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Perinatal characteristics and longer-term outcomes in Brazilian children with confirmed or suspected congenital Zika infection: ZIKAction Paediatric Registry

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ABSTRACT

Background: Despite growing scientific knowledge of Zika virus (ZIKV) infection, questions remain regarding ZIKV infection in pregnancy and congenital ZIKV syndrome (CZS).
Methods: The ZIKAction Paediatric Registry is an international registry of children with documented ZIKV exposure in utero and/or with confirmed or suspected CZS. Its aim is to characterize these children (i.e., clinical, radiological, neurodevelopmental features) and describe outcomes, longer-term sequelae and management through retrospective case note review. This analysis described the maternal and perinatal characteristics of children in the Registry's Bahia arm, assessed their neuroimaging, ophthalmic, hearing and electroencephalography abnormalities by microcephaly classification and reported on hospitalisations. Children born in 2015-2018 and enrolled 2020-2021 in three public health facilities in Salvador were included.
Results: Of 129 (57% female) children, 15 (11·6%) had laboratory-confirmed congenital ZIKV infection and 114 (88·4%) suspected CZS. At delivery, 15 (11·6%) were normocephalic, 30 (23·3%) moderately microcephalic, and 84 (65·1%) severely microcephalic. Median birth head circumference z-score was -3·51 [IQR, -4·69,-2·73]. During follow-up, all children had abnormal neuroimaging, 80·3% (94/117) abnormal electroencephalogram, 62·2% (77/120) ophthalmic abnormalities, and 27·4% (34/124) hearing impairment. Microcephaly classification was significantly associated with gestational age, and ophthalmological and electroencephalography abnormalities. Of 125 children with hospitalisation data, 52 (41·6%) had been hospitalised by most recent follow-up, at median age of 15·8 [4·0, 34·4] months; infections were the leading cause.
Conclusion: Congenital ZIKV infection is an emerging disease with a varied and incompletely understood spectrum. Continued long-term follow-up is essential to understand longer-term prognosis and to inform future health and educational needs.

1. Introduction

Zika virus (ZIKV) is an arborvirus primarily transmitted by daytime active Aedes mosquitoes. Following reports of an unknown exanthematic "dengue-like" illness in Brazil at the end of 2014, the first laboratory-confirmed ZIKV outbreaks in May 2015 were reported in Bahia state, a north-eastern region known as an endemic area for other arboviruses such as Chikungunya virus (CHIKV) and Dengue virus (DENV) [1]. In October 2015, physicians in Pernambuco state reported an increased incidence of newborns with microcephaly, with reports from other North-Eastern

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states following shortly afterwards [2], and proposed a potential causative association with maternal ZIKV infection in pregnancy that was later corroborated by multiple studies [3,4]. The World Health Organization (WHO) declared the ZIKV outbreaks a Public Health Emergency of International Concern (PHEIC) in February 2016, as they were spreading rapidly through Latin America and the Caribbean and also to other regions. Between 2016 and 2017, 11,546 cases of ZIKV were confirmed in pregnant women in Brazil, with 3,563 confirmed cases of Congenital Zika Syndrome (CZS) (defined as those with laboratory-confirmed infection or with relevant clinical/radiological signs and negative for other congenital infections) from 2015 to 2020; these were mostly reported from the North-Eastern region (2,207; 61·9%), with Bahia State accounting for 16% of all CZS cases nationally [5]. These figures underestimate the true burden of the infection in Brazil, owing to under-ascertainment particularly at the start of the outbreak.

Children exposed in utero to ZIKV can be seriously affected, with neurological abnormalities including microcephaly, hydrocephalus, extrapyramidal movements, hemiparesis, hyperexcitability, hyperirritability, and epilepsy [3,6,7]. Microcephaly, the most prominent feature of CZS, occurs in some fetuses but not others, with some studies describing infants with definite or probable CZS who presented with normal head circumference (HC) at birth [3,4]. Reduced fetal movement subsequent to ZIKV-related brain damage can result in arthrogryposis and other congenital contractures [3]. Other adverse outcomes include ocular anomalies, hearing impairment, cerebral palsy, motor impairment, and functional changes and major delays in neurocognitive development among other neurologic sequelae that can result in important long-term disabilities and negative impact on the quality of life and socioeconomic status of these children and their families [3,8–11].

