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The economic burden of congenital Zika Syndrome in Brazil: an overview at 5 years and 10 years

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ABSTRACT

Background The aim of this paper is to estimate the economic burden of children with congenital Zika Syndrome (CZS) in Brazil over 5–10 years.

Methods We conducted a modelling study based on data collected in a case–control study in Brazil, including children with CZS (cases) and typically developing children (controls), born in 2015 and 2016. In total, 484 participants were recruited in two sites, Recife and Rio de Janeiro. Social and economic information was collected in a survey from the carers of cases and controls, and detailed healthcare utilisation was recorded for each child in the Rio de Janeiro cohort prospectively in a database. We used this information to estimate the cost per child with severe, moderate and no CZS and incremental cost per child with severe and moderate versus no CZS from a disaggregated societal perspective. These estimates were incorporated into an economic burden model to estimate the incremental burden of the CZS epidemic in Brazil over 5 years and 10 years.

Findings The societal cost per child with severe CZS was US$50 523 to 10 years of age (born in 2015 and 2016), substantially higher than the costs for moderate CZS (US$29 283) and without CZS (US$12 331). The incremental economic burden of severe versus no CZS in Brazil over 10 years was US$69.4 million from the household and US$129.0 million from the government perspective. For moderate CZS, these figures amounted to US$204.1 million and US$86.6 million. Over 10 years, 97% of the total societal economic cost of severe CZS is borne by the government, but only 46% for moderate CZS.

Interpretation The economic burden of CZS is high at the household, provider and government levels. The compensatory government payments helped to alleviate some of the additional costs incurred by families with a child qualifying for the disability benefits, and could be scaled to include the children with moderate CZS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Some studies have published modelled estimates of the economic burden of congenital Zika Syndrome (CZS) in the Latin American region; however, none of them based their model on locally collected data of children with CZS but used extrapolation of proxy measures such as the lifetime cost of intellectual impairment in the USA.

WHAT THIS STUDY ADDS

⇒ Our study will be the first to describe in detail the economic burden to family, government and society of having a baby with CZS by modelling data collected from babies with CZS as well as controls and their caretakers in two sites in Brazil.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study shows the high economic burden to the household, provider and government; however, it also shows that the compensatory government payments helped to alleviate some of the additional costs incurred by families with a child qualifying for the disability benefit in Brazil, which could be scaled to include a broader range of children with CZS, but also other disabilities.

INTRODUCTION

Since 2009, WHO has declared a total of six Public Health Emergency of International Concern, all of which have been caused by infectious diseases and have, therefore, brought the threat of widespread global transmission leading to death, illness and adverse social and economic consequences. In 2015, the world's attention was drawn to Brazil when the mosquito-transmitted Zika virus (ZIKV) infection during pregnancy was linked to the birth of thousands of babies born with microcephaly.[1–3] Microcephaly is a condition where a baby is either born with a small head or the head stops growing normally after birth.[4]

Between late 2015 and end of 2017, a total of 18 282 suspected cases of microcephaly were recorded in Brazil, of which 3474 (19%) were confirmed as cases by December 2019 with the true number likely to be much higher.[5] But microcephaly is only one of the possible

complications found in neonates exposed to ZIKV during pregnancy. Evidence has emerged that ZIKV infection during pregnancy is also linked to a broader range of conditions in the child, including visual, hearing, cognitive and musculoskeletal abnormalities, collectively called 'congenital Zika Syndrome' (CZS), which is the term we will use in this paper.[6–9] CZS shares similarities with cerebral palsy (CP),[10] as both are neurodevelopment disorders associated with a broad range of impairments. Indeed, Marques *et al* showed that in their study sample, 90% of 39 children with CZS met the criteria for the diagnosis of CP.[11] A clear case definition of CZS is currently still lacking, as more evidence of the syndrome is emerging over time.

The immediate emphasis in response to the ZIKV epidemic was on the prevention of infection, development of diagnosis and treatment, and avoidance of pregnancy. Mitigating the social and economic impacts of CZS received less attention, although these are likely to be substantial, for both families and the government. Carers of children with disabilities experience increased costs, both direct costs (eg, drugs) and indirect costs (eg, foregone wages of carer),[12] often leading to financial difficulties.[13] These financial pressures further increase the risk of anxiety and depression, which are already commonly experienced by parents of disabled children.[14–16] Purely model-based estimates suggest that the lifetime costs per microcephaly case are around $191 102 and $28 818 ($ refer to US$ unless is otherwise specified) for Latin America and the Caribbean, respectively. These estimates were calculated without collecting data on resource use or cost and were conservatively based on the extrapolation of the lifetime costs of a case of intellectual impairment in the USA.[17] Another study conducted by UNDP assessing the socioeconomic impact of Zika used the same modelled cost data in their model.[18] A third study conducted in Puerto Rico evaluating the cost effectiveness of contraception during the Zika outbreak used the MarketScan Commercial Database based on US residents covered by employer-sponsored insurance to estimate a lifetime cost of $3 788 843 ($2 243 124–$5 545 652) per severe case of CZS[19] and was based on a sample size of four children with CZS. While the Brazilian unified health system (Sístema único de Saúde) is providing universal access to healthcare services for its population, including children with CZS,[20] there is likely a gap between what the health system provides and what services families access. A better understanding of the true social and economic burden experienced by the families and their support needs is paramount for governments to be able to tailor services and budget adequately.

The aim of this paper is to estimate the economic burden of children affected by CZS to the government, household and society in Brazil, measured over the medium term, taken here to represent up to 5–10 years of age. The term 'burden' is used to be consistent with the economic literature, but not to suggest that children with CZS are themselves a burden. This paper builds on our previous work estimating the incremental cost of having a baby with CZS measured over the first 2 years of life[21] (incremental cost is the additional cost experienced by one group vs another in this case of a baby with vs a baby without CZS). The lessons learnt in this paper could be applicable to future epidemics, where an infection during pregnancy causes congenital brain abnormalities. Furthermore, to the best of our knowledge, this paper is the first describing in detail the economic burden to both family and government of having a baby with a severe congenital disability by using a mixture of bottom-up and reference costing methods.

METHODS

Overview and setting

We conducted a modelling study based on data collected in a case–control study, including children with microcephaly or other CZS manifestation (cases) and children without microcephaly or other CZS manifestation (controls), born from late 2015 through 2016.[10] (To clarify, the term modelling the costs refers to simulating the costs based on a model over a longer than measured time period.) The case–control study was undertaken in two different sites in Brazil: Recife in Pernambuco State, which was the epicentre of the epidemic, and Rio de Janeiro, which was less affected. Social and economic information was collected in a survey from the carers of cases and controls in both sites, and detailed healthcare utilisation was recorded for each child in the Rio de Janeiro Cohort prospectively in a database over time.[10] The survey information was used to estimate the household costs and the healthcare utilisation information to estimate the health provider cost. This information allowed us to estimate the cost per child with severe, moderate and no CZS as well as the incremental (=additional) costs of a child with (1) severe and (2) moderate CZS versus no CZS from the health provider, government, family and societal perspective over 5 years and 10 years. These estimates were incorporated into an economic burden model to estimate the total economic burden of the CZS epidemic in Brazil to 5 years and 10 years of age by calculating the total and incremental cost for all estimated cases of severe and moderate versus no CZS in Brazil.

