Trends in Microbiology

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The Aftermath of Zika: Need for Long-Term Monitoring of Exposed Children

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Pregnancy infections with Zika virus are associated with a spectrum of fetal brain injuries beyond microcephaly. Nonmicrocephalic children exposed to Zika virus *in utero* or early life should undergo neurodevelopmental testing to identify deficits and allow for early intervention. Additionally, long-term monitoring for higher order neurocognitive deficits should be implemented.

The Zika virus (ZIKV) epidemic in the Americas in 2014–2016 became linked to an unexpected surge in congenital microcephaly cases, and was declared a global public health emergency by the World Health Organization [1]. ZIKV is a mosquito-transmitted flavivirus that can infect a variety of cells in the fetal brain, including highly vulnerable neural stem and progenitor cells, as well as neurons, astrocytes, and microglia [2]. Congenital Zika Syndrome (CZS) describes infants with a severe fetal brain injury, including microcephaly, subcortical calcifications, hypertonia, congenital contractures, and ocular injury[i]. Several studies estimate the occurrence of ZIKV-associated birth defects to be 5–13%, depending on when the infection occurs during pregnancy [3,4]. Interestingly, the isolated diagnosis of microcephaly does not necessarily capture infants with abnormal brain structure by imaging [5,6]. By 1 year of age, some infants exposed to ZIKV *in utero* with a normal head size at birth have been diagnosed with an array of major neurological defects, including postnatal microcephaly (brain growth failure), ocular injury, hemiparesis, seizures/epilepsy, and hydrocephalus. The Centers for Disease Control (CDC) have recommended that healthcare providers 'remain alert for any new findings of possible congenital Zika virus infection' in infants without clinical findings of CZS[i]. We argue that evidence is accumulating to support a stronger recommendation for referral to a developmental specialist even for nonmicrocephalic infants exposed to ZIKV.

Despite the intense scientific investigation of congenital microcephaly, we are only beginning to understand the greater spectrum of ZIKV-associated injury and neurodevelopmental outcomes for nonmicrocephalic fetuses. Congenital exposure to ZIKV was recently found to induce a spectrum of subtle and 'silent' injuries to the fetal brain that are challenging to detect prenatally, but would result in poor neurodevelopmental outcomes [7]. In a pregnant nonhuman primate model, exposure to ZIKV via maternal subcutaneous inoculation led to significant loss of neural stem cell activity and output in both the late fetal cortical subventricular zone and hippocampal subgranular zone; these sites are specialized neurogenic niches that continue to undergo active neurogenesis during late fetal life [8]. Injury to hippocampal neural stem and progenitor cells is particularly ominous because these cells are critical for forming new memories, learning, and maintaining one's mental health [9]. Indeed, abnormalities in hippocampal neurogenesis underlie the progression of severe neurocognitive and psychological behaviors, including spatial pattern recognition, learning and memory, emotional and behavioral regulation, seizures, and later onset schizophrenia, depression, and neurodegenerative disorders such as Alzheimer's disease [8,10–12]. Consistent with our findings, cell death and loss of neural stem cells in late neurogenic niches was observed in a ZIKV-exposed adult mouse model [13]. Further, a recent study in young nonhuman primates correlated a postnatal ZIKV infection with hippocampal growth arrest, deficits in socioemotional processing, and abnormal functional connectivity between the hippocampus and the amygdala [14]. This evidence strongly suggests that neurodevelopmental outcomes should be studied through childhood and adolescence for all infants exposed to ZIKV *in utero*, regardless of head size at birth, and for children exposed in early life.

Understanding the impact of fetal or early postnatal ZIKV exposure to these specialized and vulnerable hippocampal neural stem and progenitor cells is crucial because the resulting deficits may not manifest until higher order processing and cognitive behaviors emerge in childhood and adolescence. We recommend frequent assessment and monitoring of ZIKV-exposed children throughout the first 24 months of age[i,ii,iii]. Because motor, language, and cognitive development are highly interrelated in infancy through early childhood, assessment of multiple domains of development (motor, language/communication, cognition/learning, social-emotional, and adaptive) is needed to fully determine the impact of a fetal brain injury. In addition, magnetoencephalography is a viable measure of neural activity in infants and has the advantages of being quiet, allowing patient movement, and not requiring sedation. Early detection is essential for accessing early interventions, which promote better outcomes in children with neurodevelopmental disabilities. Assessment instruments at later ages should include more specific, nuanced measures