Despite the growing scientific knowledge of ZIKV infection, many questions remain regarding maternal ZIKV infection in pregnancy and vertical transmission [12]. In addition, congenital ZIKV infection is an emerging disease with a varied and poorly understood clinical spectrum, particularly in the medium to longer-term. The international, multi-site ZIKAction Paediatric Registry was set up to capture information on children with confirmed or suspected CZS and/or born to mothers with diagnosed ZIKV infection in pregnancy. Here, we describe the maternal, pregnancy and perinatal characteristics of children participating in the Bahia arm of the Registry, assess their neuroimaging, ophthalmic, hearing and electroencephalography abnormalities by microcephaly classification and report on their hospitalisations to date.

2. Methods

The multi-centre international ZIKAction Paediatric Registry is a disease/exposure hospital-based paediatric registry, the protocol of which has been published; specific objectives were to describe the clinical features, neurodevelopmental characteristics and growth of included children, to assess their long-term sequelae and management and to provide a platform for future studies [13]. The Registry was established in Brazil (in Bahia state), in Argentina (in Buenos Aires) and in Jamaica (national). This analysis is restricted to the retrospective data collected within the ZIKAction Registry in Bahia by July 2021.

2.1. Setting

The study was conducted in three public health facilities in Salvador (the Bahia state capital) dedicated to children with congenital ZIKV infection: the Centro Estadual de Prevenção e Reabilitação da Pessoa com Deficiência, a rehabilitation clinic; the Rede SARAH de Hospitais de Reabilitação, a rehabilitation hospital, and the Centro de Referência de Arboviroses de Feira de Santana, a clinic specialised in arboviral infections. The identification of potential cases was conducted using the records of children attending these three health facilities with the enrolment period from August 2020 to July 2021. Due to COVID-19 pandemic restrictions, the recruitment of participants was conducted remotely (by phone) or at a non-profit civil association called "Abraço a microcefalia".

2.2. Participants

Children were enrolled in the Registry if they met any of the following criteria: (1) children who were exposed to ZIKV in utero (i.e. laboratory confirmation of ZIKV infection during pregnancy through positive RT-PCR, IgM or IgG seroconversion), (2) have laboratory-confirmed congenital ZIKV infection with or without CZS, and (3) meet the suspected CZS definition without laboratory evidence of in utero exposure or congenital infection. A case was categorised as suspected CZS if any of the following features were present: congenital or postnatal microcephaly (see definitions), fetal brain disruption sequence (FBDS), intracranial calcifications, malformations of cortical development (including simplified gyral pattern, polymicrogyria and pachygyria), arthrogryposis, or joint contractures. Cases were excluded if children had a laboratory-confirmed congenital infection other than ZIKV or had a genetic or other confirmed cause of microcephaly.

The data were collected retrospectively by extraction from the medical records of the mothers and children and included socio-demographic information, maternal/obstetric history, pregnancy and delivery data, newborn assessment, a comprehensive history of the child's health including clinical and radiological evaluations (physical, neurological, developmental, ophthalmological, audiological), and laboratory results. Data were also collected from the mothers during Registry enrolment, as they kept written copies of the evaluations and tests results on their children (e.g., those conducted in other hospitals). The information was recorded by clinical staff on a paper version of standardised case report forms written in Portuguese, and later entered as pseudonymised data onto the Registry REDCap database (Research Electronic Data Capture: https://projectredcap.org/) hosted on a secure server at Penta Foundation Onlus.

2.2.1. Definitions

Consistent with other epidemiological studies in Brazil, this study included a racial classification based on maternal reporting of their skin colour and that of their child. Likewise, the study adopted a family income stratum based on monthly income relative to minimum wage (MW) in Brazil at the time of enrolment (i.e., in 2020, R$1,045 per month and in 2021, R$ 1,100 per month). Very low-income was defined as <1 times MW, low-income of 1 to 2 times MW, medium income of 3 to 4 times MW, and high-income of ≥5 times MW.

HC-for-gestational-age z-scores were calculated, using WHO reference standards for full term infants and the Intergrowth reference standards for preterm infants [14,15]. These z-scores were used to classify children as normocephalic, moderately microcephalic and severely microcephalic at birth. Moderate microcephaly was classified as -2 SD below the reference mean and severe microcephaly as -3 SD below the reference mean. Infants were classified as small for gestational age (SGA) if their weight centile was below the 10th percentile using Intergrowth standards; birthweight z-scores were also calculated using Intergrowth standards [14]. Preterm delivery was defined as delivery before 37 completed gestational weeks. Conception date was estimated based on gestational age at delivery. Reasons for hospitalisation used the reported discharge diagnosis, and were classified using the International Classification of Disease (ICD)-10 chapters, with the exception of surgical procedures, which were classified as such. If multiple reasons were reported, the primary discharge diagnosis was used unless the reason for hospitalisation included a surgical procedure, which took precedence.