Recruitment and data collection

In Pernambuco, cases and controls were selected from two different studies. Most cases came from an existing case–control study and some from an ongoing cohort of children with microcephaly. Cases were children born with a head circumference by at least two SD smaller than the mean for their sex and gestational age on the Fenton growth chart (case control) or Intergrowth standard (cohort).[22] A very similar definition was used by the Ministry of Health in Brazil for all cases of suspected microcephaly that were being included for further clinical investigation, although their approach has changed

Table 1 Definition of cases and controls used in study and by Ministry of Health in Brazil

	CZS/microcephaly cases	Controls/not microcephaly cases	Other disabilities included in controls
Ministry of Health, Brazil	In the beginning of the microcephaly epidemic, the Brazilian Ministry of Health defined a more sensitive parameter (HC ≤33 cm, for both sex), but it changed in December 2015 (HC ≤32 cm), to reduce the number of false positive cases. In March of 2016, under WHO recommendation, it was modified to 31.5 cm for girls and 31.9 cm for boys, for full-term newborn. From August 2021, the Intergrowth standard was adopted, being even more specific, as the HC 30.24 cm for girls and 30.54 cm for boys, for those born at 37 weeks or more. Suspected microcephaly cases sent for investigation: ► Term newborns: <–2 SD (WHO Standards) ► Preterm newborns: <–2 SD of Intergrowth[22] reference by gestational age and sex If <–3 SD classified as severe microcephaly	See changing case definition over time	n/a
Case–control study in Pernambuco	Severe CZS included children with head circumference at least –3 SD than the mean for sex and gestational age on the Fenton growth chart and mild/moderate if at least –2 SD. All cases had mothers with a laboratory confirmed ZIKV infection during pregnancy	Above –2 SD HC than the mean for sex and gestational age on the Fenton growth chart for children from the case–control study and compared with the Intergrowth standard in the cohort study	Excluded based on Denver II Developmental Screening Test conducted with caregivers of controls
Cohort study in Rio de Janeiro	Born to mothers that were ZIKV positive during pregnancy with microcephaly or significant developmental delays. Microcephaly was assessed as above, defining an HC of –3 SD as severe and of –2 SD as moderate (using Intergrowth standard) and other children were assessed using the Bayley Scale of Infant Development[25]) and/or by assessment by two paediatricians Severe: Bayley score of <70 Moderate: Bayley score of 70–<85	A head circumference of above -2SD on the Intergrowth standard and a Bayley score of ≥85 between 6 months and 36 months of age	Included N=3, prevalence of 1.6% in control group. As comparison, the prevalence of at least one disability in the 0–9 year age group in the National Health Survey in 2013 was 1.6%[28]

CZS, congenital Zika Syndrome; HC, head circumference; SD, Standard Deviation; ZIKV, Zika virus.

3× since 2015 (table 1).[23] In Pernambuco, cases were classified as 'severe' if the head circumference was more than 3 SDs below the mean and as 'mild/moderate' if head circumference was between 2 SDs and 3 SDs smaller. Controls had a head circumference above –2 SDs, did not have any neurological or other health problems, were born in the same hospitals and were matched to cases by expected date of delivery and maternal residence. During the follow-up period, the Denver II Developmental Screening Test was conducted and if this identified developmental delays in a child in the control group, this child was excluded from the study and referred for further investigation (see the online supplemental appendix, p3 for more detail).

In Rio de Janeiro, cases and controls were recruited from an existing cohort study (ClinicalTrials.gov) set up to study the impact of CZS.[24] Cases were born to mothers known to be ZIKV positive with either (1) microcephaly or significant developmental delay and/or other clinical conditions consistent with CZS ('severe CZS') or (2) less severe developmental delay ('mild/moderate CZS'). Control subjects were born to mothers without a history of symptoms and without developmental delay. Assessment of both cases and controls without microcephaly was based on the Bayley Scale of Infant Development[25] following the recommended guidelines and/or assessment by two paediatricians based on the child's medical records (see table 1 for an overview and online supplemental appendix, p3 for more detail).

According to case and control definitions, children in both settings were categorised 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.

In both sites, caregivers were interviewed by trained female interviewers either in their home, health facility or occasionally their workplace between May 2017 and January 2018. The questionnaire collected information on healthcare utilisation, direct and indirect costs, socioeconomic status of caregivers, and other parental indicators (eg, mental health indicators and social support). An electronic medical records database recorded detailed healthcare utilisation for each child in the Rio de Janeiro cohort prospectively between August 2015 and 31 May 2018. Hospital data from electronic medical records that included hospitalisations, tests and exams were not

available for Pernambuco. Costs for each procedure or resource were taken from the Brazilian cost reference table (SIGTAP), and when not available they were calculated using an ingredients approach.[26 27] A small number of additional parameters (eg, to calculate the cost of a wheelchair) were based on expert opinion. Details can be found in table 2 and on p4 in the online supplemental appendix.

Data analysis

Costs to the health provider, government, household and society as well as health burden were estimated separately for three groups: (1) 'severe CZS', (2) 'mild/moderate CZS' and (3) controls= 'no CZS'. Costs were subsequently modelled over 5 years and 10 years. First, the total cost per child for each group and the incremental cost per child of severe CZS as well as mild/moderate CZS compared with 'no CZS' was calculated. Thereafter, the cost per child and the estimated number of cases of CZS in Brazil were used to model for the whole of Brazil the total economic burden for each group as well as the incremental economic burden of severe CZS and mild/moderate CZS compared with 'no CZS'.

Children with a ZIKV-unrelated disability in the control group in Rio (not in Pernambuco) were included in the analysis (N=3, equals 1.6% prevalence in the control group; conditions were dwarfism, osteogenesis imperfecta and hypoxic ischaemic lesions) to ensure the control group and its estimated cost is relatively representative of the general population in Brazil. For comparison, the prevalence of at least one disability in the 0–9 year age group was 1.6% in the National Health Survey 2013 (95% CI 1.4% to 1.9%).[28]

Health provider costs

Health provider costs were calculated from health utilisation data recorded prospectively from 280 children in Rio de Janeiro, of which 95 had severe CZS, 19 moderate CZS and 166 no CZS. The health provider costs were calculated by multiplying the number of consumed resources (eg, specialist or non-specialist outpatient visits) from the medical records database from Rio de Janeiro times the cost for each procedure/resource as indicated on SIGTAP.[27] Costs on SIGTAP have been shown to underestimate the true cost to the health provider and hence we followed the national cost-effectiveness literature, which suggests to adjust costs indicated on the database by a factor of 3.51.[29 30] Provider costs were split into four cost categories: visits (specialised and non-specialised), hospitalisations, drugs/tests and other. The 'other' group included special interventions such as orthopaedic surgery or prothesis. Costs were estimated per group (severe, moderate and no CZS) and per year (table 3) up to the first 3 years of age, depending on the date of birth of the child, with data from 280, 277 and 109 children in the first year, second year and third year, respectively (for more detail on sample size per group and year and extrapolation of costs, please see online supplemental appendix table S1 and p4).

Household costs

First year and second year of life out of pocket payments and indirect costs (ie, lost household income due to caregiving) were estimated using the survey data stratified by children's age (≤1 year and >1 year). In total, 484 caregivers, 271 from Rio de Janeiro and 213 from Recife were interviewed. The average cost per year and per child was calculated for the first year and second year of life and presented in 12 cost subcategories grouped into irregular and regular (ie, recurring costs) to facilitate subsequent modelling. The irregular costs were not modelled beyond the measured years due to too much uncertainty (see table 3).

Data analysis

Data analysis was conducted in SPSS 25, STATA SE 16, Microsoft Excel 2013 and R. Cost results per child stratified by group (severe CZS, moderate/mild CZS and control) were valued in 2017 US$ using an exchange rate of R$/US$3.19.[31]

Epidemiological parameters

Estimates of the number of severe CZS cases in Brazil were obtained from the Ministry of Health up to December 2019: 3474 cases were confirmed from a total of 18 282 suspected cases, with a case definition consistent with severe CZS. In addition, 743 cases were probable, 615 inconclusive and 2659 under investigation.[5] The base analysis (minimum) used the confirmed cases only. The number of children with mild/moderate CZS in Brazil is unknown, but a cohort study from Rio de Janeiro conducted with children exposed to ZIKV infection in pregnancy provides insights for the model. Out of a total of 216 children at 7–32 months of age, 2.7% had microcephaly (3.7%, but in two cases microcephaly resolved during follow-up), 31.5% scored below average in neurodevelopment and/or abnormal eye or hearing assessments with 12% scoring below −2 SDs in at least one domain.[32] Based on these findings and discussion with researchers and physicians working with the children with CZS in Brazil, the number of cases of mild/moderate CZS in Brazil in our model were conservatively assumed to be 5× the number of cases of severe CZS. Specific annual mortality rates were applied to each group at the end of each year in the model, with annual mortality rates as observed in the Rio de Janeiro cohort used for severe CZS and national mortality rates for mild/moderate CZS and controls (table 2). Disability adjusted life years (DALYs) were calculated for each group using disability weights from a report on the economic impact of CP in Australia, verified by study physicians and researchers working with the children in Recife and Rio de Janeiro[33] (table 2).

