RESEARCH ARTICLE

Estimating the cost of congenital Zika syndrome to families and healthcare providers in Rio de Janeiro and Pernambuco, Brazil: results of a case-control study [version 1; peer review: 2 approved with reservations]

Márcia Pinto[1], Silke Fernandes[2], Letícia Barros[1], Sandra Valongueiro[3], Maria Elisabeth Lopes Moreira[1], Thália Velho Barreto de Araújo[3], Mireia Jofre-Bonet[4], Aline Entringer[5], Tereza Maciel Lyra[3,6], Hannah Kuper[2]

[1]Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil
[2]London School of Hygiene & Tropical Medicine, London, UK
[3]Universidade Federal de Pernambuco, Recife, Brazil
[4]Office of Health Economics, London, UK
[5]Universidade Federal do Espírito Santo, Av. Fernando Ferrari, 514 - Goiabeiras, Vitória - ES, 29075-910, Brazil
[6]Instituto Aggeu Magalhães, Fundação Oswaldo Cruz, Recife, Brazil

v1 **First published:** 09 Apr 2021, **6**:78
https://doi.org/10.12688/wellcomeopenres.16623.1
Latest published: 09 Apr 2021, **6**:78
https://doi.org/10.12688/wellcomeopenres.16623.1

Abstract

Background: Children with congenital Zika syndrome (CZS) have a wide range of additional healthcare needs. This study aimed to estimate the direct costs of CZS from the health provider and family perspectives, and the indirect costs for families, in two Brazilian states: Rio de Janeiro and Pernambuco.

Methods: A case-control study was undertaken between May 2017-January 2018 recruiting 174 cases with severe CZS, 41 with mild/moderate CZS and 269 children with no CZS, across the two sites, from existing studies. The primary caregiver was interviewed using a structured questionnaire to collect information on healthcare use and costs incurred during the previous 12 months. In Rio de Janeiro, health care utilization data was also extracted from electronic medical records. We estimated direct and indirect costs incurred as a result of CZS from the perspective of the health system and families.

Results: Children with CZS accessed more healthcare facilities and reported longer travel and waiting times than children unaffected by CZS. Total costs from the health provider perspective of outpatient visits, were highest for children with severe CZS (U$1,411) followed by children with mild/moderate CZS (U$264) and children without CZS

Open Peer Review

Reviewer Status ? ?

	Invited Reviewers	
	1	**2**
version 1 09 Apr 2021	? report	? report

1. **Hugo Turner**, Imperial College London, London, UK

2. **Shenglan Tang**, Duke Kunshan University, Jiangsu, China

Any reports and responses or comments on the article can be found at the end of the article.

(U$107). This pattern was apparent for direct costs incurred by families, while median indirect costs were low. Families of children with CZS reported high levels of catastrophic expenditures; Expenses incurred by families to meet their child's needs as a proportion of household income was 30% (IQR=14%-67%, p<0.01) for children with severe CZS, 11% (IQR=4%-33%, p<0.01) for mild/moderate CZS, and 1% (IQR=0%-8%) for controls. Costs incurred by families were generally higher in Rio de Janeiro than Pernambuco.

Conclusions: Families of children affected by CZS in Brazil may need additional public health resources and social benefits to protect them from incurring catastrophic expenses while meeting the needs of their children.

Keywords
Congenital Zika Syndrome, Brazil, case-control study, economic, expenditure, costs, impact

Corresponding author: Hannah Kuper (Hannah.Kuper@lshtm.ac.uk)

Author roles: Pinto M: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Writing – Review & Editing; **Fernandes S**: Data Curation, Formal Analysis, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Barros L**: Data Curation, Formal Analysis, Investigation, Methodology, Writing – Review & Editing; **Valongueiro S**: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Supervision, Writing – Review & Editing; **Moreira MEL**: Conceptualization, Funding Acquisition, Investigation, Methodology, Supervision, Writing – Review & Editing; **Barreto de Araújo TV** : Conceptualization, Funding Acquisition, Investigation, Methodology, Supervision, Writing – Review & Editing; **Jofre-Bonet M**: Conceptualization, Investigation, Methodology, Supervision, Writing – Review & Editing; **Entringer A**: Formal Analysis, Investigation, Methodology, Project Administration, Writing – Review & Editing; **Lyra TM**: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Writing – Review & Editing; **Kuper H**: Conceptualization, Funding Acquisition, Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This study was supported by The Wellcome Trust and the Department for International Development (grant: 206016/Z/17/Z). This study was also supported by a supplementary grant from the European Union's Horizon 2020 research and innovation programme, under Zika-PLAN grant agreement no. 734584.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Pinto M, Fernandes S, Barros L *et al.* **Estimating the cost of congenital Zika syndrome to families and healthcare providers in Rio de Janeiro and Pernambuco, Brazil: results of a case-control study [version 1; peer review: 2 approved with reservations]** Wellcome Open Research 2021, **6**:78 https://doi.org/10.12688/wellcomeopenres.16623.1

First published: 09 Apr 2021, **6**:78 https://doi.org/10.12688/wellcomeopenres.16623.1

Introduction

In 2016, the world health organization (WHO declared the Zika virus (ZIKV) epidemic a "public health emergency of international concern", because of its association with a wide spectrum of congenital anomalies, now collectively called "congenital Zika syndrome" (CZS)[1]. Brazil was the most severely affected among the countries and territories reporting outbreaks; by 2018 there were 2,952 cases of "confirmed congenital syndrome associated with Zika virus infection" in Brazil, making up 79% of cases for the PAHO region[2]. The true number is likely to be far higher. ZIKV spread throughout all Brazilian regions, but the epicenter of the epidemic was in the Northeast region[3,4].

Microcephaly is the most severe CZS complication in children, but congenital infection with ZIKV is also associated with a range of other conditions, including hypertonicity, seizures, ophthalmic abnormalities, arthrogryposis, cardiac conditions and early development delay[5–7]. Consequently, children with CZS are likely to experience a wide range of additional health and social needs during their lifetime, including for specialized health care and education[8]. Moreover, families of children with CZS can experience substantial financial impacts, as they try to meet the needs of their child, for instance paying for travel to receive healthcare or purchasing assistive technologies. Additionally, mothers often assume the role of the main caregiver and may not return to employment[9].

The outbreak of ZIKV in Brazil occurred in the middle of an economic crisis that began in 2014 and resulted in a set of fiscal austerity measures implemented from 2016, including freezing the social and health care spending[10]. The national health system (Sistema Único de Saúde - SUS) provides universal health care with its services financed and delivered at the federal, state and municipal level. While total public health expenditure per capita by municipalities grew by 226% from 2003 to 2014, it has decreased by 6.3% since 2015[11]. Provision of efficient and effective healthcare services tailored to children affected by CZS is therefore challenging for the SUS, due to the funding constraints and the high and diverse needs of the children for public resources, including for a broad range of medical specialties and technologies.

