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Neurodevelopmental Abnormalities Associated With In Utero Zika Virus Infection in Infants and Children—The Unfolding Story

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In the United States, more than 7400 pregnancies with laboratory evidence of confirmed or possible Zika virus infection were identified and included in the national surveillance network, the US Zika Pregnancy and Infant Registry, during the Zika virus outbreak in the Region of the Americas from 2015 to 2017.[1] These pregnancies included those completed from December 1, 2015, through March 31, 2018, meaning the children from these pregnancies ranged in age from 18 months to nearly 4 years by the fall of 2019. Although between 5% and 10% of these children have received a diagnosis of serious defects of the brain or eye, including microcephaly, many of them have not undergone the recommended postnatal brain imaging and ophthalmological examinations to fully identify these health problems.[2–6] Some infants with a standard head circumference measurement at birth may have underlying brain and/or eye defects. In a report from the US territories and freely associated states, 23 children without microcephaly had brain and/or eye defects that would have been missed without the recommended neuroimaging and/or ophthalmological examinations.[4]

Although infants with Zika virus-associated birth defects of the brain and/or eye are likely to have severe neurodevelopmental disabilities,[7] it remains unknown whether the 90% to 95% of infants potentially congenitally exposed but without Zika virus-associated birth defects have a higher-than-baseline risk of neurodevelopmental abnormalities and, if so, how these disabilities may manifest over time. In the US territories and freely associated states with surveillance data on children at least 1 year of age, about three-quarters of children were

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given a developmental assessment with a standardized tool; 9% had 1 or more neurodevelopmental disabilities, including hearing abnormalities; congenital contractures; seizures; body tone, movement, or swallowing disorders; vision impairment; possible developmental delay; and postnatal onset microcephaly.[4] In Salvador, Brazil, 10 of 29 normocephalic children with congenital Zika virus exposure (34%) had neurodevelopmental delay when evaluated at a mean age of 18 months.[8] In Rio de Janeiro, Brazil, follow-up of a cohort of infants from women with confirmed Zika virus infection during pregnancy also demonstrated severe developmental delay in these children, approximately 12% of whom scored at least 2 SDs below the mean when assessed with the Bayley Scales of Infant and Toddler Development, Third Edition, with the language domain being the most affected.[9]

Despite a recommendation from the American Academy of Pediatrics for universal developmental screening, based on data from the 2016 National Survey of Children's Health, less than 40% of children are receiving this recommended screening.[10] Although developmental screening is important for all children to ensure that neurodevelopmental delays are promptly recognized and families are referred to appropriate services as early as possible, this standard of care is even more important for children with a possible congenital infection that might put them at a greater risk of neurodevelopmental disabilities. In addition, because most cases of Zika virus infection have either no or mild symptoms, the more than 7400 pregnancies and resulting infants in the US Zika Pregnancy and Infant Registry represent only a portion of the pregnancies in the United States with a Zika virus infection during this period. An increase in birth defects potentially associated with Zika virus infection was reported by birth defect surveillance systems in areas of the United States with local transmission of Zika virus, and three-quarters of these cases did not undergo maternal, infant, or placental Zika virus testing.[11]

In this issue of *JAMA Pediatrics*, Mulkey et al[12] provide intriguing data on neurodevelopmental disabilities that might be associated with Zika virus exposure in utero based on the authors' continued follow-up of a cohort of children in Atlántico Department, Colombia, from symptomatic pregnancies with laboratory evidence of probable Zika virus infection. The authors followed up 77 infants who had a clinically normal presentation at birth. Although the initial developmental assessments (beginning at age 4 months) were reassuring, the overall scores declined as the children aged, with the most decreases seen in the mobility and social cognition domains, highlighting the importance of long-term follow-up and continued developmental screenings. A caveat is that the outcomes measures used have not been previously validated in the Colombian population, and no concurrent control group was evaluated.

In the cohort followed by Mulkey et al,[12] nonspecific findings on postnatal imaging (lenticulostriate vasculopathy, germinolytic/subependymal cysts, and choroid plexus cysts) were associated with lower scores in the social cognition domain. Although the clinical significance of these nonspecific findings is not yet clear, the importance of postnatal neuroimaging for all children with Zika virus exposure in utero was made extremely clear. The remote scoring method the authors used offer learning opportunities for care and standardized assessments through review of video files. This method could be applied to

rural health care in the United States and elsewhere to minimize the challenges associated with distance to available care.

Mulkey et al[13] did not report the results of Zika virus or antibody testing for the infants in this cohort, and the reported laboratory evidence of Zika virus infection in pregnancy varied. From the limited laboratory data provided in the present article and the previous description of this cohort,[13] all but 1 of the identified infections were based on serological evidence; it was not clear whether a dengue serological test was also conducted and which cases with Zika PRNT (plaque reduction neutralization tests) >10 result did not also have dengue PRNT>10 results. This ambiguity in reported laboratory testing and results was a limitation of the current study. Although the sensitivity and specificity of available diagnostic tests for congenital infection remain to be elucidated, a thorough laboratory evaluation of the infant as early as possible after birth remains essential to associate potential congenital Zika virus infection with longer-term neurodevelopmental outcomes. Identifying a reliable biological marker of congenital Zika virus infection that can be used in a range of laboratory settings remains 1 of the major unresolved issues after the Zika virus outbreak in the Region of the Americas and is a priority for the public health and research communities.

Despite the limitations of the Mulkey et al[12] study, the findings add to the growing evidence of the need for long-term follow-up for all children with Zika virus exposure in utero to ensure they receive the recommended clinical evaluations even when no structural defects are identified at birth; we are currently far from meeting that objective. In New York City, 404 infants were born to women with laboratory evidence of confirmed or possible Zika virus infection, but among the 380 of these children who reached 12 months of age, follow-up data were available for only 168 (44%).[14] Similar challenges with following up infants and ensuring all of them receive the recommended evaluations have been reported by other jurisdictions.[4] In US territories and freely associated states, on the basis of data reported to the surveillance network and among infants who were not lost to follow-up and had reached at least 1 year of age, only about 60% had received postnatal neuroimaging, 36% had received an ophthalmological evaluation, and 76% had received at least 1 developmental screening or assessment.[4] Evaluation of infants solely at the time of birth is clearly inadequate, as growing evidence exists of infants with clinically normal assessments who subsequently developed neurodevelopmental issues and infants with documented microcephaly at birth whose microcephaly was resolved and whose neurodevelopmental assessment results were normal on follow-up.[9]

Although the major Zika virus outbreak in the Region of the Americas has ended, follow-up of the affected children in the United States and throughout the region is still in the early stages, and continued follow-up is needed. In giving children every opportunity to thrive, the importance of compliance with the recommendations for evaluations, including developmental screening, is increasingly evident. Identifying potential cases of Zika virus exposure and documenting them in medical records to communicate the information with other health care practitioners can help facilitate the provision of all recommended screenings and evaluations. In addition, pregnant travelers will continue to be at risk for Zika virus in parts of the world with endemic transmission and in which Zika virus outbreaks can occur with little warning.[15] Understanding the full spectrum of effects associated with

congenital Zika virus exposure will help public health respond quickly to future outbreaks, prevent Zika virus infection whenever possible, and provide the most up-to-date clinical guidance for the care of infants and children with congenital Zika virus exposure.

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