ORIGINAL ARTICLE

First 12 Months of Life for Infants in New York City, New York, With Possible Congenital Zika Virus Exposure

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Background. Our goal was to characterize the epidemiology and clinical significance of congenital Zika virus (ZIKV) exposure by prospectively following a cohort of infants with possible congenital exposure through their first year of life.

Methods. We included infants born in New York City between 2016 and 2017 who had or were born to a woman who had laboratory evidence of ZIKV infection during pregnancy. We conducted provider/patient interviews and reviewed medical records to collect information about the pregnant women and, for infants, clinical and neurodevelopmental status at birth and 2, 6, and 12 months of age.

Results. Of the 404 infants who met inclusion criteria, most (385 [95.3%]) appeared well, whereas 19 (4.7%) had a possible ZIKV-associated birth defect. Seven had congenital ZIKV syndrome, and 12 were microcephalic without other abnormalities. Although infants with congenital ZIKV syndrome manifested clinical and neurodevelopmental sequelae during their first year of life, all 12 infants with isolated microcephaly were normocephalic and appeared well by 2 months of age. Laboratory evidence of ZIKV was detected for 22 of the infants, including 7 (31.8%) with a birth defect. Among 148 infants without a birth defect and negative/no laboratory results on ZIKV testing, and for whom information was available at 1 year, 4 presented with a developmental delay.

Conclusions. Among infants with possible congenital ZIKV exposure, a small proportion had possible ZIKV-associated findings at birth or at follow-up, or laboratory evidence of ZIKV. Identifying and monitoring infants with possible ZIKV exposure requires extensive efforts by providers and public health departments. Longitudinal studies using standardized clinical and developmental assessments are needed for infants after possible congenital ZIKV exposure.

Key words. birth defects; congenital Zika syndrome; microcephaly; surveillance; Zika virus.

Congenital Zika virus (ZIKV) infection has been linked to severe abnormalities of the central nervous system, and the spectrum of sequelae has yet to be fully defined. Data from the United States and its territories suggest that among infants born to a woman who had laboratory evidence of ZIKV infection, approximately 5% to 6% have a birth defect and 9% have a neurodevelopmental abnormality possibly associated with ZIKV [1–4]. The range of possible ZIKV-associated defects and abnormalities is broad and can include manifestations of other etiologies; the relationship between these findings and ZIKV testing results is not well understood [5]. In addition, the Centers

for Disease Control and Prevention (CDC) recommends routine ZIKV testing for all infants born to a woman with laboratory evidence of ZIKV infection during pregnancy [6]; however, the significance of a positive result with such testing, particularly for infants without clinical findings at birth, is unknown.

New York City has a large and diverse population of frequent travelers and persons born in an area with active ZIKV transmission. During the 2015–2017 outbreak in the Americas, approximately 20% of all pregnant women in the continental United States with ZIKV infection delivered their infant in New York City [2, 7]. Here, we describe clinical, laboratory, and epidemiological findings for a large cohort of infants with possible congenital ZIKV exposure born in this metropolitan area and highlight outcomes within the first year of life for infants for whom laboratory evidence of ZIKV infection was detected and for infants with a possible ZIKV-related birth defect.

METHODS

Epidemiologic and Clinical Investigation of Mothers and Infants

In January 2016, the New York City Health Department began conducting enhanced ZIKV surveillance by investigating cases of ZIKV infection in women during pregnancy, facilitating ZIKV testing and evaluation of their infant at birth, and

following these infants through infancy [8]. Using standardized forms, we collected demographic, clinical, and epidemiologic data on the mothers and infants through provider and patient interviews and medical record reviews. We used the citywide immunization registry, which maintains records of immunizations for New York City residents, to help track when and where medical care was sought for the infants through their first year of life. For this report, we included infants born in New York City between 2016 and 2017 who had or were born to a woman who had laboratory evidence of ZIKV infection during pregnancy; we characterized these infants as having possible congenital exposure to ZIKV. Because of incomplete data, we excluded women who had experienced pregnancy loss. We report data available as of September 28, 2018. Data from a portion of this cohort were included in previous reports [1, 2, 9]. The New York City Health Department Institutional Review Board deemed this activity public health surveillance.