To date, the economic impact of CZS for families and the health provider is unknown. One model created to inform a cost-effectiveness tool, by AlfaroMurillo *et al.*, predicted that each case of microcephaly incurs direct medical costs of $91,102 and $28,818 over the lifetime for Latin America and the Caribbean, respectively[12]. However, these results were estimated by extrapolating the costs of a case of intellectual disability from the United States, and actual data has not been generated for the Zika epidemic. Other analyses have focused on the economic burden of microcephaly in the USA, but the findings may not be relevant to Brazil or other Latin American settings[13]. The lack of data on economic impacts of CZS is an important gap, as understanding the social and economic consequences of CZS in Brazil could help decision-makers in allocating optimal resources to support these children's healthcare and social needs.

The aim of this study was to estimate the direct cost of caring for a child with CZS from the health provider perspective and the direct and indirect cost for families over a 12 month period, in two Brazilian settings: Rio de Janeiro city, capital of the state of Rio de Janeiro and in Recife city, capital of the state of Pernambuco.

Methods

Study setting

A case-control study was carried out in two contrasting sites in Brazil, selected from where research was ongoing and the teams had good access to families of children with CZS[14]. The first was Recife city and Jaboatão dos Guararapes, in the State of Pernambuco in Northeast Brazil. The Northeast region has a high number of suspected and confirmed cases of CZS and is considered the epicenter of the epidemic. For contrast, the second site was Rio de Janeiro city, in the state of Rio de Janeiro, where symptomatic ZIKV was less prevalent and reports of CZS far lower. Collectively, the States of Rio de Janeiro and Pernambuco accounted for 25% of confirmed CZS cases in the country[4]. Furthermore, Rio de Janeiro and Pernambuco have among the largest public health care networks in Brazil, with most of hospitals and outpatient facilities linked to the SUS[15,16]. The protocol of the study has been published in full previously[14].

Children in the study were born from late 2015 through 2016. Economic data (health provider costs, and direct and indirect costs incurred by the families) was collected between May 2017 and January 2018 through use of a questionnaire completed by the child's caregiver and electronic medical records (Rio de Janeiro only).

Cases and controls

In Pernambuco, the majority of cases and controls were identified from an existing case-control study initiated in January 2016[17]. In Rio de Janeiro, the main source of the cases and controls was from an ongoing cohort study.

Case selection. In Pernambuco, cases were children born with microcephaly, head circumferences < 2 standard deviations (SD) than the mean in eight public maternity hospitals. Additional cases with microcephaly were identified from an ongoing cohort of pregnant women who presented with a rash (a common symptom of ZIKV infection), and from outpatient clinics of children with CZS (mostly from Oswaldo Cruz hospital). They were classified as severe or moderate CZS, based on their head circumference ("severe" head circumference <3 SDs below the mean for age and sex).

In Rio de Janeiro, the source of the cases was the Vertical Exposure to Zika Virus and Its Consequences for Child Neurodevelopment: Cohort Study in Fiocruz/IFF (ClinicalTrials.gov Identifier: NCT03255369). Cases were children born to mothers known to be ZIKV positive, who either 1)

had microcephaly or significant developmental delay (i.e. had a composite score <70 on the Bayley Scale of Infant Development scale[18] between 6 and 36 months) and presented with other clinical conditions with eye or hearing abnormalities or other brain malformations ("Severe CZS"), or 2) had less severe developmental delay indicated by a composite Bayley score of 70–84 ("Mild/moderate CZS").

Control selection. In Pernambuco, controls were children born in the same hospitals, but without microcephaly and without neurological or other health problems (determined from transfontanelle ultrasonography, and through physical examination by the study neonatologist), with both examinations performed soon after birth[17]. Controls were matched to cases on the basis of expected date of delivery and place of mother's residence (by health region). During the follow-up interview in 2017/2018, parents were asked whether there were any developmental delays (using the Denver Developmental Screening Test)[19], and if the response was positive, they were excluded from the study and referred for further investigation.

In Rio de Janeiro, control subjects were born to mothers without a history of symptoms and without developmental delay, as shown by: 1) a composite Score ≥85 on the Bayley Scale of Infant Development scale[18], conducted between 6 and 36 months following the recommended guidelines and/or 2) assessment by two paediatricians based on the child's medical records[14]. In Rio de Janeiro, the sample of controls included nine pairs of twins and, for each pair, one child was randomly selected for inclusion as a control, in order to avoid double-counting of families.

According to case and controls definitions, children in both settings were categorized into three groups: (1) children with severe CZS (microcephaly or with serious developmental delay); (2) children with mild/moderate CZS; and (3) children not affected by CZS.

Sample size justification

The sample size for the overall study was powered to detect a difference in depression prevalence between the control and case mothers, as this was one of the study's primary outcomes[14]. We aimed to recruit 100 cases and 100 controls per setting, which would provide the power to detect an odds ratio (OR) of 2.6 in each site for the association between depression and CZS, assuming 95% confidence, 80% power and a prevalence of depression of 15% in unaffected mothers. Across the two samples (i.e. 200 cases and 200 controls), the sample size would be adequate to detect an OR of 2.1 for the same association. We considered that the sample size would be sufficient for the current analyses, given the large expected economic impacts of CZS.

Data collection

Two sources of data were used to estimate the direct and indirect costs of CZS.

First, the primary caregiver (usually the mother) was interviewed using a semi-structured questionnaire, between May 2017 and January 2018 (full questionnaire available as extended data[20]. Data were collected on socio-economic status, clinical data, direct costs (e.g. travel, food, parking, hospital/exam fees) and indirect costs from families and main caregiver (e.g. productivity loss/opportunity cost), health care resource utilization (frequency of outpatient visits to different types of health professionals, and number of hospitalizations), and coping strategies (selling of assets, borrowing money). The effort of the caregiver in seeking care was also estimated by asking about the number of healthcare facilities where the child received care, transportation time and waiting time at the health care facility for a typical visit. The reference period was the last 12 months. The cost component of the questionnaire used a tool developed by the *UK working party on patient costs* as a template and adjusted it to the context[21]. Additionally, the questionnaire was used to collect data from the caregiver on the family monthly income and other socio-demographic characteristics, as well as parental indicators (e.g. age, marital status, schooling, depression, anxiety and stress, social support). For analysis, monthly income was converted into yearly income.

The second data source was the CZS cohort´s electronic medical records database that recorded resource utilization (hospitalizations, tests and exams) for each child in the Rio de Janeiro sample, between June 2016 and April 2018. Hospital data from electronic medical records that included hospitalizations, tests and exams were not available for Pernambuco.

