenza vaccine strain selection. DoD VE estimates from the Defense Health Agency Armed Forces Health Surveillance Branch (AFHSB) and Naval Health Research Center (NHRC) are presented in this report.

METHODS

The AFHSB–Air Force Satellite Cell (AFHSB-AF) conducted a test-negative case-control study using data from the U.S. Air Force School of Aerospace Medicine's worldwide sentinel site-based program, the DoD Global, Laboratory-Based, Influenza Surveillance Program. Respiratory specimens were collected from DoD dependents presenting to outpatient military treatment facilities with influenza-like illness (ILI). Influenza cases were identified using reverse transcription–polymerase chain reaction (RT-PCR) or viral culture; controls were ILI patients who tested negative for influenza. From 2 October 2016 through 18 February 2017, a total of 534 cases and 838 test-negative controls were identified. Vaccination status was ascertained via electronic immunization records (Air Force Complete Immunization Tracking Application and the Aeromedical Services Information Management System) and self-report from patient questionnaires. Individuals were considered vaccinated if they received the current season's vaccine at least 14 days before illness onset. Those who were vaccinated within 14 days of illness onset were excluded.

NHRC's study utilized a test-negative case-control design using data from their febrile respiratory illness (FRI) surveillance program, which included outpatient DoD dependents in Southern California, Arizona, and Illinois, as well as outpatient civilians presenting at clinics in California near the U.S.–Mexico border. Cases were identified using RT-PCR; controls were FRI patients who tested negative for influenza. From 29 December 2016 through 16 February 2017, a total of 75 cases and 224 test-negative controls were identified. Vaccination status was ascertained by medical chart review when possible and self-report when necessary. Individuals were considered vaccinated if illness occurred between 14 and 180 days since vaccination.

AFHSB conducted a matched case-control study using data from the Defense Medical Surveillance System (DMSS) and Standard Ancillary Service–processed laboratory data from the Navy and Marine Corps Public Health Center to evaluate VE among active component, nonrecruit service members worldwide, across all services. Cases were defined as service members with influenza-positive laboratory tests (rapid antigen tests, RT-PCR or culture). Healthy controls were identified using medical encounters for injuries or mental health conditions without any ILIs reported at the encounter and no medical encounters for influenza during the season. Healthy controls were matched to cases by sex, age, date of encounter (±3 days), and treatment facility. From 1 December 2016 through 25 February 2017, a total of 909 cases and 3,424 matched healthy controls were identified. Vaccination status was ascertained by electronic immunization records from DMSS.

Multivariable logistic regression was used to calculate adjusted odds ratios (AORs) using SAS 9.3 (SAS Institute Inc., Cary, NC). VE was calculated as (1−AOR) × 100. Given the predominance of influenza A(H3N2), VE analyses against influenza A(H1N1)pdm09 were not possible, and only one study (AFHSB-AF) was able to conduct an influenza B VE analysis. All analyses evaluated the effectiveness of inactivated influenza vaccines because the live attenuated influenza vaccine was not used during the 2016–2017 influenza season in the U.S.[1] AFHSB-AF adjusted for age group, month of illness, and region for the overall and influenza A(H3N2) analyses; the influenza B analysis was adjusted for month of illness only. NHRC adjusted for age group and surveillance population. AFHSB adjusted for 5-year influenza vaccination history (at least one influenza vaccination in the previous 5 years vs. no influenza vaccinations during the previous 5 years). Control selection methods varied between the studies and were chosen based on the characteristics of the population and the data available.

