Dengue Virus Exposures among Deployed U.S. Military Personnel

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Abstract. Dengue virus infections have adversely impacted U.S. military operations since the Spanish–American War. The erosion of mission capabilities and lost duty days are underestimated. Appreciating the incidence and prevalence of dengue infections in U.S. military personnel is important to inform disease prevention strategies. Banked pre- and post-deployment serum samples from 1,000 U.S. military personnel with a single deployment to a dengue-endemic region were tested using a screening microneutralization assay to detect anti-dengue-virus-neutralizing antibodies. A total of 76 (7.6%) post-deployment samples were positive and 15 of the pre-deployment samples were negative. These figures represent an infection incidence of 1.5% and total of 17.6 seroconversions per 10,000 deployment months. These data represent a deploying military population with a relatively high background rate of dengue seropositivity, a low level of infection during deployment compared with background infection rates in the local populations, and the potential for worsening clinical attack rates with increased frequency of deployment. Additional studies are required to more clearly elucidate the dengue infection and disease risk in U.S. military personnel.

BACKGROUND

Dengue virus (DENV) transmission is endemic in more than 120 countries with an estimated 100 million clinically apparent infections occurring annually, making it the world’s most important arthropod-borne viral disease. The spectrum of clinical phenotypes following infection may include a nonspecific viral syndrome, classic dengue fever, severe dengue (dengue hemorrhagic fever [DHF], or dengue shock syndrome [DSS]),3 severe dengue is characterized by plasma leakage, intravascular volume depletion, hemorrhagic manifestations, end-organ dysfunction, and the potential for significant morbidity and/or death. The clinical and immunopathologic mechanisms responsible for mild, uncomplicated, and severe dengue are incompletely understood.4,5 It is theorized complex interactions between innate and adaptive immune responses following infection result in a high DENV burden and a predominantly pro-inflammatory response impairing vascular integrity and coagulation mechanisms.6 The risk of severe dengue is significantly increased when experiencing a second dengue infection with a DENV type different from the one that caused the first infection.7 Currently, no vaccine or specific antiviral therapeutic is available to U.S. military members to prevent or treat dengue.

Dengue is a significant infectious disease threat among travelers to endemic areas. Between 2000 and 2010, dengue was the third most commonly diagnosed illness among returning travelers, behind malaria and infectious diarrhea.8 A review of four prospective studies of travelers to dengue-endemic regions demonstrated an incidence of dengue that ranged from 10.2 to 30 infections per 1,000 person-months, endemic regions demonstrated an incidence of dengue that ranged from 10.2 to 30 infections per 1,000 person-months,9

Methods

Study design. This was a retrospective serosurveillance of U.S. service members deployed to dengue-endemic regions. Two hundred and fifty pre- and post-deployment
sample pairs were chosen from first-time deployers to each of the following regions: South America, Central America, southeast Asia, and Africa. The Defense Medical Surveillance System (DMSS), a relational database for military and medical experiences of service members, was queried for eligible subjects based on deployment history, as determined by self-reports on the Post Deployment Health Assessment (PDHA). Inclusion criteria were completion of a PDHA (required for all personnel deployed for greater than 30 days); a deployment of 6 months or greater to any country in South America, Central America, southeast Asia, or Africa; no previous deployments; a pre-deployment serum sample within 1 year of the start date of deployment; and a post-deployment serum sample within 1 year of the deployment end date. There were no specific exclusion criteria beyond failure to meet inclusion criteria (data from DMSS, the Armed Forces Health Surveillance Center, U.S. Department of Defense, Silver Spring, MD [data from 1998 to 2011; released February 2012]). Serum specimens from the Department of Defense Serum Repository: the Armed Forces Health Surveillance Center, U.S. Department of Defense, Silver Spring, MD (serum specimens from 1998 to 2011; released February 2012).

Neutralizing antibody. All post-deployment serum samples were analyzed for the presence of neutralizing antibody against all four DENV serotypes by using a dengue microneutralization antibody assay in a screening format and end point format for positive screeners. This assay showed good agreement and comparable sensitivity in measuring dengue-neutralizing antibodies when compared with the widely accepted plaque reduction neutralization test. Briefly, in a polypropylene U-bottom 96-well plate, a 4-fold increase in MN50 titers between pre- and post-deployment sera were analyzed with the initial 1:30 dilution of the serum sample to obtain the dengue-neutralization titers. We used de-identified demographic information from the service member’s PDHA to determine risk factors of dengue infection through multivariate logistic regression analysis. Demographics obtained from this form are age, gender, service branch, component, pay grade, military occupational specialty, and self-reports of diethyltoluamide (DEET) use and wear of permethrin-treated uniforms. For each demographic of interest, we used a Kruskal–Wallis equality of populations rank test to assess for homogeneity between deployment locations. In addition, we used responses in the PDHA to questions regarding symptoms experienced during deployment and performed a χ² analysis to assess for association between dengue infection and experienced symptoms.