Definitions

Small for gestational age (SGA) was defined as a weight of <10th percentile for gestational age [10]. "Birth defects" and "neurodevelopmental abnormalities" possibly associated with ZIKV infection have been defined for surveillance purposes by the CDC [4, 11]. Microcephaly was defined as a head circumference of <3rd percentile for sex and gestational age according to the INTERGROWTH-21st standards for all available measurements during the birth hospitalization [10]. Postnatal-onset microcephaly was defined as a head circumference that was normal at birth but at <3rd percentile for sex and age at 2 consecutive follow-up visits beyond the neonatal period, including the most recent visit [12, 13]. Congenital Zika syndrome (CZS) was defined as having abnormal brain anatomy and at least 1 of the following: microcephaly, structural eye anomaly, congenital contractures, and hypertonia [14, 15]. We further characterized CZS as definite or possible in the presence or absence of laboratory evidence of ZIKV infection in the infant, respectively. An infant was considered to have a developmental delay if this diagnosis was documented in their medical record without subsequent report of resolution.

Laboratory Testing

Laboratory evidence of ZIKV infection was used to classify cases as confirmed or probable. Confirmed cases included those with either (1) ZIKV RNA detected by nucleic acid amplification testing (NAAT) of urine, serum, and, for mothers, placental or umbilical cord tissue samples or (2) a nonnegative (ie, presumptive positive, equivocal) result on ZIKV immunoglobulin M (IgM) antibody testing by capture enzyme-linked or chemi-luminescence immunoassay [16, 17] of serum or cerebrospinal

fluid, with plaque reduction neutralization testing (PRNT) positive for ZIKV and negative for dengue antibodies. Probable cases included those who had a nonnegative result on ZIKV-specific IgM testing and PRNT positive for both ZIKV and dengue antibodies, indicating previous flavivirus infection [18].

Repeat ZIKV-specific IgM testing was requested for infants with an initial nonnegative IgM result. Pregnant women with a negative IgM result but abnormal findings on prenatal imaging or whose infant presented with findings potentially consistent with congenital ZIKV infection were tested by PRNT to capture evidence of ZIKV immunoglobulin G antibodies. Testing was performed by commercial laboratories, the New York City Health Department's Public Health Laboratory, New York State Wadsworth Center Laboratory, and the CDC; only Wadsworth Center Laboratory and the CDC performed PRNT.

RESULTS

Clinical Findings at Birth

We identified 404 infants, including 6 sets of twins, born in New York City between January 2016 and December 2017 with possible congenital exposure to ZIKV (Table 1). Of these

Table 1. Characteristics of Infants Born Between 2016 and 2017 With Possible Congenital ZIKV Exposure, New York City, New York

Characteristic	Values
Possible congenital ZIKV exposure (n [%])	404 (100)
Twin gestation (n [%])	12 (3.0)
Gestational age (median [range]) (weeks)	39 (24–42)
Preterm birth (n [%])	43 (10.6)
Small for gestational age (n [%])	44 (10.9)
Defect identified at birth (n [%])[a]	
Possible ZIKV-associated defect identified at birth[b]	19 (4.7)
Microcephaly	18 (4.5)
Microcephaly as isolated finding	12 (3.0)
Intracranial abnormality	7 (1.7)
Congenital contractures	4 (1.0)
Hypertonia	7 (1.7)
Eye abnormality	2 (0.5)
ZIKV testing, performed at any time (n/N [%])	
Any ZIKV testing performed	347 (85.9)
Serum IgM testing	329 (81.4)
Nonnegative (ie, positive or equivocal) result	22/329 (6.7)
Negative result	301/329 (91.5)
Indeterminate result	6/329 (1.8)
NAAT (serum and/or urine)	339 (83.9)
ZIKV RNA detected in serum	0/311 (0.0)
ZIKV RNA detected in urine	1/309 (0.3)

Abbreviations: IgM, immunoglobulin M; NAAT, nucleic acid amplification test; ZIKV, Zika virus.
[a]Categories of birth defects are not mutually exclusive; an infant can be represented in >1 category.
[b]Possible ZIKV-associated birth defects, as defined by the Centers for Disease Control and Prevention, include selected congenital brain anomalies (intracranial calcifications, cerebral atrophy, abnormal cortical formation, corpus callosum abnormalities, cerebellar abnormalities, porencephaly, hydranencephaly, ventriculomegaly/hydrocephaly), selected congenital eye anomalies (microphthalmia or anophthalmia, coloboma, cataract, intraocular calcifications, chorioretinal anomalies involving the macula, excluding retinopathy of prematurity, and optic nerve atrophy, pallor, and other optic nerve abnormalities), and/or microcephaly at birth [11].

infants, 43 (10.6%) were born prematurely, and 44 (10.9%) were SGA. Information from the physical examination at birth was available for all the infants, and 321 (79.5%) underwent postnatal neuroimaging. Data on hearing and ophthalmology evaluations were available for 385 (95.3%) and 43 (10.6%) of the infants, respectively. Most (385 [95.3%]) of the infants were well-appearing, with no defects identified at birth (Figure 1).

