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EDITORIAL COMMENTARY

Age and Sex in the Zika Pandemic Era

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(See the Major Article by Lozier et al, on pages 1678–89.)

Following its discovery in the Zika forest in Uganda [1], Zika virus (ZIKV) was initially thought to cause only sporadic benign human disease in Africa and Asia [2]. The first documented ZIKV outbreak, on Yap Island, Micronesia, in 2007 [3], was followed by a large epidemic in French Polynesia in 2013–2014, before spreading across the Pacific and eventually to the Americas. ZIKV is currently considered to be an emerging arthropod-borne virus [2, 4, 5]. The first documented evidence of ZIKV autochthonous transmission in Brazil occurred in May 2015, after some patients presented with a dengue-like syndrome in the city of Natal, located in the state of Rio Grande do Norte [6].

During the early days of the Brazilian outbreak, information regarding the clinical features of Zika was obtained primarily from the Yap Island outbreak [7] and indicated that the clinical syndrome (including mild fever, rash, arthralgia, and conjunctivitis) could be confused with other arboviral diseases, notably dengue and chikungunya [8]. The most frequently reported symptoms and signs included fever, conjunctivitis, headache, myalgia, and pruritus for 4–7 days. Less frequently reported symptoms included retro-orbital pain, anorexia, vomiting, diarrhea, and abdominal pain [9]. Importantly, a substantial number of ZIKV infections are estimated to be asymptomatic [3].

Interestingly, one unique hallmark of the western hemisphere outbreak was the high incidence of neurological disease, primarily newborn microcephaly, in the northeastern states of Brazil, which led to the association between ZIKV infection during pregnancy and fetal malformations [10]. On 1 February 2016, the World Health Organization declared ZIKV infection and its association with neurologic complications as a public health emergency of international concern [11]. ZIKV was detected in amniotic fluid of fetuses with microcephaly [12, 13] and in brain of fetuses with central nervous system abnormalities [10], in addition to its association with meningoencephalitis [14] and Guillain-Barré syndrome [15]. Microcephaly represents only a part of the broad spectrum of teratogenic outcomes of intrauterine ZIKV infection, now called congenital Zika syndrome [16]. Intrauterine growth restriction, ocular abnormalities, placental damage, and fetal demise are other findings that may be associated with ZIKV infection in pregnancy [10, 17–19].

Before the arrival and subsequent spread of ZIKV, dengue virus (DENV) and chikungunya virus (CHIKV) were the predominant arboviruses affecting humans in Latin America and the Caribbean [20]. The concurrent circulation of these arboviruses has become an important public health concern [21] and has led to difficulties in accurately diagnosing ZIKV infection. The study developed by Lozier et al [22] in this issue of *The Journal of Infectious Diseases* is a retrospective case-control study, based on household-based clusters, that describes the distribution of ZIKV infection and estimates the proportion of symptomatic ZIKV infections and risk factors associated with the Zika outbreak in Puerto Rico in 2016. The goals of the study were to identify the household infection prevalence, quantify the percentage of cases that were asymptomatic, identify infection risk factors, and characterize patients who sought treatment, all in context with other endemic arboviral diseases. Index cases who tested positive for ZIKV infection by reverse transcription–polymerase chain reaction (RT-PCR) initiated a surveillance focus of 100 m, where mosquitoes were collected, household contacts were screened for infection, and demographic information was analyzed. Within the 6-week study, 19 foci were studied, with an enrolled study population of 367 residents, who were skewed toward female residents and senior citizens (aged >65 years) as compared to the general population of Puerto Rico. Testing of blood, urine, and serum specimens by RT-PCR indicated that 31.1% of participants tested positive for ZIKV. During this time, 7% were identified who had recent DENV or CHIKV infection. Epidemiological analyses concluded that sex, age, and economic status were not associated with increased prevalence of ZIKV infection; however, factors such as leaving windows open and having at least 1 mosquito bite per week, especially in the morning and at home, were associated with a higher prevalence of ZIKV infection. Like previous reports, ZIKV was associated with fever,

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rash, arthralgia, and arthritis. During the study, 43% of confirmed infections were symptomatic and were strongly associated with female sex, age of <40 years, and preexisting asthma. Viremia levels were not different between patients with and those without symptoms. This is significant since asymptomatic infected individuals are also capable of transmitting to ZIKV to feeding mosquitoes.

Anthropophilic *Aedes aegypti,* besides being the major vectors of transmission for DENV and CHIKV, has been shown in experiments [23, 24], as well as documented in field studies, to be a competent vector of ZIKV transmission [25]. The majority of homes in the observed foci of transmission in the study by Lozier et al were tested (86.5%), and at least 1 female (biting) mosquito was found in 51.6% of these homes. However, none of the pools tested positive for ZIKV, DENV, or CHIKV viral RNA by the Trioplex RT-PCR assay. The use of a geoprocessing system that can determine geographic clusters and associate symptomatic cases and infected mosquitoes is an important factor in demonstrating how environmental parameters modulate the transmission chain and the spatial heterogeneity. This aspect differentiates this study from previous studies that focused on microcephaly. Importantly, understanding the rates of symptomatic and asymptomatic ZIKV infections allows the investigators to derive inferences about the transmission chain of the epidemic and its impact in the studied population and, thus, to link social and environmental factors as determinants of illness.

Despite these key findings, there are some limitations of the study by Lozier et al. The household and participant rates were low, although the study was conducted after the peak of the Zika outbreak in Puerto Rico. First, the foci were limited to a small geographical area and evaluated for only a 6-week period. This resulted in an older, female-predominant data set that was somewhat unlike the rest of the population in Puerto Rico. Second, the study could not address rarer neurological outcomes because of the small sample size. Third, the effects of ZIKV infection in pregnant women also could not be answered in this population. Fourth, in regard to the immunoglobulin M assay used, because of the cross-reactogenicity between flaviviruses (eg, DENV and ZIKV), some recent infections may have been misclassified, and some cases might have been missed because of the timing of blood specimen collection. In addition, caution must be used when extrapolating these findings to other populations with different population densities, travel capabilities, mosquito species, and prevalence of other endemic arboviruses. Despite these caveats, this study is critical in understanding the epidemiology of ZIKV in an outbreak situation.

Notes

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