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Seroconversion to Japanese Encephalitis Virus among U.S. Infantry Forces in Korea

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Abstract. Japanese encephalitis virus (JEV) is endemic in the Republic of Korea (ROK), posing a medical threat to more than 29,000 U.S. Forces military personnel currently deployed in the ROK. The objective of this study was to provide data on the risk of JEV exposure among U.S. Forces in the ROK. One thousand U.S. Army Soldiers were randomly selected for the study from the cohort of infantry Soldiers deployed in the ROK for a period of at least 330 days from 2008 to 2011. Pre- and post-deployment serum specimens were tested for the presence of JEV antibodies by plaque reduction neutralization test. A total of 2/1,000 (0.2%) U.S. Army Soldiers post-deployment specimens tested positive for JEV antibody. Results from the pre-deployment specimens indicated one true seroconversion and one with titers suggestive of a JEV infection. These results indicate a low, but nonzero risk of JEV exposure among U.S. Army Soldiers in the ROK.

Japanese encephalitis virus (JEV) infections can result in serious outcomes. The case fatality rate is reported to be between 20% and 30%, with 30–50% of the survivors having long-term neurologic and psychiatric sequelae that often lead to an early death.[1] JEV is endemic in the Republic of Korea (ROK), with > 2,500 cases reported for years 1964 (966 deaths), 1966 (695 deaths), and 1967 (810 deaths). For this reason, the ROK government initiated a mandatory childhood National Immunization Program in 1967 that became fully established by 1983, when only 139 cases (12 deaths) were reported.[2,3] From 1984 to 2009, there were only 0–7 cases reported annually as a result of the mandatory childhood vaccination policy.[2,3] However, even with these measures in place, JEV remains present in the mosquito populations, through zoonotic transmission, as indicated by outbreaks from 2010 to 2014 (89 cases, 18 deaths) (T. A. Klein, pers. comm.).[2,4]

The continued presence of JEV in the ROK poses a potential threat to the greater than 29,000 U.S. Forces military personnel deployed and greater than 13,000 beneficiaries (civilians and family members) who currently reside in the ROK. Historically, Department of Defense (DoD) policy only recommended, but did not require, JEV vaccination for service members visiting or deploying in the Pacific Command region, including the ROK, for more than 30 days or for short-term nonurban travel.[5,6] However, in 2015, the Air Force and U.S. Forces Korea began requiring JEV vaccinations for service members who will be in the ROK for 30 days or more.[7,8] During the Korean War (1950–1953), there were 299 cases of confirmed/suspected JE cases among U.S. service members during 1950 alone.[9,10] JE has also been identified in vectors where U.S. Army personnel train and military installations throughout the ROK. For example, during 2010 there were more than 80 pools of *Culex tritaeniorhynchus*, the primary vector of JEV in the ROK, collected near the Demilitarized Zone that were positive for JEV Genotype I and one pool that was positive for Genotype V, which had not been reported previously from the ROK.[4,11,12] However, there is little data beyond case reports to determine the current risk of JEV in U.S. Forces deployed in the ROK. There have been no published epidemiologic studies, and information derived from passive surveillance does not provide reliable risk estimates because symptoms are nonspecific and JEV testing is not routinely conducted.[4] In addition, more than 99% of all JEV cases are asymptomatic, which reduces the value of clinical surveillance compared with serosurveillance.

The aim of this serosurvey was to provide preliminary data on JEV infection risks among U.S. Forces in the ROK.

The Defense Medical Surveillance System, maintained by the Armed Forces Health Surveillance Center (AFHSC), was used to identify a cohort of U.S. Army service members who were deployed in the ROK for the first time for a minimum of 330 continuous days from January 1, 2008 to December 31, 2011.[13] The cohort was further restricted to Army Soldiers with a military occupational specialty (MOS) of 11B (Infantryman), 11C (Indirect Fire Infantryman), 11H (Heavy Anti-armor Weapons Infantryman), or 11M (Fighting Vehicle Infantryman). These individuals were likely to work and train in field conditions that placed them at risk for JEV infection, as they may be exposed to biting mosquitoes and may reside at installations where the primary JEV vector is collected. Individuals were excluded if they received a JEV vaccine before the end of their follow-up for the study and no subjects had a prior diagnosis of Japanese encephalitis.

The DoD Serum Repository, maintained by the AFHSC, was queried to restrict the study population to individuals with a serum specimen collected within the 365 days before the ROK deployment (pre-deployment) and an additional specimen collected within the 365 days after the ROK deployment (post-deployment).[13,14] If multiple specimens qualified, specimens collected closest to the ROK deployment start and end dates were selected. From the eligible study population, an attempt was made to randomly select 250 Soldiers deployed during each of the JEV exposure seasons (July 1–October 31) for years 2008–2011. As there were only 117 eligible subjects during 2009, a total of 383 subjects were included in the 2010 sample period.