2.2.2. Statistical analyses

Analysis of timing of reported rash and/or fever in pregnancy was restricted to the first reported episode. Univariable comparisons of categorical variables were assessed using chi-squared or Fisher exact tests. Continuous variables were assessed using t-tests, one way ANOVA or

Kruskal–Wallis tests. STATA version 17 (Stata Corp, College Station, Texas, USA) was used to conduct the analyses.

3. Results

A total of 129 children were enrolled, of whom 15 (11·6%) had laboratory confirmed congenital ZIKV infection (all of whom also met at least one of the clinical criteria for suspected CZS) and 114 (88·4%) had suspected CZS (i.e. without laboratory confirmation). Most children were born in 2015 (83/129, 64·3%), with 33·3% born in 2016 (43/129), one born in 2017 and two in 2018. The earliest estimated conception date was 10th June 2014. Median follow-up time was 5·11 years (IQR 4·89, 5·29).

3.1. Maternal and pregnancy characteristics

Median age at delivery was 27 (IQR 21, 32) years, with 18 (14·0%) of mothers aged between 15 and 19 years at delivery. Overall, 123 women self-reported skin colour, with the majority having brown skin (74/123, 60·2%), 27·9% (36/123) black skin, and 10·1% (13/123) white skin. Just over half of mothers were married or cohabiting (71/126, 56·4%) with 41·3% (52/126) single and three separated or divorced. The majority (94·4%) of mothers reported urban residence (117/124), with seven living in a rural area; place of residence was missing for five women. Family income level was reported by 117 women, of whom 91% (106/117) were in low-income classification, with 5·1% (6/117) in a very-low income, and 4·3% (5/117) in the medium income classification. For 57·6% (72/125) mothers, it was their first pregnancy. Four women (3·2%) reported smoking in pregnancy (5 missing data), including two of the four women in total who reported a history of recreational drug use (3·4%, 4/117). Overall, 18 mothers were known to have a comorbidity, most commonly hypertension (in 10 women).

Ninety-seven (75·2%) mothers reported having at least one rash and 50 (38·8%) at least one fever during pregnancy. Among 84 mothers with timing reported, 35 experienced rash and fever in the same calendar month, 42 had rash only and seven had fever only; symptoms occurred in the first trimester of pregnancy respectively in 85·7% (30/35), 81·0% (34/42) and 28·6% (2/7). Of the 12 women hospitalised during their pregnancy, this admission was related to infection in four cases (one arbovirus symptoms, three urinary tract infections) and the remainder to pregnancy complications. There were no statistically significant differences in maternal characteristics, including presence of rash/fever between the children with confirmed and suspected CZS (data not shown).

3.2. Perinatal characteristics

Fifty-five (42·6%) of the infants were male and 74 (57·4%) female. Just over half had brown skin (55·3% 68/123), 33·3% (41/123) had black skin, and 11·4% (14/123) had white skin. Median gestational age at delivery was 38 weeks (range, 32-41 weeks) and 14·7% infants were delivered preterm. Around half (52·3%) of infants were delivered vaginally (67/128), with a high proportion of elective (38·3%, 49/128) and emergency (9·4%, 12/128) caesarean section deliveries. Overall median birthweight was 2·65kg (range, 1·09, 4·02).

Fifteen (11·6%) infants were normocephalic, 30 (23·3%) moderately microcephalic and 84 (65·1%) severely microcephalic. Median birth HC z-score was -3·51 (IQR -4·69, -2·73). Table 1 presents neonatal characteristics, by microcephaly classification. Significant associations between microcephaly classification and preterm delivery, birth weight, birth length and SGA status were found; whilst neonates with microcephaly had lower birth weight and were more likely to be SGA than normocephalic neonates, the latter had a higher preterm delivery rate (Table 1). There was no association between maternal age or infant skin colour and microcephaly classification (data not shown). Supplementary Figure 1 presents a scatter plot of z-scores for HC and birthweight.

