

# Initial Description of the Presumed Congenital Zika Syndrome

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**Objectives.** To provide an initial description of the congenital syndrome presumably associated with infection by Zika virus compared with other syndromes including congenital infections of established etiologies.

**Methods.** We provide an overview of a published case series of 35 cases, a clinical series of 104 cases, and published and unpublished reports of clinical and laboratory findings describing cases diagnosed since the beginning of the epidemic of microcephaly in Brazil.

**Results.** About 60% to 70% of mothers report rash during pregnancy; mainly in the first trimester. Principal features are microcephaly, facial disproportionality, cutis girata, hypertonia/spasticity, hyperreflexia, and irritability; abnormal neuroimages include calcifications, ventriculomegaly, and lissencephaly. Hearing and visual abnormalities may be present.

**Conclusions.** Preliminary data suggest that severe congenital abnormalities are linked to Zika virus infection. Cases have severe abnormalities, and although sharing many characteristics with congenital abnormalities associated with other viral infections, abnormalities presumably linked to the Zika virus may have distinguishing characteristics. These severe neurologic abnormalities may result in marked mental retardation and motor disabilities for many surviving offspring.

**Policy Implications.** Affected nations need to prepare to provide complex and costly multidisciplinary care that children diagnosed with this new congenital syndrome will require. (*Am J Public Health.* 2016;106:598–600. doi:10.2105/AJPH.2016.303115)

The Brazilian epidemic of Primary Microcephaly, presumably caused by congenital infection with Zika virus (ZIKV),<sup>1</sup> is an international concern. The ZIKV was first confirmed in May 2015, as the cause of an outbreak of a dengue-like disease in Northeastern Brazil.<sup>2</sup> ZIKV is now spreading explosively in the Americas, and could spread throughout the world.<sup>3</sup> The Brazilian epidemic, with more than 4000 suspected microcephaly cases reported in 6 months, caught the scientific and public health communities by surprise: ZIKV was perceived as a virus of little public health importance, and knowledge of the epidemiology and the pathogenesis is scarce.<sup>4</sup> The evidence for a causal link is strong and is considered sufficient to justify public health interventions. This is the first time a mosquito-transmitted infection is

known to cause severe congenital malformations in humans. To describe the Zika congenital infection syndrome, we collected data and reports from a published case series of 35 cases,<sup>5</sup> a clinical series of 104 cases (Microcephaly Epidemic Research Group, unpublished data, 2016), and published and unpublished case reports, additionally drawing

from the clinical experience of 2 of the authors (M. A. W. R. and R. C. F. R.).

## FEATURES OF CONGENITAL MICROCEPHALY

Common features of congenital microcephaly include facial disproportionality (the face appears large in comparison with the small head) and “cutis girata” (skin scalp folds, caused by the continued growth of the skin as the brain development slows down; Figure 1). Usually, neonates have the archaic reflexes preserved; most feed well, although some have dysphagia. Abnormalities at neurological examination include hypertonia or spasticity, hyperreflexia, irritability, tremors, and convulsions. Neuroimages often reveal calcifications, ventriculomegaly, and cortical disorders (lissencephaly) (Microcephaly Epidemic Research Group, unpublished data, 2016).<sup>5</sup> Hearing and visual abnormalities appear to be present, although only a small number were tested. Ventura et al. reported macular atrophy in 3 children.<sup>6</sup> Umbilical hernia, clubfoot (talipes equinovarus), and arthrogryposis have been described, the latter probably as a consequence of the neurological abnormalities. The prematurity observed in these children is similar to that in the Brazilian population.<sup>7</sup> There have been 68 notified deaths to date (between stillbirths and early mortality).<sup>8</sup>

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**FIGURE 1—Newborn Microcephaly and Arthrogryposis in Legs and Arms**

## CONGENITAL ZIKA COMPARED TO OTHER CONGENITAL INFECTIONS

In Table 1, we summarize some characteristics of the other well-established congenital infections (toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis [TORCH]).<sup>9</sup> Preliminary data suggest that congenital Zika cases have no hepatosplenomegaly, no petechiae or purpura rash, nor other skin lesions; calcifications are common as in toxoplasmosis and cytomegalovirus infection, and may be more

severe; hearing abnormalities can be present (in contrast to congenital parvovirus B19, toxoplasmosis, and syphilis); and like in all congenital TORCH infections, ocular abnormalities may be present. Early indications are that congenital Zika cases tend to have severe neurological findings, but this may be a consequence of early detection bias, with only severe cases being identified. About 60% to 70% of mothers of microcephalic newborns report having had rash during pregnancy; most frequently in the first trimester

(Microcephaly Epidemic Research Group, unpublished data, 2016).<sup>5</sup> However, these data were derived from case series without a control group.

