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Zika Virus: Learning from the Past as We Prepare for the Future

The current pandemic from coronavirus disease (COVID-19) is a sobering reminder that our society is always under a threat of new infectious agents and diseases.[1] One of the more recent epidemics that had particular relevance to pediatrics was the 2015-2016 epidemic of Zika virus (ZIKV), centered in the Americas. ZIKV, a mosquito-borne flavivirus, had been known since 1947,[2] but attracted relatively little attention because the virus was thought to cause only mild febrile illness (Zika fever) in humans. During the 2015 epidemic, however, a sudden increase in the incidence of congenital microcephaly was noted in northeastern Brazil after an outbreak of ZIKV infection.[3] A causal link between congenital ZIKV infection and microcephaly was established and eventually led to the identification of a novel clinical entity known as congenital Zika syndrome.[4,5] The clinical spectrum has continued to expand since. The birth incidence of congenital brain anomalies reached as high as 2.24 in 100 live birth in Salvador, Brazil, during the height of the epidemic in December 2015, highlighting the devastating impact on the areas that were severely affected by the epidemic.[6] Currently, there are no outbreaks of ZIKV, but there is a continued concern for future outbreaks (www.who.int/emergencies/diseases/zika/epidemiology-update/en/). Despite substantial research and development efforts, there are no clinically available vaccines or interventions proven to decrease the risk of fetal transmission of ZIKV in humans. A lack of ongoing outbreaks has made the conduct of clinical trials for vaccines and therapeutics in the pipeline very challenging. Still, we can and should learn from the recent epidemic to prepare better for the potential reemergence of ZIKV in the future.

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In this volume of *The Journal*, Galang et al present a study of the Zika epidemic in Colombia that adds valuable information toward a better preparation for the next ZIKV epidemic.[7] Galang et al used clinical and laboratory data from individuals with microcephaly and central nervous system defects reported to the Colombian national surveillance system between 2015 and 2017 and classified the subjects according to etiologic categories. Among 858 subjects with sufficient information, they concluded that 58% were potentially attributable to congenital ZIKV infection. The strength of evidence for congenital ZIKV infection was highly variable, and only 124 subjects (14.5%) had strong evidence for ZIKV. In contrast, 265 subjects (30.9%) were classified in the unknown etiology category.

This study by Galang et al underscores the challenges in making a diagnosis of congenital ZIKV infection. A relatively short period of viremia, and asymptomatic infections make detection of ZIKV infections in pregnant women challenging.[8,9] In postnatal infants with congenital ZIKV infection, isolation of ZIKV RNA has been reported but may be infrequent, and the sensitivity of serologic testing is unknown.[8,10] In this study, fetal/infant serology (ZIKV IgM in fetal/infant serum or cerebrospinal fluid) was positive in only about one-half of the tested individuals in the strong evidence of congenital ZIKV category. The authors, therefore, devised a classification system for the strength of evidence for congenital ZIKV infection by combining the laboratory evidence and types of birth defects. Similar attempts to classify subjects according to the strength of evidence have been made in previous studies, but this investigation uses a more detailed classification of birth defects, based on the current knowledge of their specificity to congenital ZIKV infection.[11,12] As the virologic and serologic diagnostic tests improve and our understanding of congenital ZIKV syndrome deepens, the classification system will inevitably have to be modified. However, the scheme presented in this study may serve as a prototype for future surveillance programs.

This study relied on voluntary reporting of individuals to the national surveillance system and therefore tended to introduce a selection bias, as the authors acknowledge. It is likely that mildly affected individuals, such as those without microcephaly or noticeable neurologic abnormalities during the newborn period, were under-reported. Recent studies suggest that children who were exposed to ZIKV in utero but asymptomatic at birth may be at risk of developmental delay.[13,14] Future surveillance protocols have to consider such new information to allow better postnatal tracking of children at risk. Along with surveillance protocols, the current clinical guidelines for evaluation and management of the neonates and infants with potential ZIKV exposure in utero by the Centers for Disease Control and Prevention and the World Health Organization (www.who.int/csr/resources/publications/zika/assessment-infants/en) may need to be modified as the spectrum of congenital Zika syndrome broadens.[15]

COVID-19	Coronavirus disease
ZIKV	Zika virus

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Although this study focuses on ZIKV, the work also highlights the importance of other etiologies for microcephaly and central nervous system defects. STORCH infections and genetic disorders were identified in 3.7% and 1.9% of the subjects, respectively. Among STORCH infections, congenital cytomegalovirus infection remains a major cause of neurodevelopmental disabilities throughout the world.[16] However, effective prevention and treatment strategies for congenital cytomegalovirus infection are still lacking.[17] Genetic disorders are also a common cause of microcephaly.[18] These disorders that do not cause noticeable outbreaks receive relatively little attention, particularly among the general public and media, yet continue to put a significant burden on the affected individuals, their families, and society at large.

How can we better prepare for the next potential ZIKV epidemic? We can infer from this study that robust infrastructure for surveillance in the countries and regions at risk would be highly desirable. An ideal surveillance system should allow baseline monitoring of ZIKV transmission and congenital malformations, but also versatile enough to adapt more specifically to congenital Zika syndrome to include a broader spectrum of data collection when faced with an emerging ZIKV epidemic. At the same time, efforts to develop better diagnostic tests and biomarkers for ZIKV have to continue. There are vaccines and therapeutics already in the pipeline, but novel preventive and therapeutic approaches should also be sought through a continued investigation into the pathogenesis of ZIKV infection. All these strategies would require a sustained, coordinated effort across the public health, academic, and industrial sectors and would not be an easy task with finite resources. Nevertheless, we have an obligation as a society to the children and families affected with congenital Zika syndrome to keep learning from the past and keep preparing for ZIKV and other epidemics in the future. ■

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