ORIGINAL ARTICLE

Mortality from Congenital Zika Syndrome — Nationwide Cohort Study in Brazil

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ABSTRACT

BACKGROUND

Prenatal exposure to Zika virus has potential teratogenic effects, with a wide spectrum of clinical presentation referred to as congenital Zika syndrome. Data on survival among children with congenital Zika syndrome are limited.

METHODS

In this population-based cohort study, we used linked, routinely collected data in Brazil, from January 2015 through December 2018, to estimate mortality among live-born children with congenital Zika syndrome as compared with those without the syndrome. Kaplan–Meier curves and survival models were assessed with adjustment for confounding and with stratification according to gestational age, birth weight, and status of being small for gestational age.

RESULTS

A total of 11,481,215 live-born children were followed to 36 months of age. The mortality rate was 52.6 deaths (95% confidence interval [CI], 47.6 to 58.0) per 1000 person-years among live-born children with congenital Zika syndrome, as compared with 5.6 deaths (95% CI, 5.6 to 5.7) per 1000 person-years among those without the syndrome. The mortality rate ratio among live-born children with congenital Zika syndrome, as compared with those without the syndrome, was 11.3 (95% CI, 10.2 to 12.4). Among infants born before 32 weeks of gestation or with a birth weight of less than 1500 g, the risks of death were similar regardless of congenital Zika syndrome status. Among infants born at term, those with congenital Zika syndrome were 14.3 times (95% CI, 12.4 to 16.4) as likely to die as those without the syndrome (mortality rate, 38.4 vs. 2.7 deaths per 1000 person-years). Among infants with a birth weight of 2500 g or greater, those with congenital Zika syndrome were 12.9 times (95% CI, 10.9 to 15.3) as likely to die as those without the syndrome (mortality rate, 32.6 vs. 2.5 deaths per 1000 person-years). The burden of congenital anomalies, diseases of the nervous system, and infectious diseases as recorded causes of deaths was higher among live-born children with congenital Zika syndrome than among those without the syndrome.

CONCLUSIONS

The risk of death was higher among live-born children with congenital Zika syndrome than among those without the syndrome and persisted throughout the first 3 years of life. (Funded by the Ministry of Health of Brazil and others.)

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Zika virus (ZIKV) infection is spread by *Aedes aegypti* mosquitoes, and during pregnancy, the infection can be transmitted across the placenta to the developing fetus, with potential teratogenic effects, including severe central nervous system anomalies.[1] Although most fetuses with prenatal ZIKV exposure present without detectable clinical anomalies, some congenitally infected offspring can have mild, moderate, or severe adverse outcomes,[2] which are collectively referred to as congenital Zika syndrome.[3,4] The phenotype for congenital Zika syndrome encompasses a wide spectrum of structural anomalies (e.g., cortical atrophy with microcephaly[5]), functional impairments (e.g., dysphagia[6]), and clinical sequelae (e.g., epilepsy[7,8]) that may manifest at birth or in early life.[9] The prognosis for live-born children with congenital Zika syndrome is not fully described, but the most severe phenotype seems to be associated with first-trimester exposure to ZIKV,[10] and one important prognostic factor is the severity of microcephaly.[11] Preliminary evidence indicates that affected children may have a case fatality rate of 10% in the first years of life.[12] Nevertheless, the relative risk of death among live-born children with congenital Zika syndrome, as compared with those without the syndrome, and the role of important predictors of child mortality, such as gestational age at birth and birth weight, remain unclear.

Using national population–based, linked data on more than 11.7 million live-born children between 2015 and 2018 in Brazil, a country with a considerable burden of congenital Zika syndrome during the ZIKV epidemic in the Americas, we aimed to investigate the risk of death and the causes of deaths among children born with congenital Zika syndrome, as compared with those without the syndrome; to compare mortality rates among live-born children with congenital Zika syndrome, according to microcephaly status, with the rate among children without the syndrome; to compare mortality rates among children with congenital Zika syndrome, according to the timing and presence or absence of maternal rash (a main indicator ZIKV infection), with the rate among children without the syndrome; and to examine the role of gestational age at birth and birth weight by calculating stratified mortality rate ratios.

Methods

Study Design

We conducted a retrospective population-based cohort study that included data on all singleton live births that occurred in Brazil from January 1, 2015, to December 31, 2018. These live-born children were followed from birth until an age of 36 months (3 years), death, or December 31, 2018, whichever occurred first. This study analyzed deidentified data and was approved by the ethics committee at the Institute of Collective Health, Federal University of Bahia.