Median Apgar scores overall were eight (range, 2, 10) and nine (range, 4, 10) for one and five minutes respectively, with no difference by microcephaly classification ($p = 0·62$, $p = 0·52$). Most infants with severe microcephaly had occipital bone prominence (95·0%, 57/60; missing data for 24) and/or excess scalp skin (67·7%, 21/31; missing data for 53); the respective figures were (15/17; missing data for 13) and/or (5/7; missing data for 23) among the infants with moderate microcephaly. Six infants had a hernia (one normocephalic, five with severe microcephaly) and 25·4% (30/118) had jaundice.

Overall 17 (13·2%) infants had arthrogryposis, and this feature was present in infants from every microcephaly classification group (i.e., including some with normal HC) (Table 1); however, most (82.4%, 14/17) infants with arthrogryposis had severe microcephaly. In addition to these 17 infants, there were a further seven who had contractures. Nine of the 11 infants with genital abnormalities were male and three of these nine boys also had arthrogryposis. Hypertonia was a very common finding with around three-quarters of infants having this condition, with similar proportions across the microcephaly classification groups (Table 1).

3.3. Paediatric clinical assessments

There was a total of 215 neuroimaging assessments performed for the 129 children, with abnormal neuroimaging findings reported for all regardless of microcephaly classification (i.e., were reported for the 15 children with normal HC as well as those with microcephaly). Calcifications were reported in 84·3% (83/129), ventriculomegaly in 83·7% (108/129) and cortical atrophy in 64·3% (83/129). Lissencephaly and dysgenesis of the corpus callosum were slightly less common, found in 56·6% (73/129) and 43·4% (56/129) of children respectively, whilst around 10% or fewer children had cerebellar hypoplasia (14/129, 10·9%), cisterna magna enlargement (11/129, 8·5%) and hydrocephalus (6/129, 4·7%). There was no abnormality pattern discernible by microcephaly classification (Suppl. Table 2). Consistent with the universal finding of abnormal neuroimaging, 80·3% (94/117) children had electroencephalogram (EEG) abnormalities detected, with a significant association with microcephaly classification (Table 2). Of these 94 children, 78 had their first abnormal finding at the first assessment, which was performed at a median age of 144 days (IQR 93, 367).

Overall, 120 children had undergone one or more ophthalmic examinations, at a median age at first examination of 145 days (IQR 11, 373). Most (62·2%, 77/120) had ophthalmologic abnormalities and significant differences in this proportion were apparent by microcephaly classification (Table 2). Posterior segment manifestations dominated, with 50 children having abnormal fundoscopic findings, including optic nerve abnormality (hypoplasia, pallor, cupping) (25 children), chorioretinal atrophy (16 children) and focal pigment mottling (14 children); there were no statistically significant differences in pattern of abnormalities between normocephalic children and those with microcephaly (data not shown). Anterior segment findings were less common, with two children with cataract (one bilateral), two with iris coloboma (one bilateral) and two with congenital glaucoma; all had microcephaly. Strabismus was present in half of the children with ocular findings (39/77).

There were 34 children with hearing impairment (in one or both ears) detected among the 124 children with hearing assessments (Table 2); in 23 cases this was based on an Acoustic otoemission examination and in 11 on an Automated Auditory Brainstem Response (AABR) examination. The pattern of hearing impairment and/or ocular and/or EEG abnormalities is presented in Figure 1 among the sub-set of 115 children who had at least one abnormal finding: combinations of these abnormalities were more common than isolated findings. Of the 20 children with an abnormal ophthalmological, hearing, EEG and neuroimaging assessment, 16 (80%) had severe microcephaly and three (15%) had moderate microcephaly.

3.4. Hospitalisations

Data were available on hospitalisation for 125 children, of whom 52 (41·6%) had been hospitalised at least once by the time of their most recent follow-up, with a total of 103 hospitalisations (Table 3). Of the 52 children

Table 1
Neonatal characteristics by microcephaly classification.