Calculation of health provider's costs

Costs from the national health system perspective were calculated using an ingredient approach for each child and each year, whereby each resource used was identified, quantified and valued. The number of consumed resources (outpatient visits, hospitalizations, and tests) were multiplied by the costs on the national cost reference table and adjusted by a factor of x3.51, as suggested in the literature[22,23]. This factor was estimated by an analysis of the cost of some procedures, as the national cost reference table did not reflect the real cost of these procedures as it had not been updated for approximately eight years.

The number of consumed resources for outpatient visits, hospitalization and tests and exams were estimated as follows:

- Medical appointments: The number of outpatient visits were collected from the questionnaire for both settings and included a broad range of specialties (e.g. genetics, neurology, nutrition, occupational therapy, ophthalmology, orthopaedics, paediatrics, physiotherapy, and audiology). The costs of these were estimated from the national cost reference table, with adjustment.

- Hospitalizations: The number of hospitalizations were collected from the questionnaire. For Rio de Janeiro, the electronic hospital database contained information on all procedures undertaken for these hospitalization events, which included surgical (e.g. gastrostomy tubes) and non-surgical procedures

(e.g. pneumonia treatment). These interventions were costed using the national cost reference table, with adjustment. We assumed that the mean medical direct cost of hospitalization by group of cases in Rio de Janeiro was a proxy of the cost in Pernambuco.

- Tests and exams: Tests and exams received were available for the children in the Rio de Janeiro arm of the study from the electronic hospital database, and these included reverse transcription polymerase chain reaction (RT-PCR), eye examination, hearing examination, fat and free mass composition, composite Bayley test[18], laboratory tests, and brain images (transfontanelle cerebral ultrasonography, computed tomography, and magnetic resonance imaging). The costs of these tests were estimated from the national cost reference table, with adjustment, except for the costs of RT-PCR, fat and free mass composition and composite Bayley test which were not included in the national cost reference table. Therefore, micro-costing was applied to estimate their costs using inputs from the from Brazilian government price databases and local suppliers. We did not include test and exam costs of children in the Pernambuco arm of the study.

All costs were converted into U$ 2017 at the exchange rate of 3.19 Brazilian reais/U$ (www.http://data.imf.org). No discounting or inflation rate adjustments were applied. Costs were annualized when necessary.

Calculation of family costs

Direct, and indirect costs incurred by the family were collected through the questionnaire.

- Direct costs included all out-of-pocket expenditure (food at healthcare facility, drugs, special milk formulas, glasses, and other health care expenses, as well as transportation, costs associated with family displacement from their home and the renovation of the patient's home). Costs were defined as catastrophic expenditures if total direct costs were equal or above 40% of yearly household income (estimated using the *Critério Brasil* based on assets and infrastructure of the household)[24].

- Indirect costs included the productivity loss of the caregiver and were estimated as the days of work lost to take care of the child, the time invested in transportation and the waiting time seeking for health services. The value of one workday was estimated using the median of household income provided by *Critério Brasil* divided by the number of persons living in the house and monthly working days. Coping costs (selling of assets and borrowed money) were measured through the questionnaire in order to understand how families handle these expenses.

Costs were calculated for a 12-month period. For children aged less than 12 months at interview, an extrapolation was made for the full 12 months based on monthly consumption data available.

Data analysis

Median and interquartile range (IQR), for continuous data and frequency distributions for categorical variables were used to describe the study sample, effort of main caregiver, and direct and indirect costs, all stratified by age, location and group (severe CZS, mild/moderate CZS no CZS).

Cost data was statistically analysed using the Kolmogorov-Smirnov test to assess the normality assumption. Differences between groups were verified through a pairwise comparison using the student's t-test and the Wilcoxon-Mann-Whitney. We also used chi-square test to compare categorical variables of effort of main caregiver between the groups. A 5% level was chosen as the level of significance. Data management and statistics analysis were performed using R (R Core Team. Foundation for Statistical Computing V, Austria, version 3.2.2) and Microsoft Excel (version 16.45). Costs were estimated for a one year period from the child birth date (i.e. the time horizon), and the year of analysis was 2017.

Ethical considerations

Ethical approval for the study was received from London School of Hygiene and Tropical Medicine (LSHTM) and the Fiocruz ethics committee (CAAE 60682516.2.1001.5269). All interviewees were adults and provided written informed consent, as outlined previously[14].

Results

Characteristics of study subjects

A total of 484 main caregivers were interviewed, 56% from Rio de Janeiro and 44% from Recife (Table 1). Of the 484 children, 36% (n=174) had severe CZS, 9% (n=41) mild/moderate CZS and 56% (n=269) were children not affected by CZS. The sample was made up of approximately equal numbers of boys and girls. Most of the children (70%) were more than one year old at the time of the interview. In Rio de Janeiro the children with severe CZS were on average younger than the those with no CZS, while in Pernambuco the opposite was true. Approximately half of the children lived outside of the cities of Rio de Janeiro and Recife. Mothers were the main caregivers for more than 93% of children. Overall and in Rio de Janeiro caregivers of children with severe CZS were generally younger than control caregivers, while in Pernambuco the groups were well matched on age. A high proportion of all caregivers lived with their partner (75%) and had nine or more years of education (82%). Overall, and in Rio de Janeiro, households of children with severe CZS were more likely to belong to the lowest socioeconomic class (39%) compared to controls (30%), but this difference was not observed in Pernambuco. The majority of households of children with severe CZS were receiving social benefits (62%), while this was less common in households of children with mild/moderate (34%) or no CZS (29%). Receipt of social benefits was more common in Pernambuco than Rio de Janeiro, across all three groups. Households were relatively similar in terms of household size and number of children, regardless of location and CZS status.

Table 1. Baseline characteristics of the study children and families stratified by location (Rio de Janeiro and Pernambuco) and group (severe CZS, mild/moderate CZS and no CZS), Brazil.