Economic burden model

A model to estimate the economic burden of CZS in Brazil was built in Excel 2013 and analysed from the

Table 2 Other parameters used in model

	Estimate	Distribution	Reference/source
Additional cost parameters and assumptions			
Parameters to estimate cost of wheelchair to both household and provider			
% of children needing a wheelchair: severe CZS	81.9%	Point estimate	Expert opinion
% of children needing a wheelchair: moderate CZS	5.0%	Point estimate	Expert opinion
% of children needing a wheelchair: no CZS	0.1%	Point estimate	Expert opinion
Wheelchair cost to the health provider (R$962.5) US$, 2017	301.4	Point estimate	[27]
Wheelchair cost (incl. adaptation) to the household (R$4000) US$, 2017	1252.7	Point estimate	Expert opinion
Replacement wheelchair at age (years)	3,4,5,6,7 and 10	Point estimate	Expert opinion
Other costs to the government (education and disability benefit)			
Special creche from age 3 years for CZS (federal payment per pupil R$4420.7) US$, 2017	1384.5	Gamma*	[45]
Primary education from age 4 (federal payment per pupil: R$4080.7) US$, 2017	1278.0	Gamma*	[37]
Ratio cost special needs education/cost primary education	1.2	Lognormal	Expert opinion
Disability benefit per year (monthly min. wage: R$937) US$, 2017	3521.5	Point estimate	[46]
Parameters to model costs and outcomes			
General			
Discount rate costs	5%	Point estimate	[35]
Discount rate outcomes	5%	Point estimate	[35]
Model length (years)	5 and 10	Assumption	
Exchange rate Brazilian Real to US$, 2017	0.31	Point estimate	[31]
Average annual inflation rate Brazil 2008–2017 (mean, SE)	6.1%, 1.9%	Beta	[36]
Modelling clinical burden			
Mortality severe CZS year 1 (%, alpha, beta)	4.9%, 6, 116	Beta	Estimated from Rio de Janeiro Cohort
Mortality severe CZS year 2 (%, alpha, beta)	2.6%, 3, 113	Beta	Estimated from Rio de Janeiro Cohort
Mortality severe CZS year 3 (%, alpha, beta)	0.9%, 1, 112	Beta	Estimated from Rio de Janeiro Cohort
Mortality severe CZS year 4 (%, alpha, beta)	0.9%, 1, 111	Beta	Assumed to be the same as year 3
Mortality severe CZS year 5 (%, alpha, beta)	0.9%, 1, 110	Beta	Assumed to be the same as year 3
Mortality severe CZS year 6–10 per year (%)	0.3%	Beta	Assumed to be 1/3 of mortality in years 3–5
Mortality Brazil (moderate CZS and controls) year 1 (%, alpha, beta)	1.30%, 13.0, 987.0	Beta	[47]
Mortality Brazil (moderate CZS and controls) year 2 (%, alpha, beta)	0.10%, 1.0, 999.0	Beta	Estimate based on infant and <5-year mortality[47]
Mortality Brazil (moderate CZS and controls) year 3 (%, alpha, beta)	0.03%, 0.3, 999.7	Beta	Estimate based on infant and <5-year mortality[47]
Mortality Brazil (moderate CZS and controls) year 4 (%, alpha, beta)	0.03%, 0.3, 999.7	Beta	Estimate based on infant and <5-year mortality[47]
Mortality Brazil (moderate CZS and controls) year 5 (%, alpha, beta)	0.03%, 0.3, 999.7	Beta	Estimate based on infant and <5-year mortality[47]
Mortality Brazil (moderate CZS and controls) year 6–10 per year (%, alpha, beta)	0.01%	Beta	Assumed to be 1/3 of mortality in years 3–5

Continued

Table 2 Continued

	Estimate	Distribution	Reference/source
Cases of CZS Brazil confirmed	3474	Point Estimate	[5]
Cases of CZS Brazil under investigation	2659	point estimate	[5]
Cases of CZS Brazil probable	743	Point estimate	[5]
Cases of CZS Brazil deceased (fetal death, stillbirth, infant death and child death)	505	Point estimate	[5]
Disability weight severe cerebral palsy for severe CZS	0.82	Lognormal *	[33]
Disability weight mild/moderate cerebral palsy for mild/moderate CZS	0.36	Lognormal *	[33]
Length disability=time horizon of model (years)	5 and 10	Point estimate	Decided by study team

Table 2 shows parameters used in the economic burden model, that were not estimated in the costing analysis. This includes parameters to model the cost of a wheelchair as well as other costs to the government, general model parameters such as discount rate and also parameters to model the epidemiological burden of CZS.
*Standard error assumed to be 10% of mean.
CZS, congenital Zika Syndrome.

health provider, government, household and societal perspectives of Brazil. Due to the uncertain life expectancy of children with CZS, we use two time horizons: 5 years and 10 years. The provider perspective includes the cost of healthcare and the government perspective additionally includes the disability benefits and education. The household perspective includes the direct and indirect costs incurred by a household. Finally, the societal perspective combines the costs incurred by the government and households. For children with severe CZS receiving disability benefits to prevent double counting, the disability benefit was deducted from the household costs to estimate 'net household' and 'net societal costs'.

Costs beyond the third year of life (or second year for household costs) for all three groups (severe CZS, moderate/mild CZS, no CZS) were modelled using relative cost ratios between age groups taken from a Danish national study on the lifetime cost of CP versus no CP[34]—CP being considered by experts the best proxy for CZS (for detail see online supplemental appendix figure S1 and p5). Both costs and DALYs were discounted annually by 5%, as recommended in the Brazilian guidelines, starting from year 3 (2018) as the year of analysis was 2017.[35] Costs were expressed in US$ in 2017, using annual historical exchange rates and the average annual inflation rate were used to convert costs to US$ in 2017.[31 36] A detailed overview of all cost estimates for years 1–10 (estimated and modelled), the baseline cost for modelling, as well as the relative cost ratios (derived from the Danish national study on the lifetime cost of CP), which were used when modelling the costs beyond year 2 for household costs and year 3 for provider costs can be found in the online supplemental appendix table S1.

For each perspective (health provider/government/household/societal) and group (severe CZS/moderate CZS/controls), annual costs were calculated for years 1–10 and the overall cost burden to 5–10 years of age was obtained by multiplying those costs by yearly case number in each group. The incremental economic burden at country-level was estimated as the difference in total economic cost of either severe or moderate CZS versus controls estimated for each perspective to 5 years or 10 years of age.

Results are presented as the total (severe CZS, moderate CZS and no CZS) and incremental cost (=additional cost of a child with (1) severe CZS or (2) moderate CZS versus no CZS) per child by perspective to 5 years and 10 years of age in US$, while the economic burden in Brazil is presented as the incremental burden in US$ million by perspective to 5 years and 10 years of age of either severe CZS or moderate CZS compared with no CZS. For the latter, the online supplemental appendix contains in addition the total (not incremental) cost for each group in US$ million.

The robustness of our results were tested using a probabilistic and a deterministic sensitivity analysis. The probabilistic sensitivity analysis included 10 000 iterations, which were used to estimate the mean, median and a 95% CI (based on percentiles) of key outcomes. The deterministic sensitivity analysis consisted in a scenario analysis, where the estimated case numbers of severe CZS were varied to include additional numbers of cases compared with the conservative estimate of confirmed cases only (N=3474) used in the base case analysis (=confirmed): (1) likely (N=5175)—using confirmed cases plus 50% of the cases classified as probable and under investigation and, lastly, (2) maximum (N=6876)—using the sum of confirmed, probable and under investigation cases. The number of mild/moderate CZS cases were kept at 5× the confirmed number of severe CZS cases.

