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Birth Defects Potentially Related to Zika Virus Infection During Pregnancy in the United States

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Zika remains a health threat in the United States, and public health systems are essential to monitoring the full effect of congenital Zika virus infection on infants and children. Because some healthy infants born following pregnancies complicated by Zika may have developmental problems that become evident later, developmental milestones should be closely monitored throughout the child's first years of life.

Zika virus can cause serious damage to the developing fetal brain when infection occurs during pregnancy. In addition to causing brain abnormalities and microcephaly, Zika virus infection during pregnancy has been associated with eye abnormalities, joint contractures, and potentially other birth defects and disabilities.[1] From January 2016 through December 2017, 7054 pregnancies with laboratory evidence of possible Zika virus infection in US states and territories were reported to the US Zika Pregnancy and Infant Registry coordinated by the US Centers for Disease Control and Prevention (CDC).[2] However, the total number of mothers and infants in the United States affected by congenital Zika virus infection since the emergence of the virus in the Americas is likely much higher because many women with exposure to Zika virus in pregnancy were not tested or were not tested in a timeframe that allowed identification of the infection.

Most Zika virus infections are asymptomatic and detecting Zika virus RNA is complicated by its transient presence in body fluids; thus, Zika virus infection during pregnancy cannot be ruled out by negative nucleic acid testing results. Serologic testing is affected by the timing of specimen collection, and interpretation of positive results is complicated by cross-reactivity, especially in persons previously infected with a related fla-vivirus. Birth defect surveillance systems are a vital component to detect increases independent of whether Zika virus exposure or infection is identified.

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On January 25, 2018, the CDC released the first report of population-based birth defect surveillance from 15 jurisdictions for birth defects potentially associated with congenital Zika virus infection.[3] Existing systems were enhanced to identify fetuses and infants with selected birth defects in a timely fashion (Box). The report examines pregnancies completed in 2016, and it included 3 areas with local transmission of Zika virus and areas with higher and lower travel-associated Zika virus disease cases reported. Comparing the second half of 2016 with the first half, there was an increase in total birth defects potentially associated with Zika virus infection in jurisdictions with local transmission of Zika virus that was not statistically significant, and there were no increases noted in the other jurisdictions. However, when limited to the birth defects strongly linked to Zika virus infection (brain abnormalities, microcephaly, or both; eye abnormalities; and consequences of central nervous system dysfunction), which collectively represent more than 90% of the Zika-associated birth defects in the US Zika Pregnancy and Infant Registry,[4] there was a significant 21% increase in areas with local transmission (from 2.0 to 2.4 per 1000 live births) in the latter half of 2016 compared with the first half. No increase was observed for neural tube defects and other early brain malformations, consistent with the much more limited evidence of congenital Zika virus infection as a cause for these birth defects.

Because the peak of local virus transmission in these jurisdictions occurred in the second half of 2016, and most exposed pregnancies were completed in 2017, it is critical that public health surveillance programs continue reporting the occurrence of these birth defects to monitor for trends following the Zika virus outbreak. The birth defects surveillance report identified increased prevalence of birth defects strongly linked to Zika virus infection in 2016 in US areas with local Zika virus transmission.[3] Although these birth defects are not specific to congenital Zika virus infection and have other causes, only those defects found previously to be most closely aligned with congenital Zika infection had increased prevalence. Most of the fetuses and infants described in the birth defects surveillance report had no laboratory evidence of congenital Zika virus infection and no Zika virus testing performed. For some of these infants, Zika virus testing would not have been indicated because of lack of possible maternal exposure or identification of other etiologies.

The significant increase in birth defects strongly linked to Zika virus infection is concerning, but it might represent just a portion of the full effect of congenital Zika virus infection. About 5% to 10% of pregnancies with laboratory evidence of possible Zika virus infection have been initially reported to have one of these birth defects.[5,6] However, there are also case reports of infants born with normal head circumference who developed postnatal-onset microcephaly following congenital Zika virus infection.[7] The full range of developmental disabilities and other adverse early childhood outcomes associated with congenital Zika virus infection in the United States can only be determined by following up the infants and children as they develop. Understanding what is happening with those infants might have far-reaching implications for other exposed infants whose congenital infection was not identified during pregnancy or at birth. Many infants with congenital Zika virus infection and severe microcephaly will have profound developmental delays and face significant challenges,[8] but ongoing surveillance is needed to determine the extent to which congenitally exposed infants without apparent birth defects will experience similar or other developmental issues.