	Total sample			Rio de Janeiro (n=271)			Pernambuco (n=213)		
	Severe CZS (n=174)	Mild/ moderate CZS (n=41)	No CZS (n=269)	Severe CZS (n=95)	Mild/ Moderate CZS (n=19)	No CZS (n=157)	Severe CZS (n=79)	Mild/ Moderate CZS (n=22)	No CZS (n=112)
Child									
Sex									
Female	51%	61%	49%	45%	47%	52%	57%	32%	45%
Male	49%	39%	51%	55%	53%	48%	43%	68%	55%
Age (years)									
< 1 year	32%	24%	30%	50%	16%	31%	11%	32%	29%
≥ 1 year	68%	76%	70%	50%	84%	69%	89%	68%	71%
Residence									
Within the city (Rio/Recife)	45%	52%	55%	42%	58%	52%	47%	46%	61%
Outside city	55%	48%	45%	58%	42%	48%	53%	55%	39%
Main caregiver									
Mother	97%	97%	93%	98%	100%	96%	96%	96%	90%
Father	1%	0%	1%	1%	0%	1%	0%	0%	0%
Others	2%	3%	6%	1%	0%	3%	4%	4%	10%
Age (years)									
<25	40%	22%	28%	44%	5%	22%	37%	36%	36%
25–34	47%	37%	49%	48%	42%	49%	45%	32%	48%
≥ 35	13%	41%	23%	8%	53%	29%	18%	32%	16%
Marital Status									
Living as a couple	71%	93%	75%	71%	95%	81%	71%	91%	68%
Living alone	29%	7%	22%	29%	5%	19%	28%	9%	26%
Not Answered	0%	0%	3%	0%	0%	0%	1%	0%	6%
Schooling (years)									
<9	23%	10%	16%	19%	0%	11%	28%	18%	24%
≥ 9	77%	90%	84%	81%	100%	89%	72%	82%	76%
Household									
Socio-economic status[a]									
A (highest)	0%	2%	2%	0%	5%	2%	0%	0%	1%
B	13%	32%	17%	19%	53%	27%	5%	14%	4%
C	49%	34%	51%	53%	37%	55%	44%	32%	45%
D-E (lowest)	38%	32%	30%	28%	5%	16%	51%	54%	50%
Receive social benefits	62%	34%	29%	48%	22%	16%	75%	40%	43%
Size (persons)									
≤ 3	42%	49%	36%	44%	47%	40%	41%	50%	31%

	Total sample			Rio de Janeiro (n=271)			Pernambuco (n=213)		
	Severe CZS (n=174)	Mild/ moderate CZS (n=41)	No CZS (n=269)	Severe CZS (n=95)	Mild/ Moderate CZS (n=19)	No CZS (n=157)	Severe CZS (n=79)	Mild/ Moderate CZS (n=22)	No CZS (n=112)
4–5	44%	37%	52%	43%	37%	50%	44%	36%	55%
≥ 6	14%	14%	12%	13%	16%	10%	15%	14%	14%
Additional children[b]									
0	52%	61%	52%	52%	53%	56%	50%	68%	46%
1	33%	29%	32%	33%	42%	31%	33%	18%	34%
≥ 2	15%	10%	16%	15%	5%	13%	17%	14%	20%

CZS=congenital ZIKA syndrome

1 U$ = R$ 3.19 in 2017 average exchange rate.

[a] Household income was estimated according to *Critério Brasil*. A (mean family income: U$ 6,547.8); B (mean family income: B2 U$ 1,521.0 - B1 U$ 2.900,94); C (mean family income: C2 U$ 509.4- C1 U$ 847.96); D-E (mean family income: U$ 240.75)

[b] Excluding the current one.

Effort in seeking healthcare by the main caregiver

In the previous year approximately half of children with severe CZS (56%) and with mild/moderate CZS (44%) had to access at least three health care facilities, while utilization of three facilities was much rarer among children with no CZS (7%) (Table 2). Time taken to reach the healthcare facility for families of children with severe CZS was frequently more than three hours (46%), while this proportion was lower among children with mild/moderate CZS (20%) or no CZS (28%). Waiting time at the health care facility was often more than three hours, across the three CZS groups. These patterns were consistent in both Pernambuco and Rio de Janeiro, except effort scores were particularly low among the "no CZS" group in Pernambuco.

Health provider costs

The median health provider cost of outpatient visits for children with severe CZS (U$1,411, IQR 740-2,060) were significantly higher than children with mild/moderate CZS (U$264, 174-1,144, p<0.01) and those not affected by CZS (U$107, 74-209, p<0.01) (Table 3). Similarly, cost of tests and examinations (estimated only for Rio de Janeiro) were higher among children with severe CZS (U$637, 291-966) compared to mild/moderate CZS (U$179, 101-491, p<0.01) or no CZS (U$ 373, 119-644, p=0.04) groups. Median hospitalization costs were U$288 (0-661) for children with severe CZS, but U$0 for the other two groups (p<0.01 for both comparisons). Costs of visits and hospitalizations were significantly higher for children with mild/moderate CZS than no CZS. These patterns were broadly similar when stratified by location, although data on costs of tests and exams were not available for Pernambuco.

Family direct and indirect costs

Table 4 shows the direct and indirect costs incurred by families for each group of children. Total direct costs for food, transport or other items, were consistently higher for children with severe CZS (total U$1,129) compared to those with mild/moderate CZS (total U$231), which in turn were higher than for children with no CZS (total U$38). These patterns for direct costs were consistent in Rio de Janeiro and Pernambuco, although costs were generally higher in Rio de Janeiro, in particular transport costs. Median indirect costs were generally low. Productivity costs were higher for families with children with CZS compared to children without CZS. Stratification by location revealed more substantive indirect costs associated with Severe CZS in Rio de Janeiro, but that in the other groups and in Pernambuco these costs remained low.

Families of children with severe and mild/moderate CZS reported high levels of catastrophic expenditures considering the direct and indirect costs incurred by them during the care of their child. Expenses incurred by families as a proportion of household income was 30% (IQR=14%-67%) for children with severe CZS, 11% (IQR=4%-33%) for those with mild/moderate CZS, and 1% (IQR=0%-8%) for families of children not affected with CZS (p<0.01 for each comparison). In Rio de Janeiro, these figures were 34% (IQR=18%-68%) for families of children with severe CZS, 9% (IQR=5%-29%) for those with mild/moderate CZS, and 8% (IQR=3%-22%) for families of children not affected CZS. In Pernambuco, these figures were 27% (IQR=11%-67%) for families of children with severe CZS, 13% (IQR=4-45%) for those with mild/moderate CZS reported and 0% (IQR=0%-1%) for families of children not affect by CZS.

Discussion

The main purpose of our study was to estimate the direct and indirect costs of caring for children with CZS, from the family and health provider perspective, based on a study carried out in Rio de Janeiro and Pernambuco. This analysis was based on three groups of children, selected to represent the broad

Table 2. Effort of the main caregiver stratified by group (severe CZS, mild/moderate CZS and no CZS) and location (Rio de Janeiro and Pernambuco), Brazil.