Characteristics	Total	Normocephalic	Microcephalic moderate	Microcephaly severe	*p*-value
	n = 129	n = 15	n = 30	n = 84	
Sex *n = 129*					
Female	74 (57.4%)	9 (60.0%)	16 (53.3%)	49 (58.3%)	
Male	55 (42.6%)	6 (40.0%)	14 (46.7%)	35 (41.7%)	0.872
Lab confirmed ZIKV n = 129					
Yes	15 (11.6%)	1 (6.7%)	2 (6.7%)	12 (14.3%)	
No	114 (88.4%)	14 (93.3%)	28 (93.3%)	72 (85.7%)	0.590
Gestational age *n = 129*					
<37 weeks	19 (14.7%)	5 (33.3%)	6 (20.0%)	8 (9.5%)	
≥37 weeks	110 (85.3%)	10 (66.7%)	24 (80.0%)	76 (90.5%)	0.031
Birth weight (kg) *n = 129*					
Median (IQR)	2.65 (2.29, 3.01)	3.06 (2.54, 3.67)	2.88 (2.55, 3.3)	2.55 (2.25, 2.85)	0.002
< 1.5 kg	4 (3.1%)	1 (6.7%)	0 (0%)	3 (3.6%)	
1.5-2.49 kg	42 (32.6%)	2 (13.3%)	6 (20.0%)	34 (40.5%)	
≥ 2.5 kg	83 (64.3%)	12 (80.0%)	24 (80.0%)	47 (56.0%)	0.046
SGA *n = 129*					
Yes	55 (42.6%)	1 (6.7%)	6 (20.0%)	48 (57.1%)	
No	74 (57.4%)	14 (93.3%)	24 (80.0%)	36 (42.9%)	<0.001
Birth length (cm) *n = 127*					
Median (IQR)	46.5 (45, 48)	47 (46.5, 49.5)	47 (45, 48)	46 (44, 48)	0.008
Resuscitation *n = 115*					
Yes	4 (3.5%)	2 (13.3%)	1 (4.0%)	1 (1.3%)	
No	111 (96.5%)	13 (86.7%)	24 (96.0%)	74 (98.7%)	0.072
ICU referral *n = 124*					
Yes	37 (29.8%)	4 (26.7%)	8 (26.7%)	25 (31.7%)	
No	87 (70.2%)	11 (73.3%)	22 (73.3%)	54 (68.4%)	0.917
Cardiovascular abnormalities *n = 128*					
Yes	24 (18.8%)	1 (6.7%)	3 (10.0%)	20 (24.1%)	
No	104 (81.3%)	14 (93.3%)	27 (90.0%)	63 (75.9%)	0.140
Arthrogryposis *n = 129*					
Yes	17 (13.2%)	2 (13.3%)	1 (3.3%)	14 (16.7%)	
No	112 (86.8%)	13 (86.7%)	29 (96.7%)	70 (83.3%)	0.154
Genital abnormalities *n = 127*					
Yes	11 (8.7%)	3 (20.0%)	1 (3.5%)	7 (8.4%)	
No	116 (91.3%)	12 (80.0%)	28 (96.6%)	76 (91.6%)	0.202
Stiffness / hypertonia *n = 97*					
Yes	74 (76.3%)	11 (73.3%)	16 (72.7%)	47 (78.3%)	
No	23 (23.7%)	4 (26.7%)	6 (27.3%)	13 (21.7%)	0.788
Seizures *n = 117*					
Yes	34 (29.1%)	5 (33.3%)	6 (21.4%)	23 (31.1%)	
No	83 (70.9%)	10 (66.7%)	22 (78.6%)	51 (68.9%)	0.632
Hypotonia *n = 107*					
Yes	5 (4.7%)	1 (6.7%)	0 (0.0%)	4 (5.9%)	
No	102 (95.3%)	14 (93.3%)	24 100.0%)	64 (94.1%)	0.516

Table 2
Ophthalmic, hearing and electroencephalography abnormalities reported for children in the Registry, by microcephaly classification.

	Total	Normo-cephalic	Microcephalic		p-value*
			Moderate	Severe	
Ophthalmic exam, n = 120					
Normal	43 (35.8%)	6 (40.0%)	17 (63.0%)	20 (25.6%)	
Abnormal	77 (62.2%)	9 (60.0%)	10 (37.0%)	58 (74.4%)	0.002
Hearing impairment, n = 124					
No	90 (72.6%)	11 (78.6%)	22 (73.3%)	57 (71.3%)	
Yes	34 (27.4%)	3 (21.4%)	8 (26.7%)	23 (28.8%)	0.954
EEG abnormalities, n = 117					
Normal	23 (19.7%)	5 (35.7%)	8 (29.6%)	10 (13.2%)	
Abnormal	94 (80.3%)	9 (64.3%)	19 (70.4%)	66 (86.8%)	0.041

* p value: testing for significant difference in proportions, stratified by microcephaly classification

ever hospitalised, 27 had one admission, 10 two, 10 three admissions and the remaining five had been hospitalised four to eight times. Median age at first hospitalisation was 15·8 months (IQR 4·0, 34·4) (date of admission missing for 15). Among the 82 hospitalisations with date of admission recorded, 39·0% (32/82) occurred in the first year of life and 15·9% (13/82) in the second year of life with the remainder at older ages.