Data Source

We obtained information about congenital Zika syndrome from the Public Health Event Record,[13] which has registered information about all cases of suspected microcephaly or central nervous system alterations possibly associated with congenital ZIKV infection since 2015. From this record, we retained data on final disease classification (confirmed or ruled-out congenital Zika syndrome), presence and timing of maternal rash during pregnancy, and head circumference of the live-born infant.

The Live Birth Information System (SINASC),[14] an information system with 100% coverage of the Brazilian territory,[15] records data from the Declaration of Live Births, a legal document that is completed by the health worker who assists in the delivery. From this system, we obtained information about the mother (age, educational attainment, marital status, and race and ethnic group), the pregnancy (number of prenatal appointments, length of gestation, and status of having multiple fetuses), and the newborn (birth weight and sex).

Death-related information was obtained from the Mortality Information System,[16] which records death certificates. The death certificate is a legal document that must be completed by the physician responsible for clinical care, an assistant, or other practitioner from the institution who attests to the cause of death. In cases in which the death occurs outside medical facilities, the death certificate is provided by a pathologist. We obtained information on the date of death and the underlying cause of death according to the *International Classification of Diseases, 10th Revision* (ICD-10). As of 2016, the Mortality Information System was

estimated to cover nearly 97% of deaths in Brazil.[16]

LINKAGE PROCESS

Live-birth records from the Live Births Information System were linked with the Public Health Event Record and the Mortality Information System. The mother's name, date of birth or age, and residence were used as matching variables. The linkage was performed with a Center of Data and Knowledge Integration for Health record-linkage tool that was developed to link large-scale administrative data sets at the center by applying a combination of indexing and searching-algorithms approaches.[17] All the data were extracted in 2020 and made available by the Brazilian Ministry of Health. Linkage procedures were conducted at the Center of Data and Knowledge Integration for Health in a strict data-protection environment and according to ethical and legal rules.[18]

PROCEDURES

We included data on all singleton live-born children who contributed records during the study period. We excluded records registered in the Public Health Event Record in which congenital Zika syndrome was suspected but then ruled out after epidemiologic investigation and records that were classified as cases under investigation or inconclusive.

In Brazil, live-born children who meet one or more of the following criteria have their cases reported and investigated as suspected cases of congenital Zika syndrome: microcephaly, defined as a head circumference that is more than 2 SD below the mean for age and sex (according to INTERGROWTH-21st standards[19] for infants born at <37 weeks of gestation or according to World Health Organization standards for infants born at ≥37 weeks of gestation); craniofacial disproportion (microcrania in relation to the face); central nervous system changes suggestive of congenital infection as detected on neuroimaging tests (cranial computed tomography, magnetic resonance imaging of the head, or transfontanellar ultrasonography); two or more neurologic, visual, or auditory manifestations; or a birth mother who reported fever or rash during pregnancy, which was likely or confirmed to be related to ZIKV infection, regardless of the identification of congenital malformations at birth.[20,21] After notification, all suspected cases were investigated by the epidemiologic surveillance teams and classified as confirmed, probable, inconclusive, or ruled-out cases (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Suspected cases of congenital Zika syndrome were considered to be confirmed if there were signs and symptoms consistent with the syndrome (Table S1) or laboratory evidence of ZIKV infection (from molecular or serologic testing) or the mother had reported fever or rash during pregnancy. Probable cases involved clinical changes compatible with congenital Zika syndrome and negative tests for other congenital infections although specific laboratory diagnosis for ZIKV infection was not available and the mother was asymptomatic during pregnancy. Suspected cases were ruled out if there were compatible clinical symptoms that, after clinical and epidemiologic investigation, were attributed to another cause, such as microcephaly related to restricted intrauterine growth or genetic disease. Other cases were inconclusive owing to insufficient information for proper classification or remained under investigation.[20]

We defined cases as all live births that were classified in the Public Health Event Record as confirmed or probable congenital Zika syndrome and that had a registry entry linked with a Live Births Information System record. We then classified live-born children with congenital Zika syndrome into two categories: those with microcephaly (head circumference >2 SD below the mean for age and sex, according to INTERGROWTH-21st standards) and those without microcephaly. We also classified cases of congenital Zika syndrome according to the timing of maternal rash during pregnancy (first trimester, second trimester, third trimester, or no report of rash during pregnancy). We identified live-born children who died during the study period by linking the Live Births Information System with the Mortality Information System.