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

Table 3 Input estimates—cost estimates measured in study

	Severe CZS	Moderate CZS	No CZS
Health provider costs per year (Rio de Janeiro)*†			
Cost of specialist/non-specialist visits to the health provider	Mean/SE	Mean/SE	Mean/SE
Year 1 US$, 2017 (mean, SE)	258.4, 19.7	151.3, 19.0	128.3, 8.0
Year 2 US$, 2017 (mean, SE)	275.4, 16.0	135.7, 18.5	78.9, 6.8
Year 3 US$, 2017 (mean, SE)	326.1, 122.2	126.6, 85.4	14.0, 5.1
Cost of hospitalisation to the health provider			
Year 1 US$, 2017 (mean, SE)	1098.6, 250.1	494.9, 360.9	189.1, 67.7
Year 2 US$, 2017 (mean, SE)	3.3, 1.1	0.0, 0.0	48.6, 35.5
Year 3 US$, 2017 (mean, SE)	1282.7, 816.6	346.9, 245.1	351.0, 217.9
Cost of other services to the health provider (eg, orthotics and prosthetics)			
Year 1 US$, 2017 (mean, SE)	272.9, 67.7	0.0, 0.0	0.0, 0.0
Year 2 US$, 2017 (mean, SE)	256.0, 70.8	0.0, 0.0	0.0, 0.0
Year 3 US$, 2017 (mean, SE)	2798.7, 135.9	124.6, 12.5	0.0, 0.0
Cost of diagnostic tests, physical examinations and drugs to the health provider			
Year 1 US$, 2017 (mean, SE)	638.7, 54.4	277.7, 51.1	304.5, 25.6
Year 2 US$, 2017 (mean, SE)	342.8, 42.5	325.6, 55.3	194.2, 21.4
Year 3 US$, 2017 (mean, SE)	181.1, 88.4	4.2, 4.2	50.5, 32.0
Out of pocket costs to the household per year (Rio de Janeiro, Recife)*‡			
Irregular costs to the household			
Cost of moving house/relocation due to disability of child			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	10.1, 5.7	4.7, 4.7	0.0, 0.0
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	2.3, 4.8	22.2, 20.3	0.0, 0.0
Cost of altering house due to disability of child			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	37.8, 17.7	0.0, 0.0	0.0, 0.0
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	69.1, 15.5	35.4, 24.9	0.0, 0.0
Cost of coping§ with change due to disability of child			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	261.4, 138.7	117.6, 92.3	0.0, 0.0
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	179.1, 51.0	119.8, 72.5	0.0, 0.0
Cost of special food for child (mostly special formula milk)			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	475.6, 79.0	124.1, 95.5	0.0, 0.0
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	563.6, 67.7	261.1, 105.4	0.0, 0.0
Regular costs to the household (to be modelled beyond 2 years)			
Cost of visits (includes transport, fuel, etc)			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	1087.7, 207.0	1202.8, 349.0	186.2, 40.3
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	787.9, 157.0	384.5, 175.4	193.2, 33.8
Cost of hospitalisation			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	85.7, 29.3	31.3, 31.3	241.5, 229.3
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	148.0, 68.9	29.6, 16.8	10.1, 4.6
Cost of healthcare plan (average of both years to be modelled)			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	218.3, 53.5	94.0, 94.0	80.3, 29.2
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	172.4, 33.4	364.0, 112.7	155.1, 28.3
Cost of drugs and vitamins (mostly epilepsy drugs)			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	374.7, 73.7	205.0, 86.3	0.0, 0.0
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	595.2, 77.6	208.4, 58.5	0.0, 0.0
Cost of visual aids for child (modelled for years 1–5, year 7 and year 9)			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	55.5, 10.9	0.0, 0.0	0.0, 0.0

Continued

Table 3 Continued

	Severe CZS	Moderate CZS	No CZS
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	76.9, 12.5	9.1, 6.4	0.0, 0.0
Cost of tests			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	13.7, 6.7	0.0, 0.0	0.0, 0.0
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	12.2, 4.6	0.0, 0.0	0.0, 0.0
Other direct costs to the household			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	36.5, 18.8	0.0, 0.0	0.0, 0.0
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	73.0, 21.0	0.0, 0.0	0.0, 0.0
Indirect cost of lost household income due to visits, appointments			
Year 1 (age 0–1 years) US$, 2017 (mean, SE)	722.2, 263.9	766.5, 513.8	222.2, 62.5
Year 2 (age 1–2 years) US$, 2017 (mean, SE)	132.5, 60.6	239.5, 129.3	163.9, 43.2

Table 3 shows cost parameters to the health provider and household estimated in the costing analysis. Costs are shown for each cost category (eg, cost of hospitalisation) by year (year 1–3 for health provider costs and year 1–2 for household costs) and group (severe CZS, moderate CZS and no CZS). The first value represents the mean and the second represents the SE.
*Distribution used in the model for all provider and household costs was the gamma distribution.
†Source for all provider costs was healthcare utilisation data: Rio de Janeiro.[27]
‡Source for all household costs were the cross-sectional surveys conducted in Rio de Janeiro and Recife.
§The cost of coping includes selling of assets and borrowing money to cope with the additional costs incurred because of having child with CZS.
CZS, congenital Zika Syndrome; SE, Standard error.

provided written informed consent, as outlined previously.[10]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Patient and public involvement

Carers of babies were involved in the design of the questionnaire and assisted us in developing the most appropriate questions. We have disseminated the main results at several occasions to patients as well as general public.

RESULTS

The costs of healthcare visits remained relatively similar across the 3 years for both children with severe CZS and moderate CZS but showed a decreasing trend for children without CZS. For all three groups, the cost of hospitalisation was much higher in year 1 and year 3 compared with year 2. For children with severe CZS, hospitalisation ($1099, $3 and $1283 in years 1–3) and in year 3 other services ($2799) were the highest cost contributors. The cost of other services was zero for children without CZS and comparatively low ($125 in year 3) for children with moderate CZS. A decreasing trend in the costs of tests and drugs was observed over the 3 years across all groups.

The largest contributors to the household costs for children with severe CZS were the costs of visits (including transport and fuel) and the indirect cost of income lost, followed by the cost of special food. According to the caregivers, the latter was mainly due to the cost of special thickened formula milk that these children required.

The disaggregated and total cost per child modelled over 5 years or 10 years and presented by cost bearer were estimated for children with severe CZS, moderate CZS and no CZS (table 4, online supplemental appendix figure S1 for base case results and online supplemental appendix table S2 for probabilistic sensitivity analysis results). The incremental cost per child of severe CZS and moderate CZS versus no CZS is shown by perspective in figure 1 and online supplemental appendix table S3. Our analysis demonstrates that, regardless of perspective, a child with severe CZS incurred the highest costs, followed by moderate CZS and no CZS. The societal cost per child with severe CZS was US$28 664 (95% CI 26 059 to 32 047) to 5 years and US$50 523 (95% CI 45 982 to 56 020) to 10 years, substantially higher than the costs for moderate CZS (US$14 383 (95% CI 11 799 to 17 608) and US$29 283 (95% CI 24 303 to 35 364), respectively) and without CZS (US$5554 (95% CI 4559 to 7043) and US$12 331 (95% CI 10 511 to 14 614)). For children with severe CZS, the largest share of the costs is born by the government with (US$27 703 (95% CI 25 494 to 30 764) and US$49 250 (95% CI 45 449 to 53 864) to 5 years and 10 years). Costs to households were also high (US$14 723 (95% CI 13 157 to 16 451) and US$25 932 (95% CI 22 972 to 29 254)). Interestingly, when concerning the household's total and net cost per child (net cost meaning the disability benefits paid to households with children with severe CZS was deducted from the total household cost of these families), families of children with moderate CZS suffered a far higher cost (US$8753 (95% CI 6471 to 11 549)

Table 4 Costs (US$, 2017) per child modelled to 5 years and 10 years of age (base case)

	Severe CZS	Moderate CZS	No CZS
Costs per child to the health provider/government	**Cost per child (US$, 2017)**	**Cost per child (US$, 2017)**	**Cost per child (US$, 2017)**
Cost of specialist/non-specialist visits to the health provider			
Modelled to 5 years of age	1421.59	685.21	324.07
Modelled to 10 years of age	2859.77	1376.96	480.98
Cost of hospitalisation to the health provider			
Modelled to 5 years of age	3260.21	1156.03	801.57
Modelled to 10 years of age	4132.43	1463.95	1032.43
Cost of other services to the health provider (eg, orthotics and prosthetics)			
Modelled to 5 years of age	4501.51	167.66	0.00
Modelled to 10 years of age	5718.67	213.25	0.00
Cost of diagnostic tests, physical examinations and drugs to the health provider			
Modelled to 5 years of age	1504.64	999.51	646.06
Modelled to 10 years of age	2327.93	1920.17	911.44
Cost of wheelchair to the health provider			
Modelled to 5 years of age	672.43	41.04	0.82
Modelled to 10 years of age	1236.17	75.46	1.51
Cost of education to the government			
Modelled to 5 years of age	2580.58	2580.58	1103.99
Modelled to 10 years of age	8316.22	8316.22	5883.69
Cost of disability allowance to the government			
Modelled to 5 years of age	13 762.09	n/a	n/a
Modelled to 10 years of age	24 659.20	n/a	n/a
Total costs per child to the health provider/government			
Total cost per child to the health provider			
Modelled to 5 years of age	11 360.38	3049.45	1772.52
Modelled to 10 years of age	16 274.97	5049.78	2426.36
Total cost per child to the government (incl. disability allowance if applicable and education)			
Modelled to 5 years of age	27 703.05	5630.03	2876.51
Modelled to 10 years of age	49 250.39	13 366.00	8310.05
Costs per child to the household (detail)			
Out of pocket costs of visits (and other)			
Modelled to 5 years of age	4929.32	3941.46	826.62
Modelled to 10 years of age	9909.54	7923.64	1230.41
Out of pocket costs of hospitalisation			
Modelled to 5 years of age	482.71	125.82	518.65
Modelled to 10 years of age	610.94	159.24	666.66
Out of pocket costs of drugs/vitamins			
Modelled to 5 years of age	2370.77	1010.46	0.00
Modelled to 10 years of age	4575.33	1950.08	0.00
Out of pocket costs of tests			
Modelled to 5 years of age	63.31	0.00	0.00
Modelled to 10 years of age	122.19	0.00	0.00
Out of pocket cost of healthcare plan			
Modelled to 5 years of age	922.76	1081.82	555.82
Modelled to 10 years of age	1653.42	1938.43	995.92