	Total Sample				Rio de Janeiro				Pernambuco			
	Severe CZS (n=174)	Mild/ Moderate CZS(n=41)	No CZS (n=269)	P-value	Severe CZS (n=95)	Mild/ Moderate CZS (n=19)	No CZS (n=157)	P-value	Severe CZS (n=79)	Mild/ Moderate CZS (n=22)	No CZS (n=112)	P-value
Number of health care facilities where child received care												
- 1	17%	17%	60%		14%	16%	41%		20%	18%	86%	
- 2	27%	39%	33%		26%	52%	48%		28%	27%	12%	
- ≥3	56%	44%	7%		60%	32%	11%		52%	55%	2%	
Severe vs Mild/moderate				0.27				0.05				0.96
Severe vs no				<0.01				<0.01				<0.01
Mild/moderate vs no				<0.01				0.01				<0.01
Time taken to reach the health care facility in hours												
- < 1	8%	10%	39%		7%	11%	15%		9%	10%	73%	
- 1–2	23%	50%	21%		18%	47%	23%		30%	52%	18%	
- 2–3	23%	20%	12%		24%	21%	18%		21%	19%	4%	
- > 3	46%	20%	28%		51%	21%	44%		40%	19%	5%	
Severe vs Mild/moderate				<0.01				0.02				0.23
Severe vs no				<0.01				0.17				<0.01
Mild/moderate vs no				<0.01				0.08				<0.01
Waiting time in health care facility in hours												
- < 1	4%	0%	13%		2%	0%	2%		7%	0%	29%	
- 1–2	24%	15%	16%		17%	5%	10%		33%	24%	26%	
- 2–3	23%	18%	20%		24%	11%	17%		21%	24%	24%	
- > 3	49%	67%	51%		57%	84%	71%		39%	52%	21%	
Severe vs Mild/moderate				0.14				0.16				0.47
Severe vs no				<0.01				0.13				<0.01
Mild/moderate vs no				0.06				0.65				<0.01

CZS=congenital ZIKA syndrome

Wellcome Open Research 2021, 6:78 Last updated: 17 AUG 2021

Table 3. Median and Interquartile range (IQR) of direct costs to the health provider incurred by cases of Congenital Zika Syndrome and controls, during one year (USD in 2017 values).

	Total Sample				Rio de Janeiro				Pernambuco			
Cost item (Median, IQR)	**Severe CZS (n=174)**	**Mild/ Moderate CZS(n=41)**	**No CZS (n=269)**	**P-value**	**Severe CZS (n=95)**	**Mild/ Moderate CZS (n=19)**	**No CZS (n=157)**	**P-value**	**Severe CZS (n=79)**	**Mild/ Moderate CZS (n=22)**	**No CZS (n=112)**	**P-value**
Visits	1,411 (740; 2,060)	264 (174; 1,144)	107 (74; 209)		1,397 (824; 1,946)	221 (143; 302)	144 (41; 242)		1,475 (668; 2,132)	824 (230; 1,878)	83 (83; 132)	
Severe vs Mild/ moderate				<0.01				<0.01				<0.01
Severe vs no				<0.01				<0.01				<0.01
Mild/moderate vs no				<0.01				0.01				<0.01
Tests and exams[a]	-	-	-		637 (291; 966)	179 (101; 491)	373 (119; 644)		-	-	-	
Severe vs Mild/ moderate				-				<0.01				-
Severe vs no				-				0.04				-
Mild/moderate vs no				-				0.11				-
Hospitalizations	288 (0; 661)	0 (0; 43)	0 (0; 0)		288 (288; 761)	0 (0; 0)	0 (0; 0)		0 (0; 661)	0 (0; 995)	0 (0; 0)	
Severe vs Mild/ moderate				<0.01				0.41				<0.01
Severe vs no				<0.01				<0.01				0.06
Mild/moderate vs no				0.04				0.87				<0.01

CZS=congenital ZIKA syndrome

Average exchange rate on 2017: 1 US$ = 3.19 Reais.

[a] Only estimated for Rio de Janeiro.

IQR, Interquartile range.

Wellcome Open Research 2021, 6:78 Last updated: 17 AUG 2021

Table 4. **Median and interquartile range (IQR) of direct and indirect costs incurred by families of children with Congenital Zika Syndrome and controls, during one year (USD in 2017 values).**

	Total Sample				Rio de Janeiro				Pernambuco			
Cost item (Median, IQR)	**Severe CZS (n=174)**	**Mild/ Moderate CZS(n=41)**	**No CZS (n=269)**	**P-value**	**Severe CZS (n=95)**	**Mild/ Moderate CZS (n=19)**	**No CZS (n=157)**	**P-value**	**Severe CZS (n=79)**	**Mild/ Moderate CZS (n=22)**	**No CZS (n=112)**	**P-value**
Direct costs												
Food	150 (0; 455)	38 (0; 113)	13 (0; 53)		150 (0; 451)	47 (0; 94)	38 (13; 75)		83 (0; 578)	0 (0; 207)	0 (0; 0)	
Severe vs Mild/ moderate				<0.01				<0.01				0.76
Severe vs no				<0.01				<0.01				<0.01
Mild/moderate vs no				<0.01				0.16				0.01
Transport	135 (0; 609)	80 (0; 277)	25 (0; 113)		429 (56; 978)	120 (65; 278)	75 (28; 188)		0 (0; 41)	11 (0; 256)	0 (0; 0)	
Severe vs Mild/ moderate				<0.01				<0.01				0.85
Severe vs no				<0.01				<0.01				<0.01
Mild/moderate vs no				<0.01				0.04				0.01
Other[a]	843 (226; 1,777)	113 (0; 639)	NA		940 (414; 1,625)	113 (0; 527)	NA		677 (31; 2,072)	94 (0; 987)	NA	
Severe vs Mild/ moderate				<0.01				<0.01				<0.01
Severe vs no				-								-
Mild/moderate vs no				-								-
Total direct costs	**1,129**	**231**	**38**		**1520**	**307**	**113**		**760**	**105**	**0**	
Indirect costs												
Coping costs	0 (0; 157)	0 (0; 16)	NA		31 (0; 204)	0 (0; 16)	NA		0 (0; 75)	0 (0; 27)	NA	
Severe vs Mild/ moderate				<0.01				<0.01				0.10
Severe vs no				-				-				-

Wellcome Open Research 2021, 6:78 Last updated: 17 AUG 2021

	Total Sample				Rio de Janeiro				Pernambuco			
Cost item (Median, IQR)	**Severe CZS (n=174)**	**Mild/ Moderate CZS(n=41)**	**No CZS (n=269)**	**P-value**	**Severe CZS (n=95)**	**Mild/ Moderate CZS (n=19)**	**No CZS (n=157)**	**P-value**	**Severe CZS (n=79)**	**Mild/ Moderate CZS (n=22)**	**No CZS (n=112)**	**P-value**
Mild/moderate vs no				-				-				-
Productivity loss	45 (0; 1,163)	70 (0; 663)	0 (0;196)		327 (0; 1,482)	261 (0; 829)	29 (0; 255)		0 (0; 1,1934)	54 (0; 389)	0 (0;74)	
Severe vs Mild/ moderate				0.14				0.20				-
Severe vs no				<0.01				<0.01				-
Mild/moderate vs no				1.0				0.67				-
Total indirect costs	**45**	**70**	**0**		**358**	**261**	**29**		**0**	**53.5**	**0**	

CZS=congenital ZIKA syndrome

Average exchange rate on 2017: 1 US$ = 3.19 Reais.