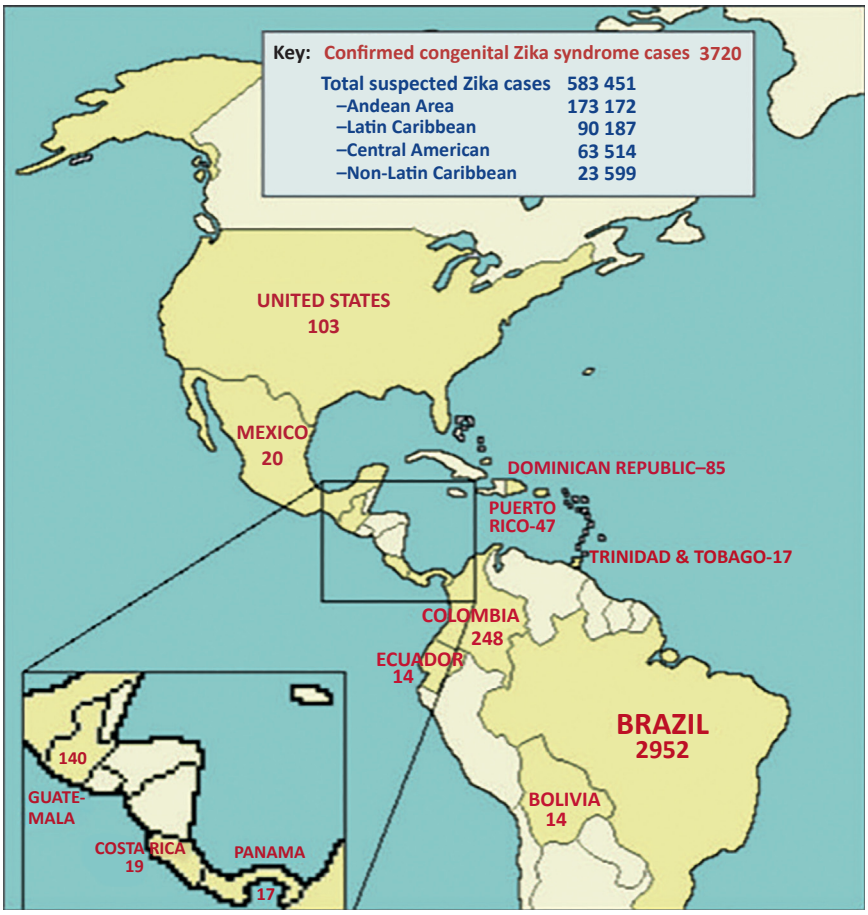

Figure 1. Cumulative Number of Confirmed Congenital Zika Syndrome Cases and Suspected ZIKV Infections from 2015 to 2017. A world map shows the cumulative number of reported congenital Zika syndrome (CZS) cases (red, countries in dark yellow) and the number of suspected ZIKV infections (includes nonpregnant individuals, blue) as reported to the Pan American Health Organization/World Health Organization by each country between 2015 and 2017[ii]. Striking and unexpected differences in numbers across regions highlight disparities in ZIKV surveillance and reporting, public health, vector control, and ecological constraints on mosquito-borne virus transmission. Countries in pale yellow have not reported any ZIKV-associated birth defects, but are in regions with likely or confirmed local transmission.

of the developmental domains and should be individualized as indicated by previous evaluation results. Identification of damage to late-onset, higher-order neurocognitive functions requires continued monitoring and evaluation even into adolescence for assessment of mental health, abstract reasoning and language, and independent functioning. From both a quality of life and societal cost perspective, continued monitoring of nonmicrocephalic infants exposed to ZIKV is a public health imperative and is essential for directing care.

The challenge of implementing developmental assessments would be formidable if it included all children in the Americas exposed to ZIKV either *in utero* or in early life. The cumulative number of pregnancies exposed to ZIKV in the Americas between 2014 and 2017 is likely in the hundreds of thousands; more precise estimates are not possible to obtain. Currently, the reporting of cumulative cases of CZS and 'suspected' ZIKV infections is strikingly inconsistent across countries with known local transmission during the recent ZIKV epidemic in the Americas (Figure 1). For example, Trinidad and Tobago, a small island nation with a population of ~1.4 million people, has nearly the same number of ZIKV-associated birth defects as the entire country of Mexico (~130 million people). If we extrapolate from data obtained in the USA and French Territories, we could multiply known cases with a birth defect by a factor of 12–20 to determine the total number of pregnancies exposed to ZIKV [3,4]. Although the cumulative number of cases in the Americas with birth defects attributed to ZIKA is only ~4000, this is likely a significant underestimate and would translate to at least ~80 000 exposed pregnancies. Even this estimate would not include children exposed to ZIKV in early life. In many ways, the ZIKV epidemic served to highlight what we already knew – the public health surveillance of pregnancy and neonatal outcomes in the Americas is completely inadequate. The US Pregnancy Zika Registry provides a model for moving forward to prepare for detection of adverse maternal–fetal outcomes with the next viral epidemic[i].