Nineteen (4.7%) infants had a birth defect, of whom 7 (1.7%) had findings consistent with CZS. Clinical, radiologic, and laboratory findings for these 7 infants are presented in Table 2. Although all of them had an intracranial abnormality, at birth 6 were microcephalic and 1 was macrocephalic; the infant with macrocephaly also had hydrocephaly and ventriculomegaly. Five infants with CZS underwent an ophthalmology examination in their neonatal period; 2 of these infants had an abnormality in the posterior segment of the eye, and no ocular abnormalities were noted for 3. Twelve (3.0%) additional infants met criteria for microcephaly (Figure 1) but had no other birth defects identified; head ultrasound results for 8 of these infants were normal, whereas neuroimaging was not performed or results were not available for the remaining 4. Eight of the 12 infants with isolated microcephaly were SGA at birth, whereas the remaining 4 infants were appropriate for gestational age. Mothers of the infants with CZS and those of the infants without birth defects were similar in their presence of symptoms, timing of exposure, and laboratory status (Table 3).

Laboratory Evaluation of Mothers and Infants
Among all the infants, 400 (99.0%) were born to a woman with laboratory evidence of ZIKV infection; 98 (24.5%) of the women had confirmed and 302 (75.5%) had probable infection. Four infants were born to a woman with no or negative results on routine ZIKV NAAT and IgM testing. Three women with negative results were identified from abnormal fetal findings on prenatal imaging; maternal testing by PRNT revealed evidence of previous flavivirus infection. Subsequent testing of their 3 infants identified detectable ZIKV-specific IgM in serum and, for 1, detectable viral RNA as well. These 3 women had been tested at least 3 months after their earliest potential ZIKV exposure. One additional mother had no ZIKV testing because she denied exposure during pregnancy; her infant presented with findings compatible with CZS, which prompted ZIKV testing at 4 weeks of life, despite the lack of prenatal exposure history. This infant had detectable ZIKV-specific IgM, and ZIKV and dengue antibodies were detected by PRNT.

Most of the infants (347 [85.9%]) underwent molecular and/or serologic testing for ZIKV (Table 1). Among 329 infants with serologic ZIKV testing performed, 22 (6.7%) had a nonnegative IgM result. Of these 22 infants, 6 (27.3%) had definite CZS, including 1 who also had ZIKV RNA detected in urine but not in serum
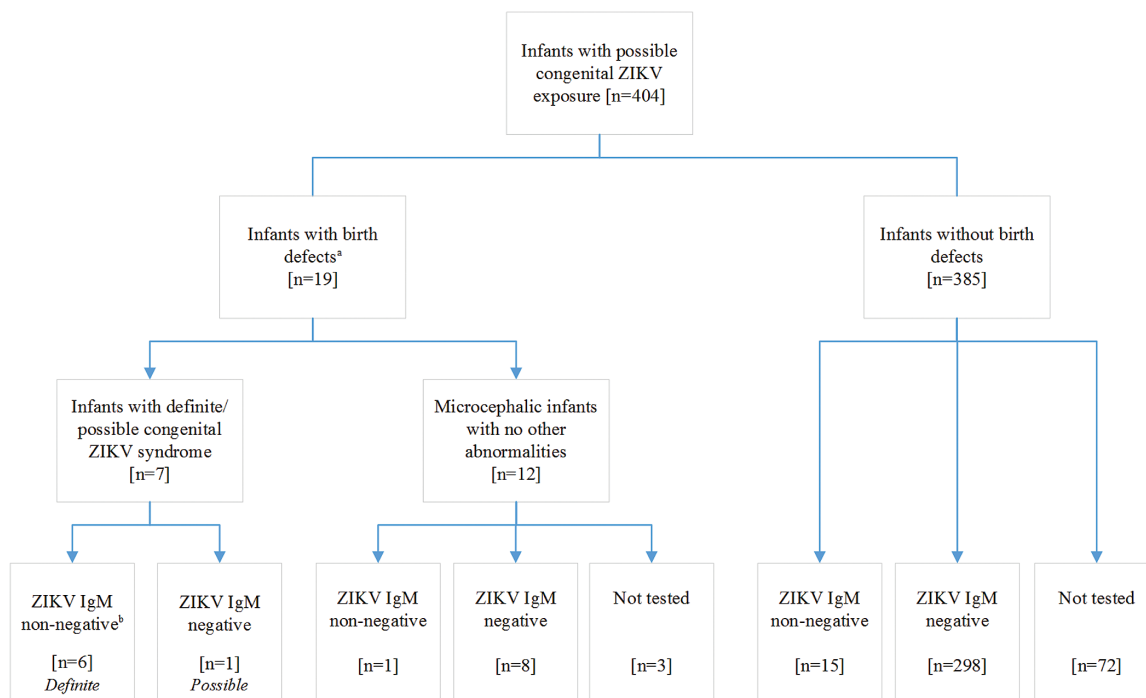