Serum specimens were tested by the Walter Reed Army Institute of Research, Viral Disease Branch for the presence of JEV antibody using plaque reduction neutralization test with the JEV SA14-14-2 attenuated vaccine strain (Genotype III) as the target.[15] The assay endpoint was a 50% or greater reduction in the number of viral plaques (for 1:10 screening assay), or the reciprocal serum dilution that gave a 50% reduction in viral plaques (calculated by SPSS probit analysis) versus a diluent only control (for titration assay). All post-deployment specimens

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TABLE 1
Demographics of study population

Characteristic	*N*	%
Sex		
Male	1,000	100
Age category (years)		
18–19	181	18
20–24	527	53
25–29	178	18
30–34	61	6
35–39	35	4
40+	18	2
Race ethnicity		
American Indian/Alaskan Native	8	1
Asian/Pacific Islander	38	4
Black	94	9
Hispanic	115	12
White	728	73
Other/unknown	17	2
JEV exposure season year		
2008	250	25
2009	117	12
2010	383	38
2011	250	25
Number of prior deployments		
0	784	78
1	121	12
2	65	7
3	22	2
4+	8	1

JEV = Japanese encephalitis virus.

were tested. Pre-deployment specimens were only tested if post-deployment specimens were positive. Descriptive statistics on age, sex, race, education level, MOS, and year of deployment were calculated for the study population. Seroconversion was defined as a 4-fold rise in titers from the pre- to post-deployment specimens. Medical encounters during and after stationing were explored for all seroconverters.

The study population consisted of all males, with the majority of the population being under 25 years of age, white, and with no prior deployments (Table 1). Post-deployment sera for 2/1,000 (0.2%) Army Soldiers in the study were positive for JEV antibody. Both Soldiers were deployed in the ROK during the 2011 JEV exposure season when local population numbers of JE (3) were low, compared with years 2010 (26) and 2011 (20). Soldier 1 had a pre-deployment titer of < 10 (undetectable) and a post-deployment titer of 34, which qualified as a true seroconversion. This Soldier had no prior deployments, no documented JEV vaccinations, was never stationed in JEV-endemic regions, and was U.S. born. The Soldier was located at Camp Casey (Dongducheon) for 396 days. Although this Soldier had multiple medical encounters from 219 to 412 days after arriving in the ROK for potential nonspecific neurologic conditions (falls, dizziness, and traumatic brain injury screening), review of the medical record by a preventive medicine physician did not indicate any association of these encounters with a JEV infection. The low post-deployment titer may be associated with the infection being subclinical. Soldier 2 had a pre-deployment titer of 84 and a post-deployment titer of 204. Although the Soldier did not meet the criteria of a 4-fold rise in titer for seroconversion, the 2.4-fold increase in titer was suggestive of a JEV exposure. The Soldier was located at Camp Stanley (Uijombu) for 394 days. This Soldier had four prior deployments, none of which were to JEV countries of risk, had no documented JEV vaccinations, and was U.S. born. However, the individual was in Singapore 12 years before deploying to the ROK and could have been exposed to JEV at that time. This may explain the pre-deployment titer of 84. This individual had no medical encounters during or after the ROK deployment, which is indicative of a clinically unapparent JEV infection. No data were available on the outdoor activities and exposure to high-risk JEV areas for the study population.

This study found a low, but non-zero risk of JEV exposure for a cohort of U.S. Army Soldiers deployed in the ROK. As neither post-deployment seropositive individual presented with clinical symptoms, these findings emphasize the potentially unrecognized JEV exposure risks for the ROK. Although there have been no documented JEV cases identified among U.S. service members in the ROK in decades, JEV testing among encephalitis cases is not routine.[4] A fatal case of JEV of a recently retired U.S. Airman living in the ROK was reported in 2012.[16] Mosquito surveillance in the ROK continues to identify infected pools, highlighting the potential risk of JEV to unvaccinated service members.[4,12,17] In addition, a similar serosurvey of JEV exposure in infantry service members in the ROK before 2006 found approximately 4% of post-deployment specimens positive for JEV antibody using the less specific enzyme-linked immunosorbant assay (R. Schoepp, pers. comm.).[11] JEV cases reported in the ROK are also temporally sporadic and regionally focal, which is partially dependent on rainfall patterns that result in large populations of the primary vector. For example, during 2010 and 2014 there were 8/26 (30.8%) and 3/26 (11.5%) of the JEV cases reported north of Seoul, respectively, while from 2011 to 2013 there were no cases reported north of Seoul.

In addition to JEV vaccine availability, the U.S. military relies on protective measures against biting mosquitoes that transmit JEV, for example, the use of repellents and permethrin-treated uniforms, when service members are outdoors at night or in JEV high-risk areas. However, these measures are not 100% protective and adherence to these preventive measures is not always met as there were 11 cases of malaria reported among U.S. personnel deployed to the ROK in 2014. All of these factors and the finding of this study support the 2015 JEV vaccination policies changes for U.S. Forces Korea. However, there may still be a need to conduct cost-effectiveness analyses to evaluate this policy.[8]

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