[a] Includes drugs, special milk formulas and glasses.

IQR, Interquartile range.

NA, not available. This information was not collected for children without CZS

Wellcome Open Research 2021, 6:78 Last updated: 17 AUG 2021

spectrum of clinical presentations of this condition: children with severe, mild/moderate and no CZS. We also examined in depth the effort of the main caregiver in their interaction with the health care system, as children with CZS had a high consumption of resources, likely to continue throughout their lifetime. To the best of our knowledge, this was the first study to quantify the costs incurred from caring for a child with CZS from the health provider and family perspectives using primary data.

This study showed that children with severe or mild/moderate CZS accessed more healthcare facilities and reported longer travel and waiting times than children unaffected by Zika. Costs of outpatient visits were highest for children with severe CZS followed by children with mild/moderate CZS and children without CZS, although there was some variation between the two settings. Direct and indirect costs incurred by families were higher for families of children affected by Zika, in particular as a result of "other" costs, such as drugs and special milk formula.

Most of the main caregivers of children with CZS were mothers who experienced high time costs in seeking and accessing care for their children. One contributing factor to this high effort is that almost half of cases lived outside the metropolitan area of Rio de Janeiro and Recife and so healthcare services were situated far from households in both cities. The transportation costs incurred by caregivers were much higher in Rio de Janeiro than in Pernambuco, potentially because in the latter setting caregivers had access to public services provided by government to allow them to reach the healthcare facilities. Thus, given such high care needs in a context of fragmented health services provision, the coordination of the health system would be very helpful to caregivers, saving time and money[25].

Our analysis also shows that many families of children with CZS in both settings faced catastrophic expenditures, using a threshold based on a multi-country study, that included Brazil[24]. Catastrophic health expenditures had a high potential to lead to impoverishment, considering that about 40% of families of children with severe CZS reported an average monthly income of U$ 240.75. This situation was exacerbated by the Brazilian economic crisis that has been experienced since 2014, through increase in unemployment and austerity measures leading to a reduction in social expenditures and cuts in the health budget. According to Brazilian public policies, these children should be guaranteed access to health care services and transport systems. However, the high costs incurred by families of children with CZS in transport and drugs show that this has not happened. The impoverishment of households in Brazil due to costs of drugs has been demonstrated previously for other conditions[26]. It is also apparent that families of children with CZS should be given social benefits in order to reduce the financial impact experienced, yet at the time of the study only 62% of caregivers of children with severe CZS and 34% of those with mild/moderate CZS received social benefits. Enhancing and coordinating social and childcare policies is essential to support families in coping with the situation.

Another concern is that there are still gaps in services for children with CZS. Between 2015 and 2018, about 79% of children with CZS in Pernambuco had access to specialized health care services but only 35% in Rio de Janeiro[4], and nutritional services are also reported to be inadequate for these children[27]. Gaps in access to required healthcare services pose specific issues that need to be addressed by policymakers, as they highlight the need for a well-structured health care network that caters to all levels of assistance and avoids caregivers of children with CZS having to access many different facilities to seek care. It is likely that provision of these services will push the costs of caring for a child with CZS higher still but may also improve health status and thereby protect from other health care costs.

Meeting these costs will be challenging, since the current economic crisis in Brazil has meant that federal health spending will be limited over the next twenty years. The annual SUS budget was approximately USD $62 billion (USD$, 2017) before the funding process changed in 2018. Early estimates suggest that the SUS budget will suffer a cumulative loss of around U$190 billion between 2017 and 2036[28]. Thus, the states and municipalities may need to increase their share of responsibility for funding SUS, although this seems difficult as the *per capita* expenditure has been declining since 2015[11]. The economic crisis and austerity measures have been shown to impact negatively on social policies and contribute to the deterioration of health care systems offering universal coverage[29]. This issue will be affected still further by the ongoing COVID-19 pandemic. The Brazilian health care system is facing scarcity of resources, inefficient resource allocation and uncoordinated care that could worsen the health outcomes of most vulnerable populations, such as children with CZS, even further.

There are few studies that provide cost analyses of CZS in countries where ZIKV have been recorded and that would allow comparison with our findings. A recent economic analysis in the US used the productivity costs associated with autism as a *proxy* to estimate the costs of microcephaly. However, results were likely to be substantially underestimated because the costs associated with autism are lower than those of microcephaly[30]. In another study, the lifetime medical costs of microcephaly to selected countries of Latin America and Caribbean amount to U$180,004 per case (in 2015 U$) and considered the costs associated with severe intellectual disability in the US in 2003[31]. Both studies had to use assumptions to calculated costs of microcephaly because there is a dearth of previous estimates of the economic impact of microcephaly in many countries, and they lacked the primary data that we collected in the current study. A third study undertaken in Texas, USA also estimated high economic costs from inpatient hospitalization for babies with microcephaly, which may

provide insights into a potential impact of Zika. However, it is hard to infer costs from USA to Brazil or other Latin American settings[13].

There are several limitations of this study. The study was conducted in only two settings and therefore does not fully represent the entire country. Nevertheless, these states included 25% of confirmed and suspected cases of CZS in Brazil[4]. In Pernambuco and Rio de Janeiro, attempts were made to include all eligible children with severe CZS, but inclusion of children with mild/moderate CZS was less comprehensive and so they may not have been representative of cases in this category overall. Additionally, the sample selection approach varied in the two sites, which may have influenced comparability across Pernambuco and Rio de Janeiro. For instance, in Pernambuco the cases and controls were matched on location while in Rio de Janeiro they were not, which explains in part the greater socio-economic differences between these groups in Rio de Janeiro than Pernambuco. Consequently, cases in Rio de Janeiro may have been more at risk of catastrophic expenditure than controls. Notwithstanding these differences, the expenditure by cases in Rio de Janeiro (whether severe CZS or mild/moderate CZS) were greater than in Pernambuco, and the difference in catastrophic expenditure between severe and no CZS groups similar in the two settings. Another limitation is that we did not consider costs associated with tests and exams in Pernambuco, due to the lack of hospital electronic medical record data, and this may bias our cost results. Furthermore, children were classified as having "no CZS" on the basis of tests and reports from when they were under two years of age. However, developmental delays may have become apparent as the child became older, and there is increasing evidence that congenital infection with Zika may cause neurodevelopmental implications in children without CZS[32]. Consequently, some of the children in the "no CZS" group may have additional needs, and this may underestimate the true economic impact of CZS.