Before this epidemic, data on microcephaly were collected in birth registrations only under malformations. When the government set up an emergency surveillance system for this epidemic, microcephaly became reportable; however, any abnormality or malformations related to congenital Zika, but not associated with microcephaly, would not have been systematically collected. However, some children with borderline head circumference have been studied and some had brain calcifications detected. As cohorts of pregnant women with Zika infection are followed, we expect isolated abnormalities will be detected if Zika, like other congenital infections, presents with a range of severity.

It is still too early to establish the severity of the prognosis because the epidemic of congenital abnormalities was detected in August and the follow-up of birth cohorts of cases is just starting. However, given the severity of the neurological abnormalities, it is likely that many of the children will have severe mental retardation and motor disabilities.

## WHY SO FEW CASES HAVE LABORATORY CONFIRMATION

ZIKV diagnosis is mainly based on molecular techniques such as reverse-transcription polymerase chain reaction (RT-PCR) and quantitative real-time PCR (qRT-PCR)

**TABLE 1—Mode of transmission and clinical findings with selected TORCH infections.**

	Mode of Transmission	Hepato Splenomegaly	Cardiac Lesions	Skin Lesions	Hydrocephalus	Microcephaly	Intracranial Calcifications	Ocular Disease	Hearing Deficits
Toxoplasmosis	Food	+	-	Petechiae/purpura maculopapular rash	++	+	+	+	-
<i>Treponema pallidum</i>	Person to person (sexual)	+	-	+		-	-	+	-
Rubella	Person to person	+	+	Petechiae/purpura		+	-	+	++
Cytomegalovirus	Person to person	+	-	Petechiae/purpura		++	+	+	++
Herpes simplex virus	Person to person	+	+	Petechiae/purpura, vesicles		+	-	+	+
Parvovirus B19	Person to person	+	+	Subcutaneous edema, petechiae		-	-	+	-
Zika virus	Arthropods	-	?	-	- <sup>a</sup>	+	+	+	+

Source. Adapted from Neu et al.<sup>10</sup>

<sup>a</sup>There is ventriculomegaly, but it is too early to determine whether this will evolve into intracranial hypertension and hydrocephalus.

using virus-specific probes.<sup>10,11</sup> By January 2016, of 4180 notified cases of microcephaly, only 6 tested positive for ZIKV. We do not know how many suspected cases were tested. But in the laboratory of some of the authors, ZIKV RNA was not detected by RT-PCR in liquor of 50 affected newborns (personal communication for the staff of the virology department about examination of liquor of cases of microcephaly reported as part of the epidemic). In some viral congenital infections (rubella and CMV) newborns remain infected and viruses can be detected after birth. It is possible that in congenital Zika, the infection usually does not last long; alternatively, the virus may be present but in undetectable levels. Even in acquired infection PCR or viral isolation is difficult because Zika viremic period is transient (3–5 days after the onset of symptoms) and viral load is low.<sup>11</sup>

There are no reliable serologic tests for ZIKV because of extensive antibody cross-reactivity with other arbovirus such as dengue and yellow fever virus in endemic areas.<sup>12</sup>

In addition, the kinetics of antibody responses during the acute infection and the duration of the immunoglobulins in the convalescent patients have not been described. The small proportion of cases with laboratory confirmation reflects the difficulty of Zika diagnosis.

## LINGERING QUESTIONS

At this stage of knowledge accrual about Zika, we have to end this review with an series of still unanswered questions:

What is the whole range of abnormalities of the syndrome, including those not associated with microcephaly?

Does the range and frequency of abnormalities in newborns vary with gestational age at infection, presence of clinical symptoms, and previous dengue infection?

What is the frequency of spontaneous abortions, the rate of stillbirth, and the life expectancy of affected newborns?

What proportion of other complications, including epilepsy, will be diagnosed with age?

How do the children neurocognitive and motor abilities evolve as they grow older?

What is the burden of the congenital ZIKV infection to the society and its health policy implications? *AJPH*

## CONTRIBUTORS

D. B. Miranda-Filho, C. Maria Turchi Martelli, R. Arraes de Alencar Ximenes, T. Velho Barreto Araújo, and L. Cunha Rodrigues contributed to the concept and design or analysis and interpretation of data. All of the authors contributed to the drafting or revision of the article and approved the final version.

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## HUMAN PARTICIPANT PROTECTION

This is a review article in which some data from a case series of patients followed up for some of the authors are quoted. Confidentiality and Human Participant Protection were guaranteed.

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