STATISTICAL ANALYSIS

Descriptive statistics are presented for the maternal sociodemographic data and newborn characteristics. Mortality rates (deaths per 1000 person-years) and crude mortality rate ratios (hazard

Table 1. Baseline Characteristics of Singleton Live-Born Children and Their Mothers in the Cohort-Linked Data in Brazil (2015–2018).*

Characteristic	Live-Born Children with Congenital Zika Syndrome (N = 3308)	Live-Born Children without Congenital Zika Syndrome (N = 11,477,907)
Mother		
Age — no./total no. (%)		
<20 yr	769/3308 (23.2)	1,958,784/11,477,757 (17.1)
20–34 yr	2179/3308 (65.9)	7,922,774/11,477,757 (69.0)
≥35 yr	360/3308 (10.9)	1,596,199/11,477,757 (13.9)
Marital status — no./total no. (%)		
Single, widowed, or divorced	1736/3268 (53.1)	5,046,501/11,349,948 (44.5)
Married or in civil union	1532/3268 (46.9)	6,303,447/11,349,948 (55.5)
Educational attainment — no./total no. (%)		
0 yr	25/3256 (0.8)	54,922/11,312,054 (0.5)
1–3 yr	106/3256 (3.3)	264,514/11,312,054 (2.3)
4–7 yr	749/3256 (23.0)	1,932,786/11,312,054 (17.1)
8–11 yr	2011/3256 (61.8)	6,834,566/11,312,054 (60.4)
≥12 yr	365/3256 (11.2)	2,225,266/11,312,054 (19.7)
Race — no./total no. (%)†		
White	584/3101 (18.8)	3,987,857/10,961,753 (36.4)
Black, mixed race, or other	2517/3101 (81.2)	6,973,896/10,961,753 (63.6)
No. of prenatal appointments — no./total no. (%)		
0	51/3176 (1.6)	64,992/11,182,062 (0.6)
1–3	307/3176 (9.7)	683,661/11,182,062 (6.1)
4–6	923/3176 (29.1)	2,609,078/11,182,062 (23.3)
≥7	1895/3176 (59.7)	7,824,331/11,182,062 (70.0)
Child		
Year of birth — no. (%)		
2015	1215 (36.7)	2,945,913 (25.7)
2016	1538 (46.5)	2,794,266 (24.3)
2017	364 (11.0)	2,857,930 (24.9)
2018	191 (5.8)	2,879,798 (25.1)
Sex — no./total no. (%)		
Female	1757/3300 (53.2)	5,591,949/11,475,906 (48.7)
Male	1543/3300 (46.8)	5,883,957/11,475,906 (51.3)
Geographic region of Brazil — no./total no. (%)		
North	181/3306 (5.5)	1,237,863/11,474,446 (10.8)
Northeast	1986/3306 (60.1)	3,224,654/11,474,446 (28.1)
Southeast	801/3306 (24.2)	4,508,232/11,474,446 (39.3)
South	73/3306 (2.2)	1,553,930/11,474,446 (13.5)
Central west	265/3306 (8.0)	949,767/11,474,446 (8.3)
Gestational age at birth — no./total no. (%)		
<32 wk	110/3197 (3.4)	155,151/11,228,963 (1.4)

Table 1. (Continued.)

Characteristic	Live-Born Children with Congenital Zika Syndrome (N=3308)	Live-Born Children without Congenital Zika Syndrome (N=11,477,907)
32–36 wk	535/3197 (16.7)	988,036/11,228,963 (8.8)
≥37 wk	2552/3197 (79.8)	10,085,776/11,228,963 (89.8)
Birth weight — no./total no. (%)		
<1500 g	155/3306 (4.7)	127,967/11,467,115 (1.1)
1500–2499 g	1048/3306 (31.7)	706,939/11,467,115 (6.2)
≥2500 g	2103/3306 (63.6)	10,632,209/11,467,115 (92.7)
Status of being small for gestational age — no./total no. (%)		
Yes	1156/3156 (36.6)	794,313/11,111,816 (7.1)
No	2000/3156 (63.4)	10,317,503/11,111,816 (92.9)

* Overall, data on various characteristics were missing for 896,987 live-born children or their mothers.
† Data on race, as initially reported by the mother, were obtained from the Live Birth Information System.

ratios) with 95% confidence intervals for the comparisons of live-born children with congenital Zika syndrome with those without the syndrome were estimated with the use of Cox proportional-hazards models. We also conducted a sensitivity analysis that involved confirmed cases only. Kaplan–Meier curves were plotted, and we compared live-born children with congenital Zika syndrome and those without the syndrome overall, as well as according to head circumference and according to the timing of maternal rash during pregnancy.