RESULTS

Study subjects. A total of 1,000 study subjects, 250 deployed to Central America, South America, southeast Asia, or Africa, were randomly selected from all active component U.S. service members who met all inclusion criteria, with a preference for service members who deployed from 2008 to 2011, as 2008 was the year of the most recent revision of the PDHA. We obtained a waiver of consent form the Walter Reed Army Institute of Research IRB, because the serum samples were collected for operational purposes and the study was considered nonhuman subjects research. The Department of Defense Serum Repository de-identified all samples prior to release to investigators and no protected health information was used in this study. Table 1 shows all self-reported demographic and deployed indices obtained from the PDHAs. The populations that deployed to each geographic region were significantly different for all demographic categories, as demonstrated with P values less than 0.05 by the Kruskal–Wallis equality of populations rank test.

Post-deployment prevalence to dengue-neutralizing antibodies. Of the 1,000 post-deployment serum samples tested, 76, or 7.6%, had the presence of anti-dengue-neutralizing antibodies. Deployers to South America had the highest prevalence of dengue-neutralizing antibodies at 12.4%, followed by southeast Asia at 7.2%, Africa at 6.0%, and Central America at 4.8%. Service members in the Army had the highest seroprevalence at 11.2%, followed by the Navy at 7.2%, Air Force at 6.6%, and Marine Corps at 5.0%. None of the seven Coast Guardsmen in the study had positive dengue antibodies. Health-care workers had the highest seroprevalence at 14.3%; those in law enforcement and security occupations had the lowest prevalence of dengue antibodies at 3.3%.

Dengue infection during deployment. Of the 76 dengue antibody positive post-deployment samples, 15 (19.7%) lacked dengue antibodies in the paired pre-deployment sample, indicating seroconversion (infection) took place during the deployment. Of these 15, four (0.4% of total cohort) had deployed to Central America, three (0.3%) to South America, five (0.5%) to Asia, and three (0.3%) to Africa. The overall incidence rate of dengue seroconversion was 1.5% across the entire cohort or 17.6 seroconversions per 10,000 deployment months, with 16.1 in Central America, 14.1 in South America, 27.0 in southeast Asia, and 14.6 in Africa.

Risk factors for dengue seroconversion. Potential risk factors for dengue seroconversion during deployment were not identified by the analysis performed. The median age of...
those who seroconverted during deployment was 27 years and the median deployment length was 220 days. There were no significant differences in age or deployment length between those who seroconverted during deployment and those who did not. Of all demographics of interest, only enlisted versus officer rank trended toward significance, with a $P$ value of 0.09. There were also no significant differences in seroconversions by self-reports of wearing DEET and wearing permethrin-treated uniforms (Table 2).

**Dengue-like symptoms experienced during deployment.**

Those who seroconverted to dengue during deployment were four times more likely to have reported to sick call for a febrile illness during deployment (odds ratio [OR] = 4.07, $P = 0.03$) and five times more likely to be put on limited duty status (OR = 5.07, $P = 0.04$) than those who did not seroconvert during deployment. There was no significant relationship between any other self-reported dengue-like symptoms including headache, rash, back pain, joint pain, muscle pain, fatigue, weakness, or dizziness.

**DISCUSSION**

In this study, we characterized the risk of dengue infection to deploying service members during a first-time

### Table 1

| Characteristics of study subjects | Central America | South America | Asia | Africa | Total |
|-----------------------------------|----------------|---------------|------|--------|-------|
| Number                            | 250            | 250           | 250  | 250    | 1,000 |
| Male (%)                          | 205 (82.0)     | 214 (85.6)    | 233 (93.2) | 232 (92.8) | 884 (88.4) |
| Median deployment year (range)    | 2009 (2007–2011) | 2006 (1998–2011) | 2009 (2006–2011) | 2010 (2006–2011) | 2009 (1998–2011) |
| Median deployment length, days (range) | 337.5 (180–580) | 213.5 (180–578) | 203 (180–653) | 208.5 (180–711) | 213 (180–711) |

**Service**

- Army (%) 37 (14.8) vs 136 (54.4) vs 53 (21.1) vs 24 (9.6) vs 250 (25.0)
- Navy (%) 175 (70.0) vs 43 (17.2) vs 82 (32.8) vs 118 (47.2) vs 418 (41.8)
- Air Force (%) 13 (5.2) vs 66 (26.4) vs 6 (2.4) vs 21 (8.4) vs 106 (10.6)
- Marine Corps (%) 20 (8.0) vs 5 (2.0) vs 109 (43.6) vs 85 (34.0) vs 219 (21.9)
- Coast Guard (%) 5 (2.0) vs – vs – vs 2 (0.8) vs 7 (0.7)

**Rank**

- Enlisted (%) 216 (86.4) vs 204 (81.6) vs 225 (90.0) vs 201 (80.4) vs 846 (84.6)
- Officer (%) 34 (13.6) vs 46 (18.4) vs 25 (10.0) vs 49 (19.6) vs 154 (15.4)