Continued

Table 4 Continued

Costs per child to the health provider/government	Severe CZS Cost per child (US$, 2017)	Moderate CZS Cost per child (US$, 2017)	No CZS Cost per child (US$, 2017)
Out of pocket cost of moving and altering house as well as cost of coping			
Modelled to 5 years of age	559.73	299.73	0.00
Modelled to 10 years of age	559.73	299.73	0.00
Out of pocket cost of wheelchair (adaptation) and visual aids			
Modelled to 5 years of age	3107.27	192.07	3.41
Modelled to 10 years of age	5549.02	341.87	6.27
Out of pocket cost of special food			
Modelled to 5 years of age	1039.17	385.28	0.00
Modelled to 10 years of age	1039.17	385.28	0.00
Cost of income forgone			
Modelled to 5 years of age	1247.89	1716.57	772.61
Modelled to 10 years of age	1912.88	2918.48	1121.56
Total costs per child to the household			
Total cost per child to the household			
Modelled to 5 years of age	14 722.92	8753.21	2677.11
Modelled to 10 years of age	25 932.23	15 916.74	4020.83
Total net cost per child to the household (disability benefit deducted)			
Modelled to 5 years of age	960.83	8753.21	2677.11
Modelled to 10 years of age	1273.03	15 916.74	4020.83
Total cost per child to the household excluding income forgone			
Modelled to 5 years of age	13 475.04	7036.64	1904.50
Modelled to 10 years of age	24 019.35	12 998.27	2899.27
Total costs per child to the society			
Total net cost per child to society			
Modelled to 5 years of age	28 663.88	14 383.24	5553.62
Modelled to 10 years of age	50 523.42	29 282.75	12 330.88

The costs per child (US$, 2017) for severe CZS, moderate CZS and no CZS by time horizon (to 5 years and 10 years of age) are shown in this table using the results from the base case analysis. Detailed cost per child by cost category as well as total cost by perspective (health provider, government, household and societal) are shown. The net cost to the household means that the disability benefit provided by the government to families of children with severe CZS was deducted from the household cost. This net cost to the household was used when estimating the societal cost to avoid double counting. It only applies to children with severe CZS; for moderate CZS and no CZS children the net cost to the household is the same as the cost to the household, as they do not receive a disability benefit. The same results from the probabilistic sensitivity analysis can be found in the online supplemental appendix table S2.
CZS, congenital Zika Syndrome.

and US$15 917 (95% CI 11 608 to 21 213) to 5 years and 10 years) than families of children with severe CZS (US$961 (95% CI −859 to 2924) and US$1273 (95% CI −2103 to 4952)) or even no CZS (US$2677 (95% CI 1961 to 2994) and US$4021 (95% CI 3004 to 5747)) (table 4 and online supplemental appendix figure S2). This is best highlighted by looking at the incremental costs per child as shown in figure 1 (also see online supplemental appendix table S3). For families caring for a child with severe CZS compared with no CZS, the incremental net household cost to 5 years is −$1715 (95% CI −$3886 to $438) and to 10 years −$2743 (95% CI −$6476 to $1157). This is contrasted by an incremental net household cost of moderate CZS versus no CZS of $6071.1 (95% CI $3426 to $9002) to 5 years and $11 892 (95% CI $7209 to $17 276) to 10 years. These results show that the compensatory government payments cover to some extend the additional costs incurred by families with a child qualifying for the disability benefits, a policy specific to children with microcephaly. However, families with a child with moderate CZS (or a child with severe CZS not passing the disability benefit eligibility criteria) do not receive sufficient support and bear a significant cost burden.

Moving on to the economic burden of Brazil as a whole (figure 2), from the health provider and

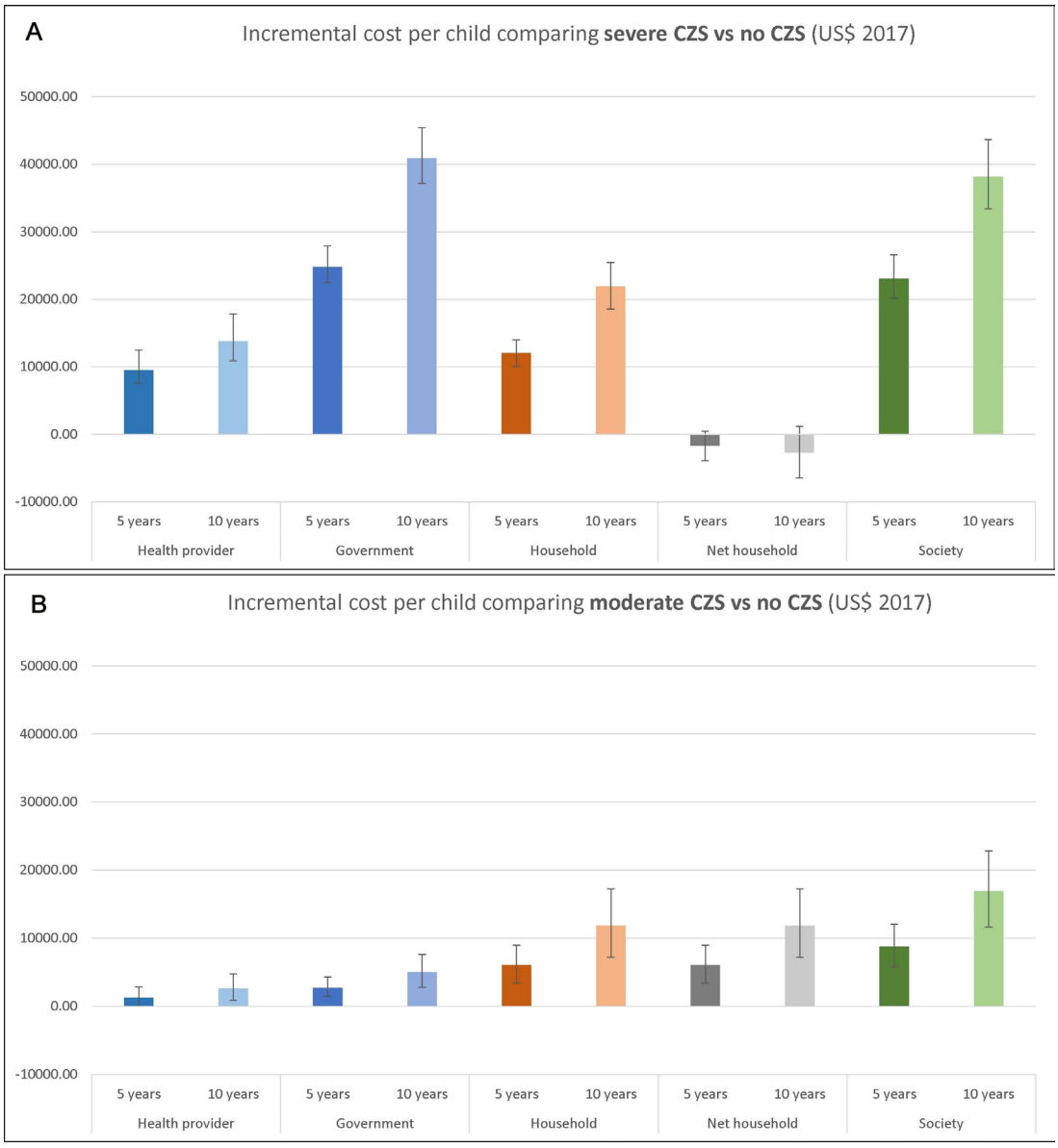

Figure 1 Incremental cost per child comparing severe and moderate CZS versus no CZS. The incremental costs per child (US$, 2017) comparing severe CZS (A) and moderate CZS (B) with no CZS modelled to 5 years and 10 years of age for each perspective. The results shown here are from the probabilistic sensitivity analysis using 10 000 iterations with the bar representing the mean and the interval lines representing the 95% CI based on percentiles. Incremental costs by perspective (health provider, government, household and societal) are shown. The net household cost means that the disability benefit provided by the government to families of children with severe CZS was deducted from the household cost. This net cost to the household was used when estimating the societal cost to avoid double counting. It only applies to children with severe CZS, since for moderate CZS and no CZS children the net cost to the household is the same as the cost to the household, as they do not receive a disability benefit. CZS, congenital Zika Syndrome.