Finally, we fitted penalized Cox proportional-hazards regression models using restricted maximum likelihood with frailty terms corresponding to random effects from a Gaussian distribution to account for within-cluster (region of maternal residency) homogeneity in outcomes.[22] We used these analyses to obtain the adjusted mortality rate ratio. The adjusted models were controlled for maternal age, educational attainment, marital status, race and ethnic group, and number of prenatal appointments and for the sex and year of birth of the newborn, with stratification according to gestational age (<32 weeks, 32 to 36 weeks, or ≥37 weeks), birth weight (<1500 g, 1500 to 2499 g, or ≥2500 g), and status of being small for gestational age (<10th percentile according to the INTERGROWTH-21st standards; yes or no). For the time scale in our survival analyses, we used age attained within the study, neonatal mortality (≤27 days of age), infant mortality (≤364 days of age), and total mortality (≤36 months of age). Data analyses were performed with the use of Stata software, version 15.0 (StataCorp).

RESULTS

CHARACTERISTICS OF THE CHILDREN

We followed 11,481,215 live-born children from birth up to 36 months of age (mean, 23 months; range, 0 to 36) (Fig. S2). The characteristics of the study population are reported in Table 1. In general, the 3308 live-born children with congenital Zika syndrome had mothers who were younger and had less educational attainment than the 11,477,907 children without the syndrome. A total of 20.2% of the live-born children with congenital Zika syndrome were born preterm (≤36 weeks of gestational age), 36.4% had a low birth weight (<2500 g), and 36.6% were small for gestational age, as compared with 10.2% of the live-born children without the syndrome being born preterm, 7.3% having a low birth weight, and 7.1% being small for gestational age.

OVERALL MORTALITY

By the end of the study period, 398 live-born children who met the study case-definition criteria for congenital Zika syndrome and 120,629 live-born children without the syndrome had died. The overall mortality rate up to 36 months of age among live-born children with congenital Zika syndrome was 11.3 times (95% confidence

Table 2. Risk of Death among Singleton Live-Born Children According to Age Group and Congenital Zika Syndrome Status in Brazil (2015–2018).

Age Group at Time of Death*	Live-Born Children with Congenital Zika Syndrome (N = 3308)		Live-Born Children without Congenital Zika Syndrome (N = 11,477,907)		Mortality Rate Ratio (95% CI)†
	No. of Deaths	No. of Deaths per 1000 Person-Yr (95% CI)	No. of Deaths	No. of Deaths per 1000 Person-Yr (95% CI)	
≤3 Yr of age	398	52.6 (47.6–58.0)	120,629	5.6 (5.6–5.7)	11.3 (10.2–12.4)
Infancy	326	109.2 (98.0–8.121)	112,181	11.3 (11.2–11.3)	10.2 (9.1–11.3)
Neonatal	163	696.5 (597.3–812.0)	80,006	95.7 (95.0–96.3)	7.2 (6.2–8.4)
Postneonatal	163	59.4 (51.0–69.3)	32,175	3.5 (3.5–3.6)	17.4 (14.9–20.3)
≥1 Yr of age	72	15.7 (12.4–19.7)	8,448	0.7 (0.7–0.8)	21.9 (17.3–27.6)

* Overall, deaths were assessed among live-born children up to 3 years (36 months) of age. Neonatal deaths occurred at or before 27 days of age, postneonatal deaths occurred at 28 to 364 days of age, and infant deaths occurred at or before 364 days of age.
† The mortality rate ratio is based on the number of deaths per 1000 person-years.

interval [CI], 10.2 to 12.4) as high as that among live-born children without the syndrome. The increased risk of death persisted throughout the observation period, with no suggestion of attenuation by the age of 3 years among children with congenital Zika syndrome. The highest mortality rate ratio, 21.9 (95% CI, 17.3 to 27.6), was found among children 1 year of age or older, when the mortality rate among children without the syndrome was 0.7 deaths per 1000 person-years (Table 2). In a restricted analysis involving live-born children with confirmed congenital Zika syndrome, results were similar to those in the primary analysis (Table S2).