Of all 103 hospitalisations, the reason for admission was an infection in nearly half, most commonly upper respiratory tract infections (n = 17) and pneumonia (n = 17). The second most common reason was due to diseases of the nervous system, mostly seizures (n = 20). Fourteen children were admitted to hospital for an invasive or surgical procedure for a total of 15 admissions. These were for orthopaedic surgery (n = 4; 3 for hip dysplasia), gastrostomy (n = 4), tracheostomy and gastrostomy (n = 3), replacement of ventriculoperitoneal shunts (n = 2), surgery to resect a pheochromocytoma (n = 1) and gastroesophageal reflux surgery (n = 1). Duration of hospital stay was available for 66 (64·1%) admissions overall, with a median of six (IQR 4, 14) days. Of note, one child was hospitalised for 7·9 months

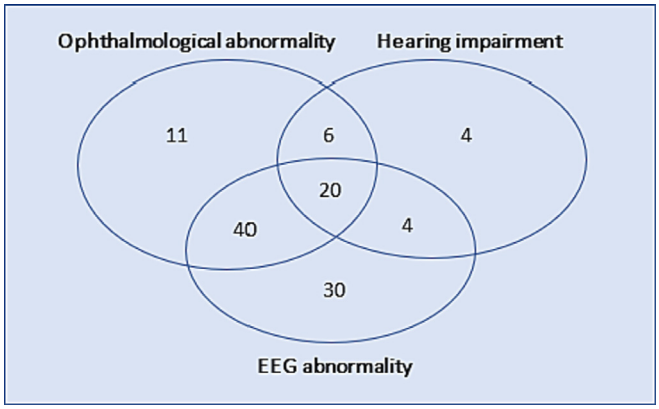

Fig. 1. Patterns of findings among children who ever had an ophthalmological abnormality, hearing impairment or EEG abnormality* (N = 115). *all children had at least one abnormal neuroimaging finding.

Table 3
Primary reason for hospitalisation (103 hospitalisations).

ICD-10 chapter	Frequency	%
Certain infectious and parasitic diseases	46	44.7
Diseases of the nervous system	21	20.4
Endocrine, nutritional and metabolic diseases	7	6.8
Diseases of the respiratory system	4	3.9
Diseases of the digestive system	3	2.9
Diseases of the circulatory system	2	1.9
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	2	1.9
Certain conditions originating in the perinatal period	1	1.0
Congenital malformations, deformations and chromosomal abnormalities	1	1.0
Diseases of the genitourinary system	1	1.0
Surgery and procedures	15	14.6

(discharge diagnosis was respiratory tract infection, tracheostomy and gastrostomy).

Two children died, one at age four years, with cause of death being respiratory failure, bacterial pneumonia and sepsis, and the other at age five years following a cardiorespiratory arrest after a seizure; this child had EEG abnormalities and seizures during the neonatal period.

4. Discussion

The ZIKAction Registry in Bahia enrolled children with laboratory-confirmed congenital ZIKV infection or with suspected CZS born in the regional epicentre of the ZIKV outbreak in Brazil and includes a sub-group representing some of the earliest cases of CZS following the introduction of ZIKV to the Americas. The data provided here contribute to the growing, but still incomplete, evidence base on CZS and its outcomes. In this Registry population, around two-thirds of the children had severe microcephaly, all had abnormal neuroimaging assessments (including those with normal HC), 76% had hypertonia, 62% had ophthalmological abnormalities and 27% had hearing impairment, demonstrating the substantial developmental disabilities associated with CZS.