It is important to note, that while this study focused on economic costs, caring for a child with disabilities can have many positive outcomes. Furthermore, children with disabilities have fundamental human rights, including access to healthcare. Our purpose in this paper is to encourage appropriate budgeting and planning of services, and not to put into question the need for healthcare investment in children with disabilities.

Conclusions

Children affected by CZS incurred greater costs, both from the perspective of the health provider and the family. This study supports the need for additional public health resources to meet the needs of those affected. Moreover, the magnitude of costs attributable to CZS for the families affected, and the high levels of catastrophic expenditure, shows a need to develop health related financial risk protection initiatives for households of children with CZS, and other comparable health situations.

Data availability

Underlying data

Data associated with this study will not be made freely available, owing to the small number of children with CZS, making data potentially identifiable, and the sensitive nature of the subjects discussed in the interviews. However, we are committed to collaborating with other researchers in the analysis of our data (full questionnaire available online)[14]. Applications for access to the raw data for this study should be made by contacting Professor Hannah Kuper (hannah.kuper@lshtm.ac.uk), Dr Tereza Maciel Lyra (terezalyra@cpqam.fiocruz.br) or Dr Maria Elisabeth Lopez Moreria (bebeth@iff.fiocruz.br) and outlining the purpose of the proposed analyses and the variables requested. These applications will be reviewed by the three researchers, and if accepted, the requested variables will be shared.

Extended data

Open Science Framework: Social and Economic Impact of Congenital Zika Syndrome questionnaire. https://doi.org/10.17605/OSF.IO/XJEP7[20].

This project contains the following extended data:

- Questionnaire

References

1. World Health Organization: **Director-General Summarizes the Outcome of the Emergency Committee Regarding Clusters of Microcephaly and GuillainBarré Syndrome**. Geneva: WHO, 2016.
Reference Source
2. PAHO: **Zika cumulative cases - 4 January 2018**. Washington DC: PAHO; 2018.
Reference Source
3. de Oliveira WK, de França GVA, Carmo EH, *et al.*: **Infection-related microcephaly after the 2015 and 2016 Zika virus outbreaks in Brazil: a surveillance-based analysis.** *Lancet.* 2017; **390**(10097): 861–70.
PubMed Abstract | Publisher Full Text
4. **Monitoramento integrado de alterações no crescimento e desenvolvimento relacionadas à infecção pelo vírus Zika e outras etiologias infecciosas, até a Semana Epidemiológica 20/2018**. 2018.
Reference Source
5. Freitas DA, Souza-Santos R, Carvalho LMA, *et al.*: **Congenital Zika syndrome: A systematic review.** *PLoS One.* 2020; **15**(12): e0242367.
PubMed Abstract | Publisher Full Text | Free Full Text
6. Orofino DHG, Passos SRL, de Oliveira RVC, *et al.*: **Cardiac findings in infants with in utero exposure to Zika virus- a cross sectional study.** *PLoS Negl Trop Dis.* 2018; **12**(3): e0006362.
PubMed Abstract | Publisher Full Text | Free Full Text
7. Lopes Moreira ME, Nielsen-Saines K, Brasil P, *et al.*: **Neurodevelopment in**

Infants Exposed to Zika Virus In Utero. *N Engl J Med.* 2018; **379**(24): 2377–9.
PubMed Abstract | Publisher Full Text | Free Full Text

8. Cohen E, Kuo DZ, Agrawal R, *et al.*: **Children with medical complexity: an emerging population for clinical and research initiatives.** *Pediatrics.* 2011; **127**(3): 529–38.
PubMed Abstract | Publisher Full Text | Free Full Text

9. de Melo APL, Lyra T, de Araújo TVB, *et al.*: **"Life Is Taking Me Where I Need to Go": Biographical Disruption and New Arrangements in the Lives of Female Family Carers of Children with Congenital Zika Syndrome in Pernambuco, Brazil.** *Viruses.* 2020; **12**(12): 1410.
PubMed Abstract | Publisher Full Text | Free Full Text

10. Doniec K, Dall'Alba R, King L: **Brazil's health catastrophe in the making.** *Lancet.* 2018; **392**(10149): 731–2.
PubMed Abstract | Publisher Full Text

11. Massuda A, Hone T, Leles FAG, *et al.*: **The Brazilian health system at crossroads: progress, crisis and resilience.** *BMJ global health.* 2018; **3**(4): e000829.
PubMed Abstract | Publisher Full Text | Free Full Text

12. Alfaro-Murillo JA, Parpia AS, Fitzpatrick MC, *et al.*: **A Cost-Effectiveness Tool for Informing Policies on Zika Virus Control.** *PLoS Negl Trop Dis.* 2016; **10**(5): e0004743.
PubMed Abstract | Publisher Full Text | Free Full Text

13. Shewale JB, Ganduglia Cazaban CM, Waller DK, *et al.*: **Microcephaly inpatient hospitalization and potential Zika outbreak in Texas: A cost and predicted economic burden analysis.** *Travel Med Infect Dis.* 2019; **30**: 67–72.
PubMed Abstract | Publisher Full Text

14. Kuper H, Lyra TM, Moreira MEL, *et al.*: **Social and economic impacts of congenital Zika syndrome in Brazil: Study protocol and rationale for a mixed-methods study [version 2; peer review: 2 approved].** *Wellcome Open Res.* 2019; **3**: 127.
PubMed Abstract | Publisher Full Text | Free Full Text

15. de Lima LD, Machado CV, O'Dwyer G, *et al.*: **Interdependence between government levels in Brazilian health policy: the implementation of Emergency Care Units in the State of Rio de Janeiro, Brazil.** *Cien Saude Colet.* 2015; **20**(2): 595–606.
PubMed Abstract | Publisher Full Text

16. Albuquerque MdSVd, Lima LP, Costa AM, *et al.*: **Regulação assistencial no recife: possibilidades e limites na promoção do acesso.** *Saúde e Sociedade.* 2013; **22**(1): 223–36.
Publisher Full Text

17. de Araujo TVB, de Alencar Ximenes RA, de Barros Miranda-Filho D, *et al.*: **Association between microcephaly, Zika virus infection, and other risk factors in Brazil: final report of a case-control study.** *Lancet Infect Dis.* 2018; **18**(3): 328–336.
PubMed Abstract | Publisher Full Text

18. Bayley N: **Bayley scales of infant and toddler development**. 3 ed. SAn Antonio, TX: Pearson; 2006.
Reference Source

19. Bryant GM, Davies KJ, Newcombe RG: **The Denver Developmental Screening Test. Achievement of test items in the first year of life by Denver and Cardiff infants.** *Dev Med Child Neurol.* 1974; **16**(4): 475–84.
PubMed Abstract | Publisher Full Text