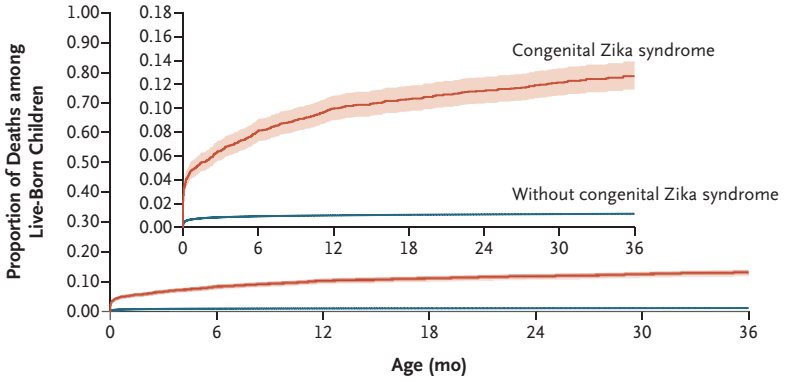
MORTALITY RATE COMPARISON

The likelihood of death in the study population from birth up to 36 months is shown in Figure 1A. The probability of death was greater among live-born children with congenital Zika syndrome than among those without the syndrome, and the difference increased with age. Information on head circumference was available for 2733 of 3308 live-born children (82.6%) with congenital Zika syndrome; 66.0% of these children had microcephaly at birth. Among 2663 live-born children with congenital Zika syndrome for whom complete information on maternal rash was available, this symptom was reported for 1364 (51.2%) during pregnancy, with 62.2% of rashes reported in the first trimester, 21.5% in the second trimester, 8.7% in the third trimester, and 7.6% an in unspecified trimester. The association of congenital Zika syndrome with mortality up to 36 months did not differ materially between live-born children with microcephaly and those without microcephaly or on the basis of whether mothers reported a rash during pregnancy and the timing of any rash. However, the numbers were relatively small, and the study may have lacked power to identify differences between these subgroups (Fig. 1B and 1C).

Mortality rates differed across categories defined on the basis of gestational age, birth weight, and status of being small for gestational age (Fig. 2). Live-born children with congenital Zika syndrome and those without the syndrome had similar mortality rates if they were born before 32 weeks of gestation or weighed less than 1500 g. If they were born after 32 weeks of gestation, children with congenital Zika syndrome were more likely than those without the syndrome to die, and the highest mortality rate ratios were observed among children born at term and among those with a normal birth weight; in these respective subgroups, children with congenital Zika syndrome were 14.3 times (95% CI, 12.4 to 16.4) and 12.9 times (95% CI, 10.9 to 15.3) as likely to die as their counterparts without the syndrome (mortality rate, 38.4 vs. 2.7 deaths per 1000 person-years and 32.6 vs. 2.5 deaths per 1000 person-years, respectively). Live-

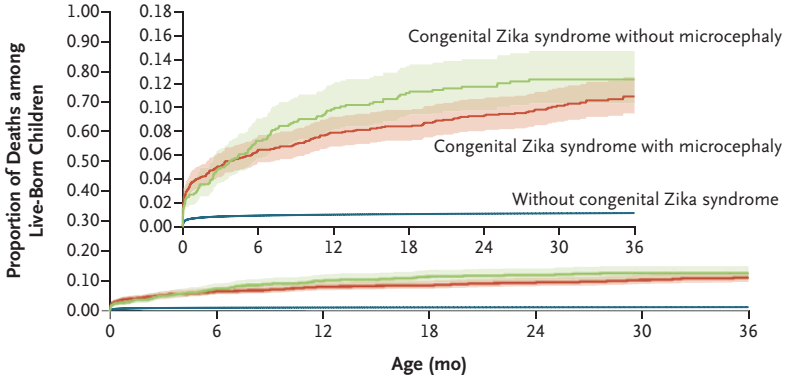
Figure 1 (facing page). Kaplan–Meier Curves of Survival up to 36 Months of Age among Live-Born Children with Congenital Zika Syndrome, as Compared with Those without the Syndrome, According to Age, Microencephaly Status, and Timing of Maternal Rash during Pregnancy.
Shading represents 95% confidence intervals. Insets show the same data on an expanded y axis.