Figure 1. Infants born in New York City, New York, between 2016 and 2017 with possible congenital Zika virus (ZIKV) exposure, according to the presence of possible ZIKV-related birth defects and ZIKV-specific immunoglobulin M (IgM) testing results. [a]See Table 1 for a list of birth defects possibly related to congenital ZIKV infection. [b]Nonnegative ZIKV IgM results include positive and equivocal results with ZIKV-specific IgM testing.

Table 2. Radiologic, Laboratory, and Clinical Information for Infants Born Between 2016 and 2017 With Congenital ZIKV Syndrome and Their Mothers, New York City, New York

Case-Patient No.	Maternal ZIKV Results	Timing of Infection/Exposure in Mother	Findings for Infant in Neonatal Period[b]					Neurodevelopmental Findings at ≥12 months
			Infant ZIKV Results[a]	Head Circumference (Percentile)	Weight (Percentile)	Head Imaging	Eyes	
1	IgM (serum) negative[c]; PRNT, Zika/dengue (serum) positive; NAAT (serum, urine), no virus detected	Asymptomatic infection, exposure during multiple trimesters (Haiti)	IgM (serum) positive; NAAT (serum, urine) no virus detected	Microcephaly (<0.01)	SGA (<0.01st)	Intracranial calcifications, mild ventriculomegaly with lissencephaly	Chorioretinal scarring, macular pigmentation, colobomas	Possible seizure-like activity, severe hypertonia, finger contractures, global developmental delays
2	IgM (serum) negative[c], PRNT, Zika/dengue (serum) positive; NAAT (serum, urine), no virus detected	Febrile illness during first trimester, exposure during multiple trimesters (Haiti)	IgM (serum) positive; NAAT (serum), no virus detected NAAT (urine), ZIKV detected	Microcephaly (<1)	SGA (8th)	Corpus callosum abnormalities, ventriculomegaly/hydrocephaly	No information available	Hypertonia and hyporeflexia, global developmental delays
3	Not tested	Unknown	IgM (serum) positive; NAAT (serum, urine), no virus detected	Microcephaly (<3)	AGA	Intracranial calcifications, corpus callosum abnormalities, abnormal sulcation, asymmetric ventricles	No information available	Unilateral spasticity and motor impairment, global developmental delays
4	IgM (serum) negative[c]; PRNT, Zika/dengue (serum) positive; NAAT (serum, urine), no virus detected; NAAT (umbilical cord tissue), ZIKV detected	Asymptomatic infection, exposure during multiple trimesters (Guyana)	IgM (serum) positive; NAAT (serum, urine), no virus detected	Microcephaly (<0.01)	AGA	Intracranial calcifications, extensive volume loss of cerebral hemispheres	Macular pigmentary changes	Hypertonia, scissoring of lower extremities, global developmental delays, failure to fix and follow, poor vision
5	IgM (serum) negative[c]; PRNT, Zika/dengue (serum) positive; NAAT (serum, urine), no virus detected	Asymptomatic infection, exposure during multiple trimesters (Guyana)	IgM (serum) positive; NAAT (serum, urine), no virus detected	Microcephaly (<3)	AGA	Intracranial calcifications, corpus callosum abnormalities, possible undersulcation of cerebral hemispheres	Normal retinal examination results	Evolving cerebral palsy, hypertonia, hyperreflexia, tremors, possible seizure-like activity, right hemiparesis, global developmental delays
6	IgM (serum) positive; PRNT, Zika/Dengue (serum) positive; NAAT (serum, urine), no virus detected	Fever, arthralgia, and rash during first trimester, exposure during multiple trimesters (Dominican Republic)	IgM (serum, CSF) positive; NAAT (serum, urine), no virus detected	Macrocephaly (>97)	AGA	Ventriculomegaly/ severe hydrocephaly, cerebral atrophy, cerebellar hypoplasia	Normal retinal examination results	Multiple contractures, diaphragmatic eventration, hypertonia, hyperreflexia, gastrostomy tube placed for feeding difficulties, seizures on EEG (examination findings at 4 mo of age, died before 6 mo of age)
7	IgM (serum) positive; PRNT, Zika/dengue (serum) positive; NAAT (serum, urine), no virus detected	Asymptomatic infection, exposure during multiple trimesters (Honduras)	IgM (serum) negative; NAAT (serum, urine), no virus detected	Microcephaly (<0.01)	SGA (3)	Possible corpus callosum abnormalities, ventriculomegaly/hydrocephaly, lip schizencephaly	Normal retinal examination results	Spastic quadriparesis, global developmental delays

Abbreviations: AGA, appropriate for gestational age; EEG, electroencephalography; IgM, immunoglobulin M; NAAT, nucleic acid amplification test; PRNT, plaque reduction neutralization test; SGA, small for gestational age; ZIKV, Zika virus.