governmental perspective, the incremental economic burden of severe versus no CZS in Brazil over 10 years was estimated to be US$44.0 million (95% CI 34.2 to 56.9) and US$129.0 million (95% CI 114.8 to 144.9), respectively. The incremental net household burden of severe versus no CZS was −US$9.6 million (95% CI −21.7 to 3.0), indicating that the payment made by the government helped this group to cope with the financial burden they face due to having a child with severe CZS (the negative number is because the net cost of a child with severe CZS is smaller than of a child with no CZS and hence the incremental cost becomes negative). For moderate CZS (using five times the confirmed cases of severe CZS), the incremental economic burden of moderate versus no CZS amounted to US$204.0 million (95% CI 123.7 to 296.6) from the household and US$86.5 million (95% CI 48.3 to 131.0) from the government perspective. Over 10 years, 97% of the total societal economic cost of severe CZS is borne by the government (157.5 million government vs 161.6 million societal cost). For moderate CZS, the government share is only 46% (229.0 million

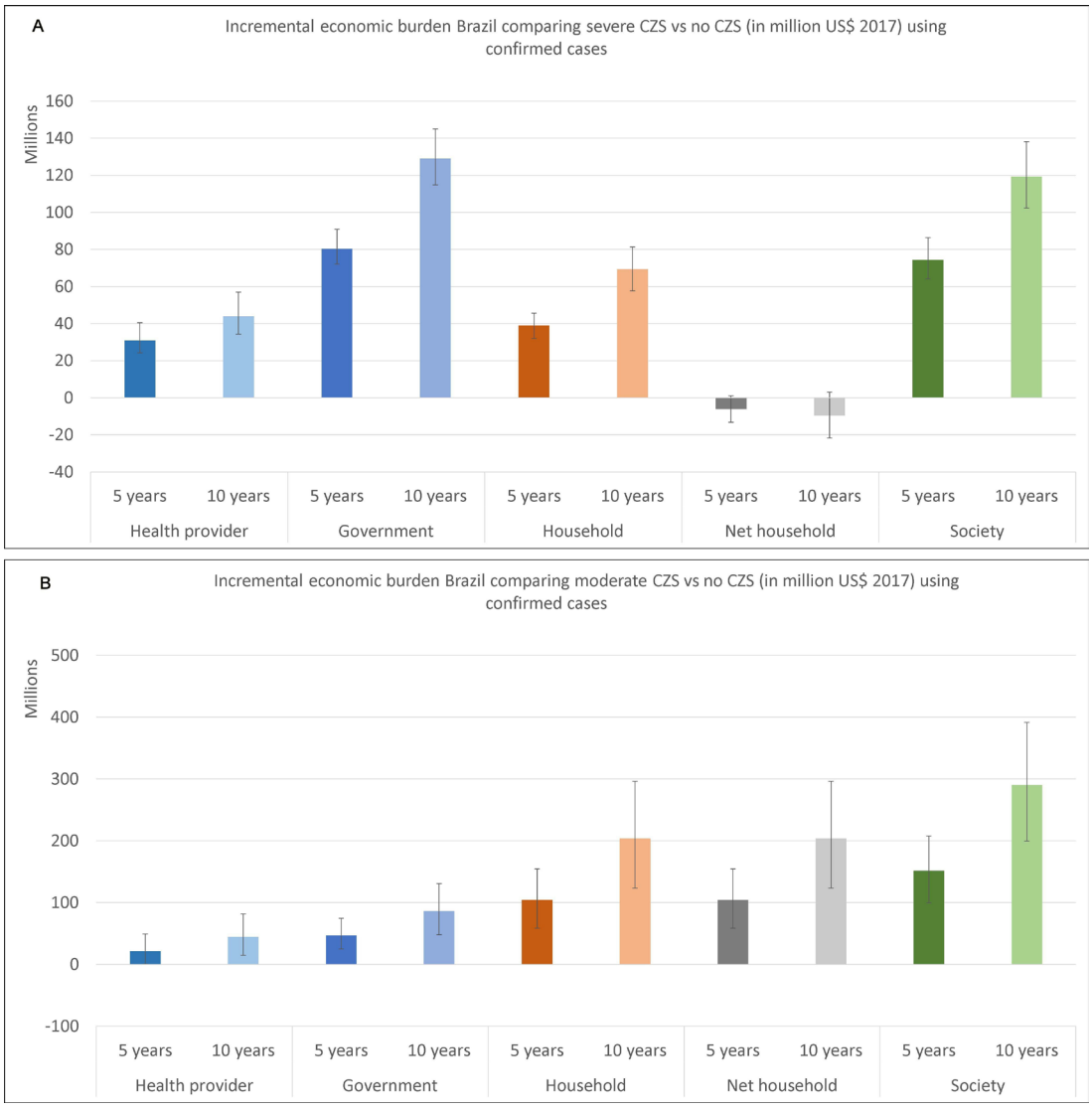

Figure 2 Incremental cost burden for Brazil comparing severe CZS and moderate CZS versus no CZS. Figure 2 shows the incremental economic burden of the whole of Brazil (US$, 2017) comparing severe CZS (A) and moderate (B) CZS vesus no CZS by time horizon (to 5 years and 10 years of age) and perspective (health provider, government, household and society). The results shown here are from the probabilistic sensitivity analysis using 10 000 iterations with the bar representing the mean and the interval lines representing the 95% CI based on percentiles. The incremental net burden to the household means that the disability benefit provided by the government to families of children with severe CZS was deducted from the household cost when calculating their economic burden. This incremental net burden to the household was used when estimating the societal burden to avoid double counting. It only applies to severe CZS, since for moderate CZS and no CZS the net burden to the household is the same as the cost to the household, as they do not receive a disability benefit. The number of confirmed cases of severe CZS was N=3474 and the number of moderate CZS was assumed to be 5× this number. CZS, congenital Zika Syndrome.

government vs 502.0 million societal cost), while 54% is incurred by the household (for details see figure 2 and online supplemental appendix table S4).

The scenario analysis where number of cases of CZS were varied is presented in online supplemental appendix table S5 and figure S2. It shows total economic burden of severe, moderate and no CZS as well as incremental economic burden of severe and moderate CZS vs no CZS by perspective, time horizon and it varies the case number using three different scenarios (called confirmed, likely, maximum).In summary, if up to the maximum number of cases of severe CZS were confirmed, the incremental economic burden for severe CZS could be up to double the amount we estimated.

The incremental DALY burden for severe CZS versus no CZS varied between 23 622 (using confirmed cases) and 46 755 (maximum cases) DALYs with years of lives lost contributing only 9% to the incremental number of DALYs (more detail on the DALY burden can be found in the online supplemental appendix table S6 and on p6).

For severe CZS, the economic and DALY burden are driven mainly by the severity of the condition, while for moderate CZS by estimated case numbers.

DISCUSSION

This study found high societal costs incurred for the care of children with severe CZS (cost per child US$28 664 to 5 years and US$50 523 to 10 years) compared with children with moderate CZS (US$14 383 and US$29 283) or without CZS (US$5554 and US$12 331). The greatest costs are incurred by the government through provision of healthcare, education and disability benefits. Strikingly, families of children with moderate CZS suffered higher costs than families of children more severely affected as they received less financial support through disability benefits. Over the course of 10 years, the estimated net household cost—which is the cost the household incurs minus the disability benefit received from the government—per child with moderate CZS was US$15 917, which was US$14 644 higher on average compared with a household with a child with severe CZS.

At a national level, the estimated incremental economic burden from the societal perspective over 10 years was around US$178 million for severe CZS and US$433 million for moderate CZS. The incremental DALY burden over 10 years was substantial, ranging between 24 000 and 47 000 DALYs for severe CZS and between 50 000 and 100 000 DALYs for moderate CZS. Both costs and DALY estimates are likely conservative as the number of children affected is thought to be greatly underestimated.