A Age



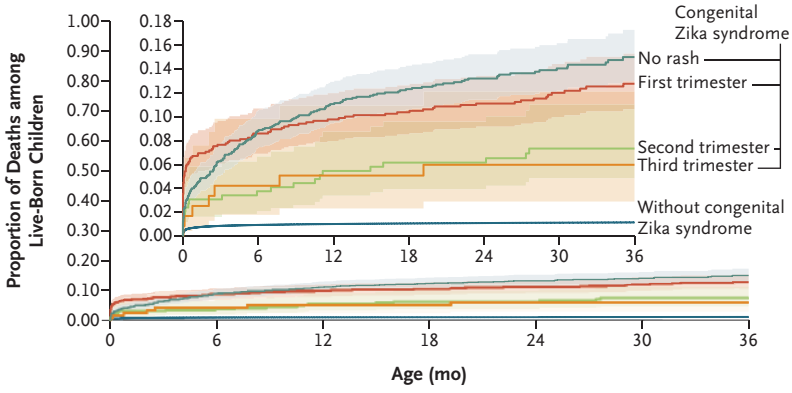
No. at Risk							
Congenital Zika syndrome	3,308	2,973	2,820	2,661	2,478	1,893	1,099
Without congenital Zika syndrome	11,500,000	9,997,496	8,505,972	7,125,492	5,667,138	4,374,716	2,900,641

B Head Circumference



No. at Risk							
Congenital Zika syndrome without microcephaly	929	822	760	696	617	473	246
Congenital Zika syndrome with microcephaly	1,804	1,663	1,589	1,516	1,445	1,060	648
Without congenital Zika syndrome	11,500,000	9,997,496	8,505,972	7,125,492	5,667,138	4,374,716	2,900,641

C Maternal Rash



No. at Risk							
Congenital Zika syndrome with no rash	1,299	1,130	1,030	931	820	584	264
Congenital Zika syndrome with maternal rash in first trimester	849	774	760	736	721	515	298
Congenital Zika syndrome with maternal rash in second trimester	293	282	276	266	256	202	133
Congenital Zika syndrome with maternal rash in third trimester	119	112	108	105	99	81	40
Without congenital Zika syndrome	11,500,000	9,997,496	8,505,972	7,125,492	5,667,138	4,374,716	2,900,641

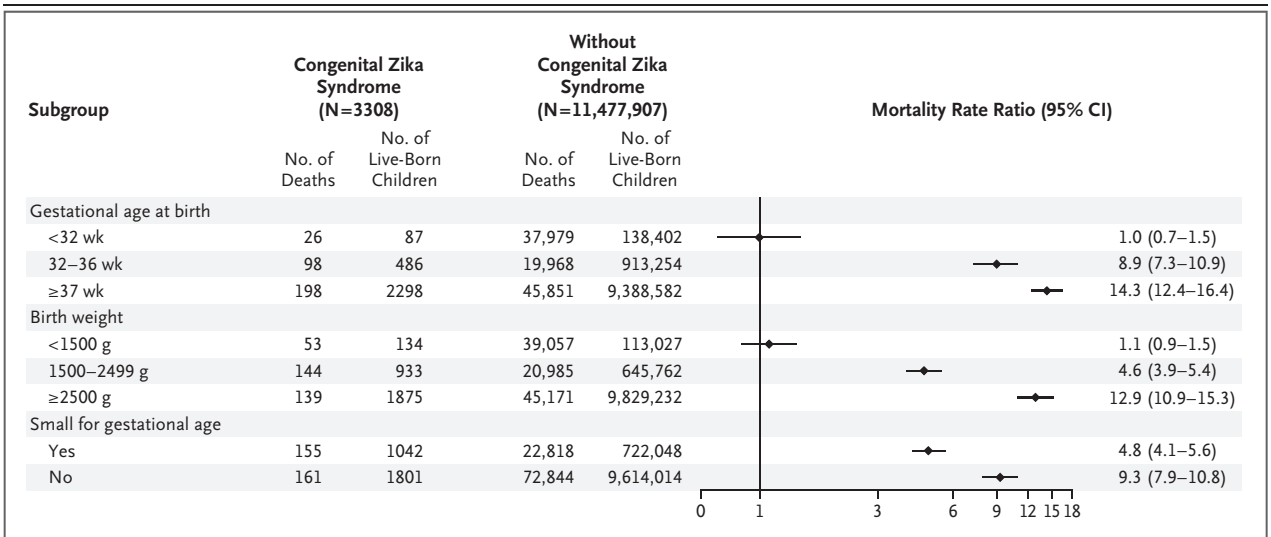


Figure 2. Subgroup Analysis of Mortality up to 36 Months of Age among Live-Born Children with Congenital Zika Syndrome, as Compared with Those without the Syndrome.

