We read with interest the report in this issue of the *Journal* from Eick and colleagues [1], who describe their study of the incidence of serologically diagnosed hepatitis E virus (HEV) infections among US military service members who were deployed to Afghanistan from 2002 through 2006. In this study, the investigators selected a random sample of 1500 paired serum samples, which were obtained from soldiers within 180 d prior to their deployment and after they had returned to the United States. Nearly two-thirds of the subjects were under age 30 years, which was similar to the overall 108,218 military service members who had been deployed to Afghanistan from 2002 through 2006. Only 16 (1.1%) subjects were seropositive for HEV antibodies at the baseline, and only 2 of them (0.1%) seroconverted during their deployment, as measured using an in-house noncommercial assay developed by the Walter Reed Army Institute of Research [2].

Among the obvious challenges faced by troops deployed to conflict zones or to humanitarian crisis settings is the access to a continuous supply of safe food and water. Concerns about the risk of HEV exposure and infection stem from numerous documented outbreaks of hepatitis E among military units deployed to areas where HEV is endemic [3–5]. However, such infections have been limited in regiments of soldiers from industrialized countries [6, 7]. Similarly, the findings of Eick et al [1] suggest that the detailed preventive measures undertaken by the Department of Defense for US troops in Afghanistan may have prevented their acquisition of viral hepatitis, in sharp contrast to the experience of Soviet troops sent to Afghanistan in the 1980s [8]. Acute viral hepatitis, of which 95% was originally believed to have been hepatitis A virus (HAV)–associated [8], was consistently responsible for nearly half of the infectious diseases among Soviet troops from 1980 through 1988 [8, 9]. While serological testing excluded HAV or hepatitis B virus (HBV) as causative among 69% of 325 cases from 1984 and 1987, HEV-specific evidence has not been reported [9]. Many of the observed infectious diseases in these troops were enterically transmitted, and it is likely that many soldiers had been exposed to HAV before deployment [9]. This is also not surprising given the abysmal hygiene and living conditions to which these soldiers were subjected—dramatically different from those of their modern US counterparts [8].

The data of Eick et al [1], however, raise several questions that are open to a few interpretations. As the authors discuss, the very low HEV seroprevalence found in subjects prior to their deployment could be related to the serum dilution used in the assay or the cutoff used for seropositivity [10]. In regards to the low rate of seroconversion, it is not clear whether all members of the sampled population were equally exposed to potential HEV infection, as the duration of deployment is not discussed in this article. Given the variable length of tours of duty and the fact that the study period spans nearly 5 years (allowing for as many as 3 consecutive tours per soldier), it may be possible that anti-HEV antibody levels among individuals infected early declined below detectable thresholds, as suggested by kinetic models by Myint and colleagues [11]. Given these potential differences in risk profiles by exposure cohort, a larger sample size would be warranted to investigate seroconversion.

There are other findings in contrast to the low prevalence that Eick et al [1] found in these US troops prior to deployment. A study of the National Health and Nutrition Examination Survey (NHANES) sample of the general US population, in which a similar assay was used, found an antibody seroprevalence of 21% to HEV.
and a seroprevalence of 8% among subjects under 30 years of age who were born in the United States [12]. Because no anti-HEV assays have been licensed by the Food and Drug Administration in the United States, this study utilized an assay developed and used widely for epidemiological studies by the Hepatitis Research Laboratory at the National Institutes of Health [13]. Samples of the reactive specimens in the NHANES study were retested and confirmed at the National Institutes of Health and National Institute of Allergy and Infectious Diseases laboratory, which also confirmed the specificity of the reaction in a sample of seroreactive specimens by use of a blocking assay with an HEV antigen (SAR55 strain) [14]. As the authors point out, there has been a decade-long debate in the literature on HEV about context-specific assay reliability and the problem of interassay comparability [15]. A study that compared the performance of 12 different HEV antibody assays found considerable discordance in results when a panel of 164 coded serum samples were tested by these different assays [13]. In pairwise comparisons of different tests, the overall concordance was 49%–94% (median, 69%). The sensitivity of the tests to detect HEV antibody in known HEV-positive serum samples varied from 17% to 100%. These investigators concluded that both false positive and false negative results occurred commonly with some of the available assays. As Bendall and colleagues [16] recently described in a study of blood donors in the United Kingdom, the choice of assay can have a dramatic effect on population HEV seroprevalence estimates. These discrepant results and the consequent uncertainty about the population burden of HEV infection underlie an urgent need for the development, licensure, and availability of reliable serological assays for detecting antibodies to HEV in the United States.

The unavailability of licensed serological assays in the United States may also be responsible, in part, for the fact that HEV infections are rarely recognized and reported by clinicians. In contrast, HEV infections have been much more commonly recognized and reported in Western European countries, where licensed HEV assays are available. For example, clinical HEV infection was diagnosed in 186 patients in the United Kingdom from 1996 through 2003 [17] and in 96 patients (45 of whom had autochthonous infection) in Germany from 2006 through 2007 [18], and a similar number of autochthonous cases were diagnosed in France [19]. The patients with autochthonous infection were infected with HEV genotype 3, which has a zoonotic reservoir in swine [18–20]. Given these findings from similarly industrialized settings, it is unclear why autochthonous HEV infections have not been recognized more frequently in the United States.

Another issue raised by this US military study by Eick et al [1] is the uncertainty about the epidemiology of HEV infection in Afghanistan. Although many outbreaks have been reported in Pakistan and other neighboring countries [15], no such outbreaks have been reported in Afghanistan. In a review in 2002, Wallace et al [21] claimed that HEV is endemic in Afghanistan, largely on the basis of circumstantial evidence. Afghanistan was not included in another recent comprehensive review in which 11 Asian countries were identified as areas where HEV genotype 1 (the genotype responsible for waterborne epidemics) is endemic [22]. A study of Thai troops deployed to Afghanistan with United Nations peacekeeping forces found that 2 of 87 subjects seroconverted to HEV [4]; these investigators used an assay similar to that used in the study reported by Eick et al [1]. There is a paucity of published data on the prevalence of HEV antibodies among the citizens of Afghanistan. One study of 102 local Afghanistan residents who visited a French military field hospital in Kabul in 2008 found an HEV antibody prevalence of 28.4% [23]. No information was included on the clinical symptoms or exposure histories of the seropositive subjects in this small study.

Clearly, our understanding of the possible infectious disease risks to US troops in Afghanistan would be improved by better data on the antibody prevalence to HEV within the local civilian population, especially in areas of substantial US troop presence. As Eick et al [1] point out, there are numerous situations in this and similar military operations when the maintenance of the highest food and water safety standards is difficult. Exposure to local food and drink can be minimized, but it is often unavoidable. Understanding the magnitude of the risks of exposure to infectious pathogens, including HEV, can help provide guidelines to minimize these risks under challenging circumstances. A research priority for both US military and civilian researchers in Afghanistan should be to evaluate the seroprevalence and exposure histories to various pathogens in the local civilian population in addition to those in the US troops serving there. It is possible that the inherent risk of exposure to HEV is substantially lower among US forces in Afghanistan than it has been in neighboring countries in the region where water contamination during monsoon rains is more frequent. Nevertheless, the findings of Eick et al [1], which suggest a negligible rate of HEV infection among US troops in Afghanistan who were included in this cohort, is very welcome news.

**References**