It is well recognised that the care of a child with CZS can have extensive social and economic impacts on the family.[37] However, data on economic burden are lacking, particularly for low-income and middle-income settings. Other studies estimating the economic burden have either used secondary cost data from the USA or conducted their cost data collection in the USA, which is greatly different from costs in Brazil.[17–19] Evidence on economic burden is more abundant for other types of childhood disability.[38–41] Most relevant to this paper, a 2018 systematic review included 22 studies exploring the economic impact of CP and found a strong positive relationship between severity and expenditure.[38] Significant costs were incurred by families and the welfare system to facilitate school and community engagement.

There are key strengths to this paper. It fills an important knowledge gap by presenting a robust economic burden analysis and modelling using cost data collected from the health provider and government in Brazil. The modelling methods and parameters are transparent and comprehensive. However, a number of limitations needs to be taken into account when interpreting the results. It is important to note that the different case definitions used in the two study sites (table 1) might have led to the inclusion of children with different levels of disability in the two CZS groups from the two sites but also compared with the children with microcephaly classified to receive disability benefits by the Ministry of Health. As noted in the introduction, the absence of microcephaly at birth does not exclude the presence of CZS, sometimes microcephaly develops after birth and in some cases microcephaly can even resolve over time without any long-term implications. This shows that using head circumference at birth has to some extend limitations for predicting long-term disabilities. But CZS is a new syndrome, which still needs to be understood better and what its implications in the long run are. Hence, the analysis presented here used available data to the best of our current understanding of the condition and situation, scrutinising parameters and assumptions vigorously. A further limitation is that the economic costs provide a narrow view of the impact, and the analysis does not take account of other dimensions, such as intangible cost, including the emotional pain of experiencing a fetal or neonatal death due to CZS or of having a child with disabilities. Moreover, the paper uses the term ‘burden’, meant from an economic perspective, but there are also many positive aspects of caring for a child with disabilities not captured in this study. Our model is based on data of healthcare utilisation and does not account for healthcare needs, which are more difficult to measure. Accounting for healthcare needs, which are likely substantially higher, would increase the economic burden from all perspectives considerably.

There were evidence gaps that constrained the development of the model. There was a relatively small sample of children with moderate CZS in both study sites, and the number of children examined in year 3 was limited across all three groups. There is little data available on the mortality rate of children with CZS, let alone by severity of CZS, and so a range of assumptions were made. We estimated that the mortality rate would be 10.2% over the first 5 years, in comparison to the government recorded 14.7% up until 2019.[5] However, the government figure included stillbirth and miscarriage, and so our estimates appear realistic. A number of costs were not included, such as the costs of physical and psychological healthcare among the family and caregivers. Other costs were likely to be underestimated, such as estimates of the costs for altering the home, and coping costs (includes selling of assets and borrowing money to cope with the additional costs incurred because of having child with CZS), which are likely to have been disproportionately accrued at older ages but were not modelled beyond the first 2 years. Moreover, the estimate of income foregone appears to be low, considering the likely impacts of a lifetime of caring for a child with disabilities on employment opportunities, particularly for women. Throughout, when having to make choices to inform our model, we consistently opted for the conservative option. Consequently, the actual economic burden is likely higher than our estimate. Basing our modelling of costs over time on cost ratios estimated in a Danish study could introduce bias into our estimates as health system, prices and access to services differ substantially between the two countries. However, this was the only sufficiently detailed data available on the costs of a comparable condition, in this case CP, over different years and reporting by different cost categories such as visits and hospitalisation. In addition, we considered applying relative cost ratios for different

cost categories from one setting to another as less prone to bias.

Policy, programmatic and research implications

The evidence indicates that the disability benefit protected the families of children with severe CZS from economic repercussions, while the families of children with moderate CZS were more economically vulnerable. Other studies have shown that greater financial stability may reduce other negative consequences of caring for a child with disabilities, such as mental health impacts.[37 42] Consideration should, therefore, be given to protecting and extending the disability benefit to include a wider range of children with disabilities. The impacts of CZS extend beyond economic, however, and families and children affected report many challenges and unmet needs (eg, emotional support, negative attitudes, barriers to educational inclusion and healthcare access and contraception).[43] Consequently, family support and other protection are required in addition to economic support.[44] In terms of further research, data collection focused on the first 2 years of life (up to 3 years for provider costs) and extending the time-frame of data collection would generate valuable information to support programmatic and policy plans.

In conclusion, this paper reports detailed estimates of provider, household, government and societal costs per child and at the country level for severe CZS and moderate CZS over 5 years or 10 years. Our study is the first economic burden study based on actual cost data collected in Brazil and, therefore, fills an important gap in the literature of CZS. It also complements the scarce literature on the costs of childhood disabilities. Lastly, we show that for families with moderate CZS, the net economic burden is highest, as they lack the disability benefit received by families of children with severe CZS. Broadening benefit support, possibly following a staggered approach, to include a wider range of families of children with disabilities should be introduced by policymakers to prevent some of the most vulnerable families in society from descending further into poverty leading to numerous negative ramifications for the family, potentially impacting the mental and physical health of the caregivers even more.

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Contributors MELM, TVBdA, TML and HK conceived and designed the study. LB oversaw statistical aspects of the study. MP, SF and MJ-B contributed to the design of the economic aspects of the study, and MP led its implementation. MP trained field workers and supervised the field work of the economic study with support from MELP, TVBdA, TML, SV and SF. MP, LB and SF analysed the cost data. SF designed and lead the economic burden analysis with input from MJ-B. The manuscript was written by SF and HK and revised by MP, LB, MELM, TVBdA, TML, SV and MJ-B. All authors approved the final draft of the manuscript. MELM, LB, MP and SF had full access to the economic and epidemiological data required for this paper. SF and HK had final responsibility for the decision to submit for publication. HK acts as the guarantor of the study, accepting full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study was approved by the ethics committees of the London School of Hygiene and Tropical Medicine and the Fiocruz (CAAE 60682516.2.1001.5269).

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Data availability statement Data are available upon reasonable request. Data requests to be made to silke.fernandes@lshtm.ac.uk.

Author note The reflexivity statement for this paper is linked as an online supplemental file 2.

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REFERENCES

1 PAHO. *Zika-Epidemiological report*, 2017.
2 de Araújo TVB, Rodrigues LC, de Alencar Ximenes RA, *et al*. Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study. *Lancet Infect Dis* 2016;16:1356–63.
3 World Health Organization. Who Director-General summarizes the outcome of the emergency Committee regarding clusters of microcephaly and Guillain-Barré syndrome, 2016. Available: https://www.who.int/en/news-room/detail/01-02-2016-who-director-general-summarizes-the-outcome-of-the-emergency-committee-