The subgroup analysis was conducted with a Cox proportional-hazards analysis, with adjustment for maternal age, educational attainment, marital status, race or ethnic group, and number of prenatal appointments and the sex and year of birth of the newborn. The subgroup analysis was stratified according to gestational age at birth, birth weight, and status of being small for gestational age. The mortality rate ratio is based on the number of deaths per 1000 person-years.

born children with congenital Zika syndrome who were small for gestational age were almost 5 times as likely to die as those without the syndrome, whereas children with congenital Zika syndrome who had a size appropriate for their gestational age were approximately 9 times as likely to die as their counterparts without the syndrome.

CODED CAUSES OF DEATH

Among children with congenital Zika syndrome, the causes of deaths coded under the ICD-10 chapters for certain infectious and parasitic diseases (A00–B99), diseases of the nervous system (G00–G99), and congenital malformations (Q00–Q99) were twice as common as they were among children without the syndrome (Fig. 3). In these three categories, the respective leading causes were sepsis due to an unspecified organism, hydrocephalus (unspecified), and microcephaly. After the first year of life, causes of death due to nervous system diseases and congenital anomalies continued to be leading causes. However, with regard to the G00–G99 chapter, the most common cause of death in this age group was cerebral palsy. Diseases of the circulatory system (I00–I99) were responsible for 58% more deaths among live-born children with congenital Zika syndrome than among those without the syndrome; leading causes of death were cardiomyopathy, other cardiac arrhythmias, and heart failure.

DISCUSSION

Analyses of Brazilian national registry–based data showed that the mortality rates among children with congenital Zika syndrome up to 3 years of age were more than 11 times as high as among those without the syndrome. Among live-born children with congenital Zika syndrome, the risk of death did not differ materially according to microcephaly status or the timing and presence or absence of maternal-reported rash. The risk of death among the smallest infants was similar regardless of congenital Zika syndrome status; however, children with congenital Zika syndrome who were born at term or who had a normal birth weight were more than 12 times as likely to die as their counterparts without the syndrome. Finally, we observed that conditions that were classified as congenital malformations, diseases of the nervous system, and certain infectious diseases were more common causes of death among children with congenital Zika syndrome than those without the syndrome.