**Occupation**

- Infantry/artillery/combat engineering (%) 20 (8.0) vs 41 (16.4) vs 104 (41.6) vs 68 (27.2) vs 233 (23.3)
- Law enforcement/security (%) 74 (29.6) vs 60 (24.0) vs 10 (4.0) vs 7 (2.8) vs 151 (15.1)
- Armor/supply/motor transport (%) 4 (1.6) vs 11 (4.4) vs 5 (2.0) vs 9 (3.6) vs 29 (2.9)
- Pilot/aircrew (%) 6 (2.4) vs 14 (5.6) vs 5 (2.0) vs 24 (9.6) vs 49 (4.9)
- Repair/engineering (%) 54 (21.6) vs 40 (16.0) vs 44 (17.6) vs 75 (30.0) vs 213 (21.3)
- Communications/intelligence (%) 35 (14.0) vs 62 (24.8) vs 66 (26.4) vs 41 (16.4) vs 204 (20.4)
- Health care (%) 53 (21.2) vs 13 (5.2) vs 12 (4.8) vs 20 (8.0) vs 98 (9.8)
- Other (%) 4 (1.6) vs 9 (3.6) vs 4 (1.6) vs 6 (2.4) vs 23 (2.3)

Kruskal–Wallis equality-of-populations test indicates that all demographic categories are significantly heterogeneous by deployment location, with a $P < 0.05$.

**Table 2**

Demographics and deployment information of those who seroconverted to dengue virus during deployment compared with those who did not

| Characteristic                          | Dengue seroconverters | Non-seroconverters | $P$ value |
|-----------------------------------------|-----------------------|--------------------|-----------|
| Male (%)                                | 13                    | 871                | 0.83      |
| Female (%)                              | 2                     | 113                |           |
| Enlisted (%)                            | 15                    | 831                | 0.09      |
| Officer (%)                             | 0                     | 154                |           |
| Army (%)                                | 4                     | 246                | 0.98      |
| Navy (%)                                | 7                     | 411                |           |
| Air Force (%)                           | 1                     | 105                |           |
| Marine Corps (%)                        | 3                     | 216                |           |
| Coast Guard (%)                         | 0                     | 7                  |           |
| Infantry/artillery/combat engineering (%) | 3                    | 230                | 0.78      |
| Law enforcement/security (%)            | 3                     | 148                |           |
| Armor/motor transport/supply (%)        | 1                     | 28                 |           |
| Pilot/aircrew (%)                       | 0                     | 49                 |           |
| Repair/engineering (%)                  | 2                     | 211                |           |
| Communications/intelligence (%)         | 5                     | 199                |           |
| Health care (%)                         | 1                     | 7                  |           |
| Median age (range)                      | 27 (21–44)            | 26 (19–56)         | 0.15      |
| Deployment length (range)               | 220 (184–383)         | 213 (180–711)      | 0.33      |
| Reported DEET use (%)                   | 6                     | 435                | 0.75      |
| Reported permethrin-treated uniforms (%) | 3                    | 275                | 0.50      |
| Total (%)                               | 15                    | 985                |           |

$P$ values calculated using χ² test. No variable is significant at $P < 0.05$. 

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deployment to a dengue-endemic area. Post-deployment, 7.6% of deployed tested positive for anti-dengue-neutralizing antibodies. There was significant heterogeneity by deployment location, with the highest prevalence among deployers to South America; the 12.4% of service members with positive dengue antibodies after deployment to this region is consistent with previous reports of 11% dengue seroprevalence among Special Forces soldiers operating in this area.18 There was also heterogeneity by occupation, with the highest rates among those in health-care fields, communications/intelligence, and supply. Although the PDHA did not assess the amount of time spent indoors versus outdoors during deployment, these are occupations that would be more likely to be indoors during the day, the time, and the location that *Aedes aegypti* typically feed.

In all, 15 service members, or 1.5% of the total cohort, developed antibodies to at least one DENV type between the pre- and post-deployment serum samples, indicating likely infection during deployment. This indicates an incidence of 17.6 infections per 10,000 deployment months, which is approximately a 10-fold lower incidence than what has previously been found in traveling populations.9 The reasons for this discrepancy are not clear, but the differences between civilian travelers in previous studies and military deployers in this report, in terms of risk-taking activities and even clothing worn, are likely a factor. Among the 15 service members who seroconverted to dengue during deployment, we did not identify any conclusive risk or protective factors for dengue seroconversion. These relationships should be explored in prospective studies. For the potential protective factors of wearing DEET and permethrin-treated uniforms, this may be subject to recall bias, as service members may not recall DEET use when filling out the PDHA, and may not know if uniforms had been treated with permethrin, if such treatments occurred prior to uniforms being issued to the individual service members.

A strength of this study is the sample set available for testing and the variables that were able to be controlled in their selection, namely, first-time deployers with pre- and post-deployment serum samples available for testing. Another strength of this study is its size. With 1,000 subjects, it is the largest study to address not only dengue seroconversions/infections occurred during the first deployment to dengue-endemic areas. These data call for prospective studies in service member populations deploying to or residing in dengue-endemic regions and a more comprehensive understanding of risk factors for vector-virus exposure and infection. These data underscore the need for a safe and efficacious dengue vaccine to protect U.S. service members from dengue disease. Additional information is required from the field to understand whether deployment policy or clinical practice guidelines require modification.

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