The hypothesis that children exposed to ZIKV might be at greater risk for poor neurodevelopmental outcomes has strong precedent across history for a number of other teratogenic viruses including: cytomegalovirus, herpes simplex viruses, parvovirus B19, human immunodeficiency virus, and Chikungunya virus. We argue that prenatal and early postnatal ZIKV exposure is a risk factor for neurodevelopmental delay, in the absence of microcephaly or another ZIKV-associated birth defect; therefore, these children should be eligible for early intervention services in the USA under the Individuals with Disabilities Education Act

Table 1. Common Assessments Appropriate for ZIKV Developmental Monitoring

Age range[a]	Common assessment tools[b]	Developmental areas
Birth–5:0	Peabody Developmental Motor Scales, Second Edition (PDMS-2)	Fine and gross motor
Birth–7:11	Preschool Language Scales, Fifth Edition (PLS-5)	Receptive and expressive language
Birth–90:0	Vineland Adaptive Behavior Scales, Third Edition (VABS-3) Adaptive Behavior Rating Scales, Third Edition (ABAS-3)	Adaptive
Birth–14:11	Sensory Profile, Second Edition (SP-2)	Sensory processing
0:1–3:6	Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)	Cognition, language, motor, adaptive, social-emotional
1:6–90:0	Achenbach Child Behavior Checklist (CBCL)	Social-emotional/behavior
2:0–21:11	Behavior Assessment Scales for Children, Third Edition (BASC-3)	
2:0–99:0	Beery-Buktenika Developmental Test of Visual Motor Integration, Sixth Edition (VMI-6)	Visual motor integration, visual perception, motor coordination
2:6–7:7	Wechsler Preschool and Primary Scales of Intelligence, Fourth Edition (WPPSI-IV)	Cognitive
2:6–17:11	Differential Ability Scales, Second Edition (DAS-2)	
5:0–95:0	Batería III Woodcock-Munoz: Pruebas de habilidades cognitivas (Batería III-COG)	
6:0–16:11	Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V)	
2:6–5:11	Developmental Indicators for Assessment of Learning, Fourth Edition (DIAL-4)	Pre-academic/academic learning
2:6–7:11	Bracken Basic Concepts Scale, Third Edition: Receptive and Expressive (BBCS-3:R & E)	
5:0–95:0	Batería III Woodcock-Munoz: Pruebas de aprovechmient (Batería III-APROV)	
3:0–16:11	Neuropsychological Assessment for Children, Second Edition (NEPSY-2)	Executive functioning
8:0–89:11	Delis-Kaplan Executive Functioning Scales (D-KEFS)	
5:0–16:11	Children's Memory Scale (CMS)	Memory
16–89:11	Wechsler Memory Scales (WMS)	
5:0–80:0	Quick Neurological Screening Test, Third Edition Revised (QNST-3R)	Neurological soft signs of possible neurological and/or learning problems
13:0–18:0	Millon Adolescent Clinical Inventory (MACI) Minnesota Multiphasic Personality Inventory, Second Edition (MMPI-2)	Personality, mental health

[a]Age range is denoted as years:months of age–years:months of age.
[b]Available in multiple languages; may also have multicultural norms.

(IDEA). Early neurodevelopmental evaluation using standardized assessments should be performed even for the non-microcephalic ZIKV-exposed children at regular intervals, at least matching the US well-child visit schedule, but more frequently if developmental delays are identified (Table 1). We also advocate for a long-term differentiated, individualized evaluation through adolescence in order to detect later developing cognitive processes (i.e., executive functioning) and mental health. The next step is to act on this information to improve early child development, and this is no small task. Rigorous implementation science research is needed to evaluate and scale early interventions in low- and middle-income countries that are culturally appropriate for each population.

Reports of recent ZIKV outbreaks in West Africa suggest that this virus will remain a contemporary problem for pregnancies in many parts of the world. In addition to vaccine efforts, we must also focus investigation on the thousands of children exposed to ZIKV that are now growing up as infants and toddlers. While the concept of microcephaly as a marker for fetal brain injury was useful in the beginning to direct scientific efforts, we are now aware that the deleterious effects of ZIKV may be subtle and challenging to detect during pregnancy. Recent evidence that fetal or early postnatal ZIKV exposure can injure neural stem cell and progenitor cell populations in the hippocampus is particularly concerning for the possible development of neurocognitive deficits, memory disorders, or psychopathologies in childhood. Early detection and intervention in these cases is critical to promote the best neurodevelopmental outcome. We need long-term studies of the development

and mental health of children exposed to ZIKV, regardless of head size at birth, similar to ongoing studies in Colombia and Brazil[i]. Unfortunately, ZIKV is not the only virus of concern; a recent study revealed that West Nile virus, a neuroinvasive virus related to ZIKV, can also infect the placenta and, presumably, the fetus [15]. As we recognize an expanding list of viruses that may damage the fetal brain, we need tool kits to rapidly implement a global public health response and to address the long-term public health challenges of fetal brain injury. Most importantly, we must take care of the children.

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Resources

[i]www.cdc.gov/zika

[ii]www.paho.org

[iii]www.who.int/csr/disease/zika/en/

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