Only 12% of included children had laboratory-confirmed ZIKV infection, with registration of the majority based on clinical presentation and careful exclusion of other congenital infections and/or genetic or other causes of microcephaly. There are multiple reasons for the lack of laboratory-confirmation, which is a common feature of studies of CZS [9,11,16]. Firstly, a proportion of these children were born before ZIKV was first detected in Brazil (in October 2015) [1]. Although there were reports of an unknown 'dengue-like' illness in North-Eastern Brazil in 2014, phylogenetic and molecular clock analyses suggest that ZIKV was introduced into the Americas in the second half of 2013 [17]. Secondly, once the first wave of the ZIKV outbreak was recognised, multiple diagnostic challenges were present [18]. For example, not only was laboratory capacity for molecular diagnostics very limited, but the transient and often low-level viremia associated with ZIKV infection and its frequent asymptomatic presentation also resulted in challenges in detecting and diagnosing infection. There was also a lack of specific and reliable serological assays due to flavivirus cross-reactivity in a population that was highly DENV-exposed. Regarding infant diagnosis, many infants with suspected congenital ZIKV infection have neither virological or serological evidence of the infection by the time they are born. For example, studies have shown an absence of IgM positivity in 50-73% of infants with CZS whilst there is, unexpectedly, a lack of persistence of IgG antibodies in congenitally infected infants [19–21].

The mothers in the Registry mainly self-described as black or brown, of low income and young (25% aged 21 years or less), with two-fifths single at the time of delivery. Several ecological studies in Brazil, including one in Salvador, have reported higher incidence of maternal ZIKV infection in pregnancy and/or microcephaly/CZS in geographic areas with poorer socioeconomic indicators (e.g. sanitation, household income, education levels), most likely reflecting greater exposure to mosquitos [22]. For families of children with CZS, any pre-existing socioeconomic inequalities are likely to be compounded by the impact of the disease and caring for a disabled child, which may include relationship breakdown, loss of employment and mental health issues, as well as social isolation, stigma, and uncertainty about unfolding health consequences [9].

Most women retrospectively reported symptoms compatible with ZIKV, mostly in the first trimester of pregnancy, although the Registry's design means that care is needed in interpreting these findings due to possibility of recall bias. Nonetheless, this is consistent with a Bayesian latent class analysis of seven prospective studies of ZIKV infection in pregnancy, in which mean transmission risk was estimated to be highest in the first trimester (47%, 95% credible interval 26, 76), and substantially lower (25-28%) later in pregnancy [12]. However, among women with ZIKV infection in pregnancy, whether there is an association between symptoms and CZS remains uncertain. A recent meta-analysis of six studies found a relative risk of microcephaly of 0·68 (95% CI 0·60, 0·77) for asymptomatic versus symptomatic maternal ZIKV infection [16].

Disruption of neurogenesis is the suggested main cause of ZIKV and other infection-related microcephaly [23]. The severe microcephaly that characterises 65% of our Registry population is consistent with ZIKV infection early in pregnancy [4], but microcephaly is one of a sub-group of birth defects that can develop following teratogenic exposure later in pregnancy, after the embryonic period, alongside other defects also seen in CZS such as arthrogryposis, cataracts and dysgenesis of the corpus callosum. The FBDS phenotype was an early observation in defining the "constellation of anomalies" in CZS [3]. In our Registry, 33% of children had FBDS characteristics (i.e., severe microcephaly, occipital bone prominence and excess scalp skin, alongside neurological impairment), but a substantial proportion lacked this distinct phenotype, including some who nonetheless had severe microcephaly. Our study design precluded robust investigation of the pattern of defects according to maternal timing of infection, given its retrospective nature and the reliance on maternal self-report of symptoms, but our findings contribute additional evidence to show that a range of microcephaly phenotypes are associated with ZIKV infection.

As seen elsewhere [11], we found significantly higher proportions of low birth weight and SGA neonates in the severe microcephaly group than in other groups. Whilst maternal ZIKV infection in pregnancy may result in intrauterine growth restriction, interpretation of these findings should also consider the contribution that the head usually makes to total newborn body weight; over 90% of normocephalic children here were appropriate weight for gestational age. Of note, the significant association between preterm delivery and microcephaly classification was in the opposite direction to that for birth weight or SGA, with infants with severe microcephaly less likely to be born preterm. This may reflect the fact that some

newborns with severe microcephaly and preterm delivery died and therefore were not included in the Registry.

Most (62%) children in our Registry had ocular anomalies, which is higher than reported in other studies [10], including a Brazilian multicentre study of 469 children with laboratory-confirmed CZS where 32% had ocular manifestations (although this varied geographically), most commonly optic nerve findings (20% of eyes) and retinal anomalies (20% of eyes) [24]. Current understanding of the range of ophthalmic anomalies in ZIKV-exposed and infected children remains incomplete. The predominance of fundus abnormalities among children with ophthalmic manifestations here is consistent with the literature, with structural defects such as microphthalmia or iris coloboma much less commonly reported in children with CZS, as was the case here [10,25]. Our Registry population included two children with congenital glaucoma, rarely reported in children with CZS to date; one of these children was reported as the first such case in the literature in 2017 [26]. Subsequently, in a case series of 43 children with CZS from Colombia and Venezuela, 12% were found to have congenital glaucoma [27].

