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Recognizing the Global Impact of Zika Virus Infection during Pregnancy

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In 2016, recognition of the causal relationship between Zika virus (ZIKV) infection during pregnancy and serious birth defects, including brain abnormalities and microcephaly, forever changed the public health approach to this virus[1]; the potential threat to pregnancies extends to residents of and travelers to nearly 100 countries and territories in which there is an ongoing risk of infection with ZIKV (https://wwwnc.cdc.gov/travel/page/zika-information). This virus has long been endemic in many countries in Africa and Asia, but reports of ZIKV disease in these settings have been relatively rare.[2] The prevalence of ZIKV infection in countries in which the virus is endemic is unknown, but seroprevalence surveys suggest a range of less than 1% to more than 50%.[2] We currently lack adequate information on the percentage of reproductive-age women who are immune before pregnancy, and conversely the percentage of pregnant women who are susceptible, as well as the percentage of women who are infected during pregnancy in these settings in which the virus is endemic.

However, with awareness of the teratogenicity of ZIKV infection during pregnancy, case reports have emerged from countries with endemic transmission, such as Vietnam.[3] In addition, two older children in the United States have been reported to have a phenotype consistent with the congenital Zika syndrome; their mothers lived in a country with endemic ZIKV transmission, had symptoms of ZIKV infection in the first half of pregnancy, and had laboratory evidence of past ZIKV infection in maternal specimens obtained years after the pregnancy.[4] Accumulating data suggest that in areas in which there is a risk of ZIKV infection, the virus has been having a teratogenic effect on pregnancies for many years, but the impact has not been recognized. And although preventing ZIKV infection is the priority, for women who receive a diagnosis of this infection during pregnancy, better information is needed on the magnitude of the risk of serious birth defects and other disabilities.

In this issue of the *Journal*, Hoen et al.[5] report data from a cohort of pregnant women with polymerase-chain-reaction–confirmed symptomatic ZIKV disease in French territories in the Americas. This report provides some of the most compelling data to date that the risk of brain abnormalities, microcephaly, and eye anomalies extends to infections in every trimester of pregnancy. Not surprisingly, the risk of severe microcephaly was limited to infections that occurred during the first or second trimester, but the overall risk of birth defects that have been associated with ZIKV infection was 12.7%, 3.6%, and 5.3% when

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infection occurred in the first, second, and third trimester, respectively. In addition, the authors report both disproportionate and proportionate microcephaly after infections in any trimester of pregnancy. The finding of proportionate microcephaly suggests that in some cases, ZIKV might affect fetal growth instead of — or in addition to — having a specific destructive effect on the fetal brain.

The findings in the French territories are remarkably similar to those in the U.S. Zika Pregnancy and Infant Registry, a surveillance network that monitors all pregnancies with laboratory evidence of ZIKV infection regardless of the presence or absence of maternal symptoms. The registry showed that in the United States, approximately 5% of pregnancies with possible ZIKV infection and 10% of the subset of pregnancies with laboratory-confirmed ZIKV infection resulted in a fetus or infant with a ZIKV-associated birth defect; the risk estimate was 15% when the confirmed infection occurred in the first trimester.[6] In the U.S. territories combined, among completed pregnancies with confirmed infections, the risk of birth defects associated with ZIKV was 8%, 5%, and 4% when infection occurred in the first, second, and third trimester, respectively.[7] Hoen et al. identified only one neural-tube defect in the French territories cohort, which is consistent with growing evidence that neural-tube defects have not increased in areas with local ZIKV transmission and are most likely not caused by ZIKV infection.[8] In the U.S. reports and in the French territories, some brain abnormalities may have been missed among babies whose mothers had confirmed infection, because not all fetuses or infants underwent the recommended brain imaging; continued efforts are needed to increase the proportion of infants who receive all recommended evaluations if their mothers have had evidence of ZIKV infection during pregnancy.[9]

Although there is growing clarity about the magnitude of the risk of serious birth defects associated with ZIKV infection detected during the newborn period, the full range of disabilities, including the possible effect on neurodevelopment, remains unknown. Follow-up of children whose mothers had confirmed ZIKV infection during pregnancy is essential for understanding the full spectrum of disabilities associated with congenital ZIKV infection and for planning for the medical care and social services needed by affected families.

It is also clear that studies of cohorts of pregnant women with laboratory-confirmed, symptomatic ZIKV infections are critically important but do not provide information on the estimated 80% of pregnant women with ZIKV infections who have no reported symptoms. Population-level increases in ZIKV-associated birth defects are unlikely to be recognized without ongoing timely and comprehensive surveillance of birth defects that captures all affected fetuses and infants regardless of whether maternal ZIKV exposure or infection was identified.[8]

The report by Hoen et al. emphasizes the serious global health threat to pregnant women and their infants posed by congenital ZIKV infection, a threat that was recognized because of the large ZIKV outbreak in the Americas in 2016–2017. There are other known and emerging threats to pregnant women and infants, including the possible teratogenicity of some related flaviviruses that might not be apparent in the absence of surveillance systems that monitor pregnancies, infants, and birth defects and in the absence of a major outbreak of disease

from these flaviviruses.[10] The approaches and lessons learned from the ZIKV outbreak in the Americas show the necessity of improved and integrated ongoing systems for surveillance of pregnancies, infectious diseases, and birth defects to rapidly address the next emerging health threat affecting pregnant women and infants.[11] Sustained commitment to better monitoring systems for these medically vulnerable populations will more promptly identify serious health threats and will provide an opportunity for the public health field to have a positive effect on infant health and prevent birth defects.

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