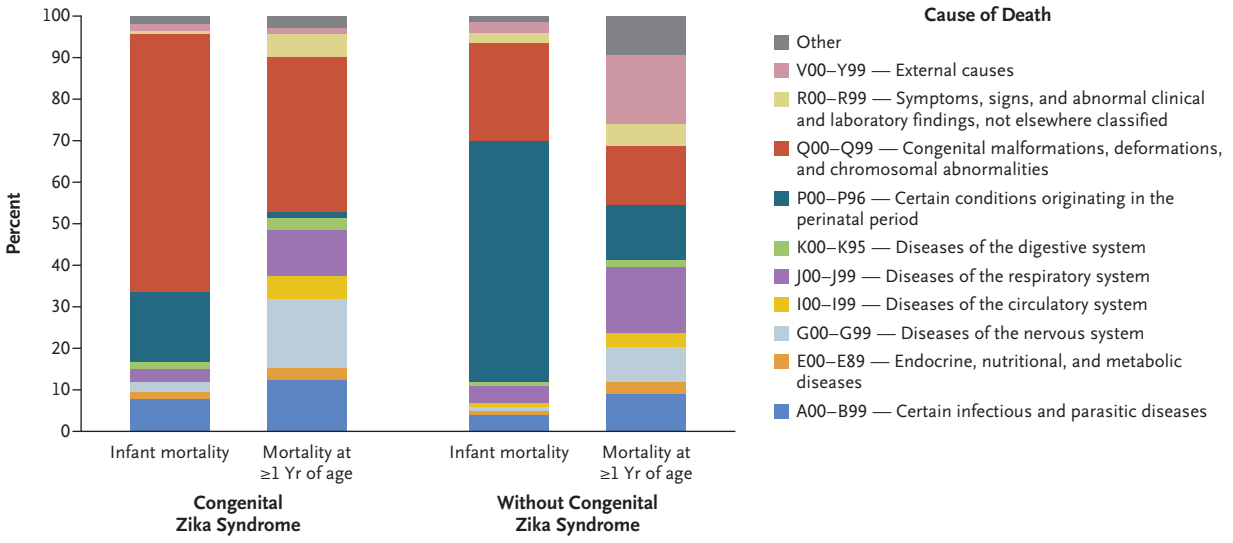


Figure 3. Causes of Death, According to Congenital Zika Syndrome Status, in Brazil (2015–2018).

Causes of death were categorized according to chapter in the *International Classification of Diseases, 10th Revision*. The analysis of infant mortality included deaths at or before 364 days of age.

Data on mortality associated with congenital Zika syndrome are scant. In a series of confirmed cases of congenital Zika syndrome in Brazil, the mortality rate up to 8 days was estimated at 41.1 deaths per 1000 live births.[23] In a U.S. population–based surveillance study involving all the infants and fetuses with congenital abnormalities deemed to be potentially related to ZIKV infection, the mortality rate among neonates was 45.9 deaths per 1000 live births.[24] A similar risk was observed in our study. However, only a longer follow-up could have revealed that after the neonatal period, the absolute mortality rates among live-born children with congenital Zika syndrome did not decrease as dramatically over time as they did among children without the syndrome.

Our understanding of the effect of congenital Zika syndrome on the brain is still emerging; the effects of central nervous system dysfunction with or without microcephaly are expected to result in a wide variety of outcomes.[4,25] Although some studies have shown that the most severe phenotype appears to be associated with exposure during the first trimester of pregnancy,[25,26] neither early exposure (with the use of rash as a proxy) nor microcephaly status showed a difference in the mortality rates, potentially owing to the small number of events. Therefore, the roles of head circumference and timing of maternal symptoms of ZIKV infection as risk factors for death among children with congenital Zika syndrome cannot be fully assessed.

Previous studies have shown that live-born children with congenital Zika syndrome had greater frequencies of low birth weight[27] and status of being small for gestational age[28,29] — features that are compatible with higher child mortality. However, in our study, the risks of death among the smallest infants did not differ according to congenital Zika syndrome status. Moreover, among children with congenital Zika syndrome, those who were born at term or had a normal birth weight, who would have had a high chance of thriving without the impairments resulting from congenital Zika syndrome, were at a strikingly elevated risk for death. Children with congenital Zika syndrome have multiple neurologic complications and long-term sequelae that confer an increased risk of death. These conditions include cerebral palsy, which was one of the main causes of deaths identified in this study, and epilepsy, which has an estimated prevalence of 67% in this group.[30] However, a better understanding of the causal mortality chain is needed.

A strength of our study was the large sample, which included all confirmed and probable cases

of congenital Zika syndrome that had been identified in the country. We also included a population-representative comparison group and were able to control for confounding. The results of the sensitivity analyses (which included only confirmed cases) were consistent with our primary findings.

However, our study has several limitations. First, the study was based on registry data, and relevant clinical data were not available. Second, at the beginning of the ZIKV epidemic, the health services network did not have specific diagnostic tests for ZIKV infections. Therefore, there may have been underreporting in the Public Health Event Record, mainly among fetuses who had been prenatally exposed to ZIKV but who did not have detectable malformations at birth. Third, the linkage process could have introduced classification bias owing to a linkage error. However, if an error had occurred in the linkage indicating exposure (i.e., congenital Zika syndrome), the measure of association probably would have been underestimated. If the error had occurred in the linkage indicating the outcome (e.g., death), the effect would probably have led to nondifferential misclassifications and thus would have been unlikely to introduce bias in the measure of association, although the absolute measures of risk may have been underestimated. Fourth, there was a slight variation in data completeness according to congenital Zika syndrome status. However, data on all the variables were more than 80% complete in the two study groups.

This study showed a higher risk of death among live-born children with congenital Zika syndrome than among those without the syndrome, and the risk persisted throughout the first 3 years of life. These findings draw attention to the importance of primary prevention of infection in women of childbearing age against *Aedes aegypti* bites.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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