To prevent these serious birth defects, the CDC continues to recommend that pregnant women not travel to areas with risk of Zika including US areas with endemic transmission. Furthermore, healthcare professionals should remain vigilant and consistently consider possible exposure to Zika virus during pregnancy, regardless of the availability of testing results. Many pregnancies with Zika virus exposure are either not tested or not tested at the right time to detect infection because there is no longer a recommendation for testing asymptomatic pregnant women with travel to areas with risk of Zika virus infection. Infants with birth defects potentially associated with Zika virus infection and possible maternal Zika virus exposure during pregnancy should be tested for evidence of Zika virus infection, other congenital infections (eg, cytomegalovirus, toxoplasmosis, syphilis, rubella, or herpes), and other causes of microcephaly or birth defects. Clinicians who provide care for young children should be mindful of the importance of ongoing developmental monitoring and use the many valuable tools and resources that allow for routine and systematic screenings.

Nearly 70 years after the Zika virus was first identified, the large outbreak in the Americas and subsequent increases in serious birth defects have highlighted the need to protect mothers and infants from emerging infectious diseases and other health threats. Real-time public health surveillance systems are critical for preparedness and response to infectious diseases to determine the risk to pregnant women and their infants and allow rapid deployment of prevention strategies. These robust public health systems can also be applied to other public health emergencies such as the epidemic of opioid misuse, which poses unique threats to infants with prenatal exposure. The foundation of birth defect surveillance can provide a powerful public health tool to help the CDC and state, local, tribal, and territorial health departments address emerging threats.

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Box

Birth Defects Potentially Related to Zika Virus Infection During Pregnancy and Monitored by Zika Birth Defects Surveillance

Brain Abnormalities With and Without Microcephaly

Congenital microcephaly defined as (1) diagnosis or mention of microcephaly or small head in the medical record and (2) for live births, head circumference less than the third percentile for gestational age and sex at birth or within the first 2 weeks of life or, for nonlive births, prenatal head circumference more than 3 SDs below the mean on prenatal ultrasound

Intracranial calcifications

Cerebral atrophy

Abnormal cortical gyral patterns (eg, polymicrogyria, lissencephaly, pachygyria, schizencephaly, and gray matter heterotopia)

Corpus callosum abnormalities

Cerebellar abnormalities

Porencephaly

Hydranencephaly

Ventriculomegaly or hydrocephaly (excluding “mild” ventriculomegaly without other brain abnormalities and hydrocephalus secondary to a cranial hemorrhage)

Fetal brain disruption sequence (severe microcephaly, collapsed skull, overlapping sutures, prominent occipital bone, scalp rugae)

Other major brain abnormalities (eg, abnormalities of the thalamus, hypothalamus, pituitary, basal ganglia, or brainstem)

Neural Tube Defects and Other Early Brain Malformations[a]

Anencephaly or acrania

Encephalocele

Spina bifida without anencephaly

Holoprosencephaly

Eye Abnormalities

Microphthalmia or anophthalmia

Coloboma

Congenital cataract

Intraocular calcification

Anomalies (eg, atrophy, scarring, and gross pigmentary changes, excluding retinopathy of prematurity)

Optic nerve atrophy, pallor, and other optic nerve abnormalities

Consequences of Central Nervous System Dysfunction

Arthrogryposis (including congenital contracture of single major joints)

Clubfoot with associated brain abnormalities

Congenital hip dislocation or developmental dysplasia of the hip with associated brain abnormalities

Congenital sensorineural hearing loss

[a]Neural tube defects and other early brain malformations are included as biologically plausible birth defects; however, the evidence for a link with Zika virus infection during pregnancy is much weaker than for defects in the other categories listed.