The burden of ocular problems among children with CZS is high, and the manifestations show similar features to other congenital infections such as CMV, toxoplasmosis and rubella [23]. The underlying pathogenesis depends on timing of ZIKV exposure, e.g., anterior segment findings including iris coloboma result from disruption of embryonic ocular fissure closure in early gestation, whilst ZIKV infection of the blood retinal barrier cells later in gestation may result in chorioretinal atrophy and macular mottling [10]. Visual impairment as a result of ZIKV may not only result from ophthalmic manifestations but may also be due to neurological abnormalities as well, which were present in all our Registry children. Our findings highlight the overlapping of visual and auditory deficits, with the majority of children with hearing impairment also having ocular manifestations of ZIKV disease. The overall proportion of children with hearing loss in our study is at the upper end of the range reported in a recent systematic review of hearing loss among 852 children with CZS and/or in utero ZIKV exposure who had objective hearing assessments (0% to 30%) [28].

Whilst most children had severe microcephaly, 12% of children in the Registry had normal HC. For a child with a normal HC to be included, by definition they had to have intracranial calcifications and/or malformations of cortical development and/or arthrogryposis/ contractures. Even considering this, the finding that every major neuroimaging abnormality seen in the children with microcephaly was also identified in the children with normal HC, with the exception of hydrocephalus, was interesting. Furthermore, we report that 73% of children with normal HC had hypertonia, 60% had ocular anomalies and 21% had hearing impairment. In a retrospective cohort study of children with in utero ZIKV exposure in Rio de Janeiro, among those with normal HC the proportions with neurologic, eye and auditory abnormalities were 68%, 18% and 10% respectively [11]. These findings underscore the importance of neurological, ophthalmic and hearing assessment and follow-up for all children with suspected ZIKV exposure and not only those with microcephaly.

Hospitalisations were reported for 42% of our children, with infections, seizures and invasive procedures or surgery accounting for most admissions; the latter were mainly required because of arthrogryposis, dysphasia and hydrocephalus. In a study of 145 children with CZS followed at a referral centre in Pernambuco [29], 49% had been hospitalised by age 24 months, with an average stay of 4 days and very similar discharge diagnoses as reported here. A smaller study from Rio de Janeiro reported gastrointestinal tract-related admissions as the main reason for hospitalisations, but with respiratory and nervous system problems as the next most important; this study also examined the nursing care required for the 41 hospitalisations studied, finding that 8% required intensive and 54% semi-intensive care (i.e., clinically unstable) [30]. The high risk of infections may partly reflect increased risk of broncho-aspirations in this population, where a high proportion may have persistent dysphagia, as well as infections associated with invasive devices.

Natural history of a congenital infection can only be fully elucidated by studies in which exposed and infected infants have been identified at birth and prospectively followed-up, usually with birth cohort studies. However, classical prospective studies have been precluded by factors including diagnostic challenges and the abrupt decline in ZIKV incidence from mid/late 2016 [12]. Whilst the ZIKAction Registry is unable to describe natural history, it has provided an important opportunity to provide a detailed characterisation of children with suspected or confirmed CZS. Limitations include the potential for misclassification of Registry cases, the relatively small number of cases with normal HC and possible selection bias (e.g., where only the more severe cases have been included). The reasons for lack of laboratory confirmation of most of these cases has been discussed above.

5. Conclusions

Congenital ZIKV infection is an emerging disease with a varied and incompletely understood spectrum. As expected for a teratogenic virus, the clinical presentation of CZS appears to be influenced by timing of exposure in relation to gestational age and fetal development, but it is clear that many children with CZS have long-term disabilities, requiring multidisciplinary and long-term care. In Brazil, children with CZS are now school-aged, emphasising the need to continue follow-up and research in order to understand their longer-term prognosis and health and educational needs.

Ethics approvals and consent to participate

The study protocol was revised and approved by the review board of the Gonçalo Moniz Institute/FIOCRUZ (CAAE: 83327517.7.2006.0040/2019). All of the parents and legal guardians of children who were enrolled signed a written informed consent.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dialog.2023.100104.

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