[a]Results for cytomegalovirus testing were negative for all infants; the results of toxoplasmosis testing were negative for 6 infants and not available for 1 infant.

[b]Head circumference and weight percentiles were calculated using INTERGROWTH-21st standards.

[c]ZIKV IgM testing was performed >12 weeks after first possible exposure.

Table 3. Characteristics of Mothers of Infants Born in New York City, New York, Between 2016 and 2017 With Congenital ZIKV Syndrome or Without Birth Defects After Possible Congenital ZIKV Exposure

Maternal Characteristic	Infants With Congenital ZIKV Syndrome (n = 7) (n/N [%])[a]	Infants Without Birth Defects[b,c] (n = 380) (n/N [%])[a]
Clinical presentation		
Any symptom compatible with ZIKV	2/6 (33)	104/378 (28)
Specific symptom		
Rash	1/6 (17)	90/378 (24)
Joint pain	2/6 (33)	43/375 (11)
Fever	2/6 (33)	35/377 (9)
Timing of maternal exposure		
Periconception[d]/first-trimester exposure	5/5 (100)	273/362 (75)
Second/third trimester only	0 (0)	89/362 (25)
Maternal ZIKV status[e]		
Confirmed	1/3 (33)	95/380 (25)
Probable	2/3 (67)	285/380 (75)

Abbreviation: ZIKV, Zika virus.

[a]Denominator is number of infants for whom information was available.

[b]Only 1 infant from each pair of twins was included; no twins had congenital ZIKV syndrome.

[c]Infants with isolated microcephaly at birth were not included.

[d]"Periconception" is defined by the Centers for Disease Control and Prevention as 6 weeks before last menstrual period.

[e]Four women with negative ZIKV results or no ZIKV testing did not have a maternal case status and were not included.

collected contemporaneously. One infant classified as having possible CZS had microcephaly and intracranial abnormalities but neither detectable RNA nor ZIKV-specific IgM. Among the other 16 infants for whom laboratory evidence of ZIKV was detected, 1 infant was microcephalic at birth but, in the absence of other clinical or neuroimaging abnormalities, did not meet the criteria for being classified as a case of CZS. The remaining 15 infants for whom laboratory evidence of ZIKV was detected had no birth defects and normal postnatal neuroimaging results.

Among infants who underwent ZIKV testing, 288 (83.0%) were tested within the first 2 days of life, as recommended by the CDC. The timing of specimen collection for infants with a nonnegative ZIKV-specific IgM result from serum ranged from the day of birth to 4 weeks of age, in the case of an infant with definite CZS (Figure 2). Repeat serum specimens were collected from 10 infants with an initial nonnegative IgM result (Figure 3). Four infants, all with CZS, had a second nonnegative IgM result on repeat testing of serum collected between days of life 1 and 15. One infant with CZS had a nonnegative result for IgM in serum at birth and in cerebrospinal fluid on day of life 40. For the remaining 6 infants who underwent repeat testing after an initial nonnegative result, IgM was no longer detectable in their serum samples collected between days of life 6 and 27; none of these infants had a birth defect.
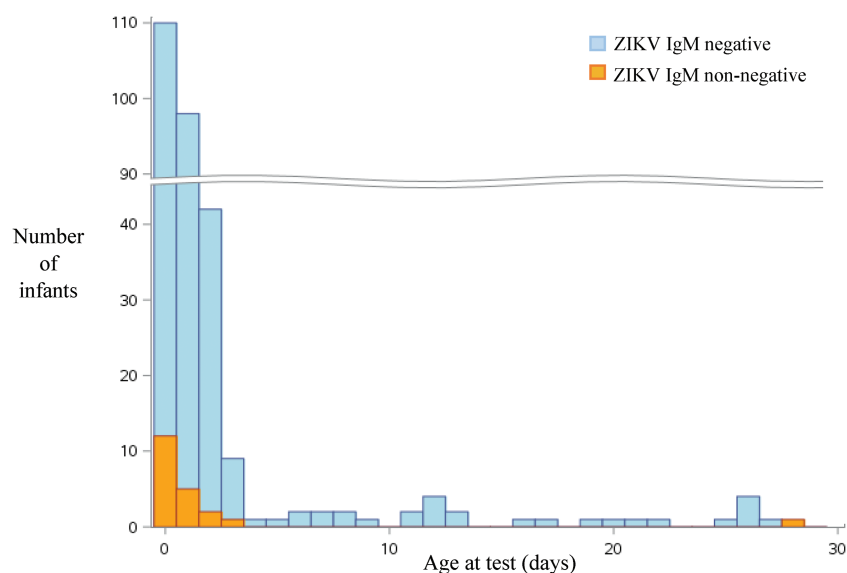