RESULTS

Adjusted VE for dependents and civilians against all influenza types was similar across studies and showed statistically significant protection **(Table)**. AFHSB-AF found that, for all influenza types, VE was 42% (95% CI: 24%–55%), similar to NHRC's overall VE of 45% (95% CI: 5%–68%). VE against influenza A(H3N2) for dependents and civilians was also similar across studies with AFHSB-AF estimating influenza A(H3N2) VE at 42% (95% CI: 24%–56%) and NHRC estimating influenza A(H3N2) VE at 46% (95% CI: 6%–70%). VE against influenza B was slightly higher at 53% (95%

TABLE. Mid-season influenza vaccine effectiveness (VE) estimates, 2016–2017

Population	Influenza type	No. of cases	% vaccinated	No. of controls	% vaccinated[a]	Crude VE	95% CI	Adjusted VE	95% CI[b]
Dependents (AFHSB-AF)	Overall	534	32	838	36	17	(-5–34)	42	(24–55)
	Influenza A(H3N2)	477	32	838	36	14	(-9–32)	42	(24–56)
	Influenza B	53	26	838	36	35	(-21–65)	53	(11–75)
Dependents and civilians (NHRC)	Overall	75	33	224	48	45	(6–68)	45	(5–68)
	Influenza A(H3N2)	70	33	224	48	47	(6–70)	46	(6–70)
Active component service members (AFHSB)	Influenza A[c]	909	91	3,424	91	5	(-23–27)	3	(-25–25)
	Influenza A(H3N2)	261	87	991	91	32	(-6–57)	33	(-6–57)

AFHSB-AF, Armed Forces Health Surveillance Branch–Air Force Satellite Cell; NHRC, Naval Health Research Center; AFHSB, Armed Forces Health Surveillance Branch

[a]AFHSB-AF and NHRC used unmatched, influenza test–negative controls; AFHSB used healthy controls (matched to cases by sex, age, date [+/– 3 days] and location).

[b]AFHSB-AF adjusted for age group, month of illness and region (overall and influenza A[H3N2]). Influenza B analysis adjusted for month of illness only; NHRC adjusted for age group and surveillance population; AFHSB adjusted for 5-year prior vaccination status (Y/N).

[c]Cases and controls include all influenza A–positive cases, subtyped and not subtyped.

CI: 11%–75%), as estimated by AFHSB-AF. Adjusted VE estimates for active component service members were not statistically significant. The AFHSB analysis found that VE against all influenza A was 3% (95% CI: -25%–25%) and VE against influenza A(H3N2) was 33% (95% CI: -6%–57%).

DISCUSSION

Mid-season influenza VE estimates indicated that vaccination reduced the odds of medically attended influenza infection by approximately 45% among DoD dependents and civilians. These results were consistent with other studies, which have also found moderate VE this season.[2,3] Additionally, the DoD's findings were similar to VE estimates from previous influenza A(H3N2)–predominant seasons without vaccine mismatch.[4,5]

VE estimates for active component service members are frequently lower than those for civilians.[6,7] There are many factors that could lead to decreased VE among military personnel, including their high influenza vaccination rates (approximately 90%), annual (repeat) vaccinations, and early-season vaccination.[6] Studying VE in a highly vaccinated population adversely affects the statistical power of the analysis given the limited number of unexposed cases and controls. Additionally, repeated vaccination has been shown in some studies to reduce VE and potentially diminish antibody response to influenza.[5,8-10] Lastly, military personnel may experience waning immunity due to the fact that the U.S. military tends to start influenza vaccinations very early in the season.[11-13] Further research is necessary to determine how these factors might influence VE in the military population.

Limitations included a relatively small number of cases, which decreased the power of the studies and prevented VE estimation against influenza A(H1N1)pdm09 and, for two of the studies, influenza B. Additionally, these studies were limited in that only ILI cases severe enough to seek medical care were included, and the study populations tended to be younger than the general population. Therefore, it is difficult to comment on VE in less severe cases or among older populations.

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Erratum: Armed Forces Health Surveillance Branch. Update: Heat illness, active component, U.S. Armed Forces, 2016. *MSMR*. 2017;24(3):9–13. On p. 12, the footnote in Table 2 should read "One heat illness per person per year." The footnote text was corrected in each online version of the *MSMR*'s annual heat illness updates for 2013–2017.

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