20. Kuper H: **Social and Economic Impact of Congenital Zika Syndrome questionnaire**. 2021.
http://www.doi.org/10.17605/OSF.IO/XJEP7

21. Thompson S, Wordsworth S: **An Annotated Cost Questionnaire for Completion by Patients**. On behalf of the UK Working Party on Patient Costs. 2001.
Reference Source

22. Pinto M, Entringer AP, Steffen R, *et al.*: **Cost analysis of nucleic acid amplification for diagnosing pulmonary tuberculosis, within the context of the Brazilian Unified Health Care System.** *J Bras Pneumol.* 2015; **41**(6): 536–8.
PubMed Abstract | Publisher Full Text | Free Full Text

23. Steffen RE, Caetano R, Pinto M, *et al.*: **Cost-effectiveness of Quantiferon®-TB Gold-in-Tube versus tuberculin skin testing for contact screening and treatment of latent tuberculosis infection in Brazil.** *PLoS One.* 2013; **8**(4): e59546.
PubMed Abstract | Publisher Full Text | Free Full Text

24. Xu K, Evans DB, Kawabata K, *et al.*: **Household catastrophic health expenditure: a multicountry analysis.** *Lancet.* 2003; **362**(9378): 111–7.
PubMed Abstract | Publisher Full Text

25. Albuquerque MSV, Lyra TM, Melo APL, *et al.*: **Access to healthcare for children with Congenital Zika Syndrome in Brazil: perspectives of mothers and health professionals.** *Health Policy Plan.* 2019; **34**(7): 499–507.
PubMed Abstract | Publisher Full Text | Free Full Text

26. Boing AC, Bertoldi AD, Posenato LG, *et al.*: **The influence of health expenditures on household impoverishment in Brazil.** *Rev Saude Publica.* 2014; **48**(5): 797–807.
PubMed Abstract | Publisher Full Text | Free Full Text

27. Dos Santos SFM, Soares FVM, de Abranches AD, *et al.*: **Infants with microcephaly due to ZIKA virus exposure: nutritional status and food practices.** *Nutr J.* 2019; **18**(1): 4.
PubMed Abstract | Publisher Full Text | Free Full Text

28. Instituto de Pesquisa Econômica Aplicada: **O impacto do Novo Regime Fiscal para o financiamento da saúde**. Brasília: Instituto de Pesquisa Econômica Aplicada, 2016.
Reference Source

29. Stuckler D, Basu S: **The body economic: why austerity kills**. New York: Basic Books, 2013.
Reference Source

30. Lee BY, Alfaro-Murillo JA, Parpia AS, *et al.*: **The potential economic burden of Zika in the continental United States.** *PLoS Negl Trop Dis.* 2017; **11**(4): e0005531.
PubMed Abstract | Publisher Full Text | Free Full Text

31. United Nations Development Programme: **A Socioeconomic Impact Assessment of the Zika Virus in Latin America and the Caribbean: with a focus on Brazil, Colombia and Suriname**. New York: UNDP, 2017.
Reference Source

32. Mulkey SB, Arroyave-Wessel M, Peyton C, *et al.*: **Neurodevelopmental Abnormalities in Children With In Utero Zika Virus Exposure Without Congenital Zika Syndrome.** *JAMA Pediatr.* 2020; **174**(3): 269–276.
PubMed Abstract | Publisher Full Text | Free Full Text

Open Peer Review

Current Peer Review Status: ? ?

Version 1

Reviewer Report 17 August 2021

https://doi.org/10.21956/wellcomeopenres.18327.r45092

?

Shenglan Tang
Global Health Research Center, Duke Kunshan University, Jiangsu, China

The paper addresses an important topic that has not been adequately studied, due to its complexity, particularly LMICs. Hence, I very much enjoyed reading the manuscript. Below are a few comments which I would like to raise.

1. While the overall study design seems appropriate, there are a few significant differences in the selection of cases and controls, and sources of information collected in the two study sittings, which could potentially result in questions on the interpretation of its findings. I understand that the authors of the paper have identified this as one of the major study limitations. I am wondering if it might be better to use one study setting to present the study, although the sample size has to reduce greatly.

2. We all know that the collection of accurate information on annual household income is a great challenge. Many households intended to under-report their income levels. I would like to know any potential under-reporting of the income level that occurred in the study.

3. Is there any reasonable assumption that the mean medical direct cost of hospitalization by group of cases in Rio de Janeiro was a proxy of the cost in Pernambuco?

4. The study did not include the test and exam costs of children in the arm of Pernambuco, which might not be small. Have the authors got any sense of the extent to which the estimated cost of healthcare in Pernambuco was under-calculated?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health service research, disease control

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 05 August 2021

https://doi.org/10.21956/wellcomeopenres.18327.r45014

?

Hugo Turner
School of Public Health, Imperial College London, London, UK

Overall this is a very well written manuscript on an important topic. The economic burden on caregivers/families is an understudied but pertinent issue in global health and I enjoyed reading this paper.

I have the following comments/suggestions:

- "Indirect costs from families and main caregiver (e.g. productivity loss/opportunity cost)". I think the different cost terms need to be expanded/more clearly defined - ideally in a box or table.

- Did you include lost unpaid work in the productivity cost calculations or just lost paid work? If unpaid work was not included, please expand on this in the discussion. This could potentially partly explain the difference in Productivity costs between the different locations.

- Are you intending to measure the incidence of catastrophic expenditure or catastrophic health expenditure (the latter was referenced in [24]). Please add more detail and justification about the methodology used for these calculations and provide more

references.

- If possible, expand more in the discussion regarding what were the cost factors that contributed most to the economic burden (i.e. transport or food etc). Consider expanding on the "other" cost category for table 4 in the methods.

- “Costs were annualized when necessary.” Did you annualize them as economic costs (if so what discount rate did you use) or as financial cost (i.e. straight line depreciation)? What was used as the lifespan of the capital items?

- *“The number of consumed resources (outpatient visits, hospitalizations, and tests) were multiplied by the costs on the national cost reference table and adjusted by a factor of x3.51, as suggested in the literature[22,23]. This factor was estimated by an analysis of the cost of some procedures, as the national cost reference table did not reflect the real cost of these procedures as it had not been updated for approximately eight year”.* Is this intended to be a cost-to charge ratio adjustment? If so I would state this more clearly.

- “First, the primary caregiver (usually the mother) was interviewed using a semi-structured questionnaire, between May 2017 and January 2018 (full questionnaire available as extended data”. This sentence is missing a bracket at the end.

- The wording used to label US$ varies between USD ,USD $, $US, and U$. Please edit to be consistent.

- Consider changing Productivity loss to Productivity costs in the results tables.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health economics, infectious diseases, global health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.