Figure 2. Age at specimen collection for Zika virus (ZIKV)–specific immunoglobulin M (IgM) testing of serum for 299 infants born in New York City, New York, between 2016 and 2017, according to result.
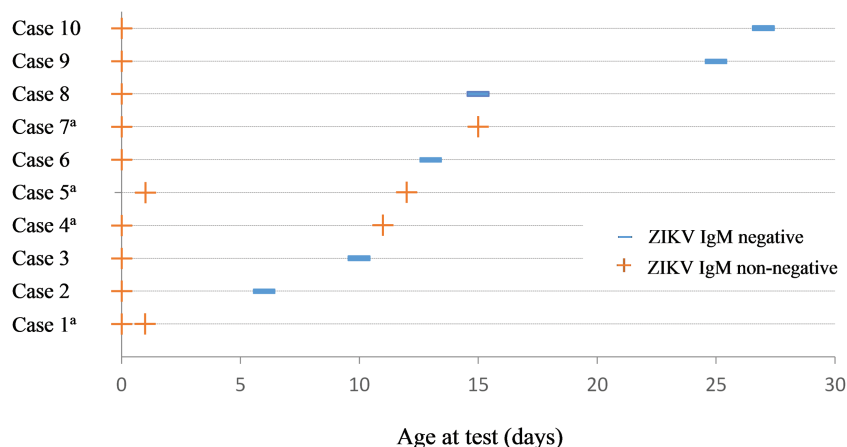
Figure 3. Age and result of Zika virus (ZIKV)–specific immunoglobulin M (IgM) testing of serum for 10 infants born in New York City, New York, between 2016 and 2017, with congenital ZIKV infection and repeat testing. [a]Infant with congenital ZIKV syndrome.

Monitoring During the First 12 Months of Life

Among the 404 infants, 17 (4.2%) had a possible ZIKV-associated neurodevelopmental abnormality, as defined by the CDC [4]. These included all 7 infants with CZS, 2 for whom laboratory evidence of ZIKV infection was detected, and 8 with neither laboratory evidence of ZIKV nor birth defects. Specific abnormalities and information available at follow-up are presented in Table 4.

Information beyond the neonatal period was available for all 7 infants with CZS; all of them manifested abnormalities of tone and global developmental delays. Three infants were described as having seizure-like activity; 1 of these infants had abnormal electroencephalography findings and was treated with antiepileptic medication. This infant also had feeding difficulties and died before the age of 6 months.

All of the 12 infants who were microcephalic at birth but had no other abnormal findings were normocephalic by 2 months of age; at 12 months of age, the 9 (75.0%) infants for whom information was available remained normocephalic and had no reported neurodevelopmental abnormalities. In 15 infants, laboratory evidence of ZIKV infection was detected but no birth defects were identified; among the 12 (80%) for whom information was available outside the neonatal period, 1 had mild hearing loss detected by the auditory brainstem response test before 2 months of age, and another had gross motor and language delays documented at the age of 6 months. Additional follow-up information was available for neither of these 2 infants. By 12 months of age, information was available for 5 of 15 with laboratory evidence of congenital ZIKV infection; all

Table 4. Availability of Follow-Up Information and Presence of Possible ZIKV-Associated Neurodevelopmental Abnormalities Among Infants Born Between 2016 and 2017 With Possible Congenital ZIKV Exposure, According to Clinical and Laboratory Status, New York City, New York

Infant Clinical and Laboratory Status	Information Available According to Age at Follow-Up[a]				Neurodevelopmental Abnormality Documented at Birth or During Follow-Up[b]
	Newborn	2 mo	6 mo	12 mo	
Infants with available follow-up data/infants who met age criteria (%)	404/404 (100)	328/404 (81.2)	225/402 (56.0)	168/380 (44.2)	17
Definite/possible congenital ZIKV syndrome (%)	7/7 (100)	7/7 (100)	6/6[c] (100)	6/6 (100)	7[d]
Microcephaly/no intracranial abnormality (%)	12/12 (100)	12/12 (100)	9/12 (75.0)	9/12 (75.0)	0
Laboratory evidence of ZIKV/no birth defect (%)	15/15 (100)	12/15 (80.0)	6/15 (40.0)	5/15 (33.3)	2[e]
Infants with no birth defects/no laboratory evidence of congenital ZIKV infection (or no ZIKV testing) (%)	370/370 (100)	297/370 (80.3)	204/369[f] (55.3)	148/347 (42.7)	8[g]

Abbreviation: ZIKV, Zika virus.

[a]As of September 28, 2018.

[b]Possible ZIKV-associated neurodevelopmental abnormalities, as defined by the Centers for Disease Control and Prevention, include hearing abnormalities, congenital contractures, seizures, body tone abnormalities, movement abnormalities, swallowing abnormalities, possible developmental delay, possible visual impairment, and/or postnatal-onset microcephaly. Microcephaly is categorized as a birth defect, not a neurodevelopmental abnormality [4].

[c]One infant with congenital ZIKV syndrome died before the age of 6 months.

[d]Neurodevelopmental abnormalities identified in infants with congenital ZIKV syndrome are listed in Table 2.

[e]Includes developmental delay (n = 1) and hearing abnormality (n = 1).

[f]Does not include 1 extremely preterm infant who died before the age of 6 months.

[g]Includes strabismus (n = 2), developmental delay (n = 4), hearing abnormality (n = 1), and swallowing abnormality (in an infant with Prader-Willi syndrome) (n = 1).

of them had experienced normal growth without any reported neurodevelopmental abnormalities.

We found 370 infants with neither birth defects nor laboratory evidence of congenital ZIKV infection, or with no ZIKV testing. By September 28, 2018, 347 of these infants were 12 months old or older; information at 12 months was available for 148 (42.7%) of them. Four of these 148 infants were reported to have a developmental delay; 2 infants demonstrated gross motor and speech delays, and 2 had isolated speech delay. One of these infants had negative results on ZIKV testing, and the remaining 3 were not tested; all of them had passed their newborn hearing screening. None of the infants met the criteria for postnatal-onset microcephaly, although 1 initially normocephalic infant had subsequent head circumference measurements at the 2nd, 1st, and 3rd percentiles at 2, 6, and 12 months of age, respectively. This infant had negative ZIKV testing results, normal neuroimaging results at birth, and no reported neurodevelopmental abnormalities at 12 months of age. Of the 22 infants younger than 12 months, follow-up information was available for 13 (59.1%); normal neurodevelopment was reported for all 13 of them.

CONCLUSIONS

We describe here the findings at birth and over the first 12 months of life for a cohort of infants born in New York City with possible congenital ZIKV exposure. Among this cohort, 5% had defects at birth potentially associated with ZIKV infection, which is comparable to the results of other studies; only 1.7% (the infants with CZS) had persistent defects [1–4, 19]. Outcomes at 12 months of life for infants with CZS were poor, a finding consistent with that of other studies [5, 20]. The remaining infants with birth defects had isolated microcephaly at birth and normal head circumference and neurodevelopment soon thereafter. Surveillance criteria for microcephaly at birth did not correlate with microcephaly beyond the first days of life in the absence of clinical or neuroimaging abnormalities. In a study of 19 Brazilian infants with microcephaly at birth and laboratory evidence of ZIKV infection, 4 infants with normal or unknown neuroimaging results no longer met criteria for microcephaly by follow-up at 19 to 24 months of age [5]. Inaccuracies in the measurement of head circumference and of gestational age might limit the utility of microcephaly as a criterion for surveillance [21]. Including isolated microcephaly among ZIKV-related birth defects might lead to an overestimation of the proportion of infants with persistent clinically significant abnormalities after possible congenital ZIKV exposure.

Communication between the health department and healthcare providers was essential for identifying infants with potential exposure to and sequelae from congenital ZIKV infection. Although routine prenatal screening for possible ZIKV exposure facilitated surveillance during the outbreak, the infants with CZS were born to women who had both positive and negative results on testing for recent ZIKV infection, and 1 infant was born to a woman who denied prenatal exposure. This situation illustrates the limitations of currently available screening and diagnostic approaches for ZIKV, described previously, including the possibility of negative maternal results once viral RNA and IgM levels have waned [22–24]. In the cases described here, providers communicated concerning prenatal/postnatal findings to the health department, which facilitated further evaluation, including PRNT, for the women and ZIKV testing for the infants.

The sensitivity of neonatal ZIKV NAAT and immunoassays for detecting congenital ZIKV infection is unknown [24]. Among 22 infants with laboratory evidence of ZIKV, 21 had a positive result for serology alone; ZIKV RNA was detected in only 1 of 2 specimen sources for 1 infant. Few cases of infants with detectable RNA in serum have been reported in the published literature [25–27], and our experience suggests that this is an uncommon occurrence, even among infants with CZS. Of the 7 infants with findings compatible with CZS, 6 had detectable ZIKV-specific IgM in serum; for 1 infant for whom compatible clinical and imaging findings were identified but for whom IgM was not detected, the role of ZIKV in the etiology of the birth defects is unknown. This infant did not undergo testing of cerebrospinal fluid, which in some cases may have a higher diagnostic yield for ZIKV testing than serum [24, 26–28].

For infants without birth defects, the significance of detectable ZIKV-specific IgM is unknown. Among this cohort, the limited number of infants with detectable IgM and no birth defects precluded our ability to characterize the frequency and nature of sequelae in the first year of life. The proportion of our cohort with a possible ZIKV-associated neurodevelopmental abnormality (4.2%) is lower than the 9% that the CDC reported for infants in the US territories [4]. Although the CDC study did not describe the availability of information for infants beyond 14 days of life, it is possible that with more complete follow-up information for our cohort, fewer abnormalities were noted because some findings (ie, developmental delays) resolved over the months of monitoring. Longer-term monitoring is needed to ensure the identification of findings that can present later in childhood.

One infant with definite CZS had detectable ZIKV-specific IgM in serum at 4 weeks of life. Persistence of IgM beyond the neonatal period has been described previously for infants with ZIKV-associated intracranial abnormalities [29]. However, our experience suggests that IgM antibodies can persist for only a brief period in neonates without birth defects, as illustrated in the 2 cases of infants with negative results from repeat testing at the ages of 6 and 10 days. If congenital ZIKV infection is considered in an infant's differential diagnosis, testing as early

as possible in the neonatal period might optimize the probability of detecting antibodies, if present.

This cohort had a relatively high proportion of infants who underwent the recommended evaluation for congenital ZIKV infection; ZIKV testing and postnatal neuroimaging were performed for 85.4% and 79.5% of them, respectively; these proportions are higher than those for testing and neuroimaging reported for similar cohorts in the continental United States (65% and 25%, respectively) and US territories (58% and 60%, respectively) [2, 4]. However, some New York City infants with possible congenital ZIKV exposure and/or infection might not have been identified. If providers were more likely to test pregnant women and infants when possible ZIKV-associated birth defects were suspected, it potentially would increase the proportion of infants with clinical or laboratory findings. In contrast, by including only live births, we might have underascertained ZIKV-associated birth defects if affected pregnancies resulted in fetal loss or termination. Because many exposed women presented for care long after viral RNA could be detected, we included women who met the serologic criteria only; as a result of serologic cross-reactivity with other flaviviruses, these probable cases might have included women without ZIKV infection.

The health department collected available information from >100 clinical sites and could not, for a surveillance activity, implement a common standardized tool for developmental assessments. As a consequence, the proportion of infants reported herein might not represent the true proportion of infants with developmental delay after possible congenital ZIKV exposure. Last, although data from beyond the neonatal period were available for 81.2% of the infants in our cohort, a sizable proportion was lost to follow-up by 12 months of age because of relocation outside the city and country. CDC investigators encountered similar challenges in the US territories; 32% of the infants aged ≥1 year in that study were lost to follow-up by 14 days of age; the proportion lost to follow-up by 12 months was not reported [4]. With the use of the citywide immunization registry to help track infants, the proportion of our cohort lost to follow-up by 2 months was lower and did not vary according to the infants' clinical or laboratory status; however, the overall loss to follow-up at 12 months limits the inferences we can make about this cohort.

In this New York City study, most infants with possible congenital ZIKV exposure were well appearing at birth and in the first year of life. A small number of infants with CZS and ZIKV infection were identified because of prompt provider reporting of infants with possible exposure. The health department's ZIKV response included surveillance, diagnostic testing, case investigation, provider education, and community outreach. Although resource-intensive, this response facilitated timely evaluation and follow-up of infants, which helped characterize the epidemiology and clinical significance of congenital ZIKV exposure in this cohort. Longitudinal studies using standardized clinical and developmental assessments are needed for infants after possible congenital ZIKV exposure. For infants already recognized at birth to have clinical and laboratory findings, and for infants with no abnormalities identified, the potential for sequelae beyond infancy is unknown and should be a priority for additional investigation.

Notes

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