regarding-clusters-of-microcephaly-and-guillain-barr%C3%A9-syndrome
4 World Health Organization. Fact sheets: microcephaly, 2018. Available: https://www.who.int/news-room/fact-sheets/detail/microcephaly
5 Secretaria de Vigilância em Saúde – Ministério da Saúde Brazil. Monitoramento integrado de alterações no crescimento e desenvolvimento relacionadas infecção pelo vírus Zika e outras etiologias infecciosas, Boletim Epidemiológica - final report Boletim Epidemiológico. Numero Especial 2019.
6 Chan JFW, Choi GKY, Yip CCY, *et al*. Zika fever and congenital Zika syndrome: an unexpected emerging arboviral disease. *J Infect* 2016;72:507–24.
7 Costa F, Sarno M, Khouri R, *et al*. Emergence of congenital Zika syndrome: viewpoint from the front lines. *Ann Intern Med* 2016;164:689–91.
8 Miranda-Filho DdeB, Martelli CMT, Ximenes RAdeA, *et al*. Initial description of the presumed congenital Zika syndrome. *Am J Public Health* 2016;106:598–600.
9 Rasmussen SA, Jamieson DJ, Honein MA, *et al*. Zika virus and birth defects-reviewing the evidence for causality. *N Engl J Med* 2016;374:1981–7.
10 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. *Wellcome Open Res* 2018;3:127.
11 Marques FJP, Teixeira MCS, Barra RR, *et al*. Children born with congenital Zika syndrome display atypical gross motor development and a higher risk for cerebral palsy. *J Child Neurol* 2019;34:81–5.
12 Stabile M, Allin S. The economic costs of childhood disability. *Future Child* 2012;22:65–96.
13 DiGiacomo M, Green A, Delaney P, *et al*. Experiences and needs of carers of Aboriginal children with a disability: a qualitative study. *BMC Fam Pract* 2017;18:96.
14 Dos Santos Oliveira SJG, Dos Reis CL, Cipolotti R, *et al*. Anxiety, depression, and quality of life in mothers of newborns with microcephaly and presumed congenital Zika virus infection: a follow-up study during the first year after birth. *Arch Womens Ment Health* 2017;20:473–5.
15 Unsal-Delialioglu S, Kaya K, Ozel S, *et al*. Depression in mothers of children with cerebral palsy and related factors in Turkey: a controlled study. *Int J Rehabil Res* 2009;32:199–204.
16 Yilmaz H, Erkin G, Nalbant L. Depression and anxiety levels in mothers of children with cerebral palsy: a controlled study. *Eur J Phys Rehabil Med* 2013;49:823–7.
17 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:e0004743.
18 United Nations Development Programme. A socio-economic impact assessment of the Zika virus in Latin America and the Caribbean: with a focus on Brazil, Colombia and Suriname 2017.
19 Li R, Simmons KB, Bertolli J, *et al*. Cost-effectiveness of increasing access to contraception during the Zika virus outbreak, Puerto Rico, 2016. *Emerg Infect Dis* 2017;23:74–82.
20 Castro MC, Massuda A, Almeida G, *et al*. Brazil's unified health system: the first 30 years and prospects for the future. *Lancet* 2019;394:345–56.
21 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. *Wellcome Open Res* 2021;6:78.
22 Villar J, Cheikh Ismail L, Victora CG, *et al*. International standards for newborn weight, length, and head circumference by gestational age and sex: the newborn cross-sectional study of the INTERGROWTH-21st project. *Lancet* 2014;384:857–68.
23 França GVA, Schuler-Faccini L, Oliveira WK, *et al*. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. *Lancet* 2016;388:891–7.
24 Moreira M, Vasconcelos Z. Vertical exposure to Zika virus and its consequences for child neurodevelopment: cohort study in Fiocruz/IFF. *Nat Lib Med*.
25 Bayley N. *Bayley scales of infant and toddler development*. 3rd edn. SAn Antonio, TX: Pearson, 2006.
26 Conteh L, Walker D. Cost and unit cost calculations using step-down accounting. *Health Policy Plan* 2004;19:127–35.
27 Ministry of Health Brazil. SIGTAP - Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS.
28 Malta DC, Stopa SR, Canuto R, *et al*. Self-reported prevalence of disability in Brazil, according to the National health survey, 2013. *Cien Saude Colet* 2016;21:3253–64.
29 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:e59546.
30 Titinger DP, Lisboa LAF, Matrangolo BLR, *et al*. Cardiac surgery costs according to the preoperative risk in the Brazilian public health system. *Arq Bras Cardiol* 2015;105:130–8.
31 FXTOP. Historical exchange rates. Available: http://fxtop.com/en/historical-exchange-rates.php
32 Nielsen-Saines K, Brasil P, Kerin T, *et al*. Delayed childhood neurodevelopment and neurosensory alterations in the second year of life in a prospective cohort of ZIKV-exposed children. *Nat Med* 2019;25:1213–7.
33 Access Economics. *The economic impact of cerebral palsy in Australia in 2007*, 2008.
34 Kruse M, Michelsen SI, Flachs EM. *Livstidsomkostminger ved cerebral Parese*, 2007.
35 Brasil. Ministério da Saúde.Secretaria de Ciência TeIE. *Diretrizes metodológicas: Diretriz de Avaliação Econômica*. 2rd edn. Brasília: Ministério da Saúde, 2014.
36 International Monetary Fund. World economic outlook database. Consumer price index by country for 2014. Available: http://www.imf.org/external/pubs/ft/weo/2014/02/weodata/index.aspx
37 Scherer N, Verhey I, Kuper H. Depression and anxiety in parents of children with intellectual and developmental disabilities: a systematic review and meta-analysis. *PLoS One* 2019;14:e0219888.
38 Tonmukayakul U, Shih STF, Bourke-Taylor H, *et al*. Systematic review of the economic impact of cerebral palsy. *Res Dev Disabil* 2018;80:93–101.
39 Fejes M, Varga B, Hollódy K. [Epidemiology, cost and economic impact of cerebral palsy in Hungary]. *Ideggyogy Sz* 2019;72:115–22.
40 Retzler J, Hex N, Bartlett C, *et al*. Economic cost of congenital CMV in the UK. *Arch Dis Child* 2019;104:559–63.
41 Wang B, Chen Y, Zhang J, *et al*. A preliminary study into the economic burden of cerebral palsy in China. *Health Policy* 2008;87:223–34.
42 Emerson E, Hatton C, Llewellyn G, *et al*. Socio-economic position, household composition, health status and indicators of the well-being of mothers of children with and without intellectual disabilities. *J Intellect Disabil Res* 2006;50:862–73.
43 Ambrogi IG, Brito L, Diniz D. The vulnerabilities of lives: Zika, women and children in Alagoas State, Brazil. *Cad Saude Publica* 2021;36:e00032020.
44 Duttine A, Smythe T, Ribiero Calheiro de Sá M, *et al*. Congenital Zika Syndrome-assessing the need for a family support programme in Brazil. *Int J Environ Res Public Health* 2020;17:17103559. doi:10.3390/ijerph17103559
45 Ministry of Education Brazil. PORTARIA INTERMINISTERIAL N° 10, DE 28 DE DEZEMBRO DE 2017 2017.
46 Government of Brazil. Benefício de Prestação Continuada, 2019. Available: http://www.antigo.previdencia.gov.br/wp-content/uploads/2019/05/Relatorio-Avaliacao-BPC-Fasico_31_05_2019.pdf
47 UNICEF. Infant and under 5 mortality. Available: https://data.unicef.org/country/bra/

Supplementary appendix

Title: The economic burden of Congenital Zika Syndrome in Brazil over 5 and 10 years

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Contents

Methods

Recruitment and data collection

In Pernambuco, cases and controls were recruited from an existing case-control study and an ongoing cohort of children with suspected CZS. Cases were children born with microcephaly, defined as a head circumferences < 2 SD than the mean. They were recruited in eight public maternity hospitals, 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). Cases were classified as severe or moderate CZS, based on their head circumference ("severe" head circumference <3 SDs below the mean for age and sex). 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. 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 II Developmental Screening Test (1)), and if these were reported the child was excluded from the study and referred for further investigation. (2)

In Rio de Janeiro, cases and controls were recruited from an existing cohort study - the Vertical Exposure to Zika Virus and Its Consequences for Child Neurodevelopment: Cohort Study in Fiocruz/IFF (ClinicalTrials.gov Identifier: NCT03255369) (3). Cases were born to mothers known to be ZIKV positive with either 1) microcephaly or significant developmental delay (i.e. had a composite score <70 on the Bayley Scale of Infant Development between 6 and 36 months) (4) and/or 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 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 (4) , conducted between 6 and 36 months following the recommended guidelines and/or 2) assessment by two paediatricians based on the child's medical records. 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.

Data analysis

Health provider costs: Provider costs were split into four cost categories: visits (specialized and non-specialized), hospitalizations, drugs/tests and other. The latter included special interventions such as orthopedic surgery or prothesis. Costs were estimated per year up to the first three years of age, depending on the date of birth of the child, with data from 280, 277 and 109 children in the first, second and third year, respectively (severe CZS: N=95 Year 1+2, N=36 Year 3; moderate CZS: N=19 Year 1+2, N=11 Year 3; No CZS: N=166 Year 1, N=163 Year 2, N=62 Year 3). If a child had not completed a full year, costs were extrapolated linearly for each individual child for the first and second year, but in aggregate for the third year as, as the average age was only 2.30, 2,13 and 2.25 years for "severe CZS", "mild/moderate CZS" and control group, respectively and extrapolating individually would have led to highly inflated costs in some outliers. Some costs in the third year were not extrapolated, based on careful review of the database and consultation with the study physicians. These costs included the costs of prothesis and orthosis for the "severe CZS" and "mild/moderate CZS" group (0 costs for controls), which are applicable only once per year, early after the second birthday and had been accounted for these children already in the database. Secondly, the costs of hospitalization for the children in the "mild/moderate CZS" group was extrapolated using the average costs for hospitalizations for all children in this group during the first three years, due to one extreme outlier with a very high cost of hospitalization in the third year.

Economic burden model

Cost modelling: Costs beyond the third year of life (or second year for household costs) for all three groups were modelled using relative cost ratios between age groups taken from a Danish national study on the lifetime cost of CP - CP being considered by experts the best proxy for CZS.

The Danish study retrieved relevant registry costs from all people with CP registered in Eastern Denmark and born between 1930-2000 (half of the people with CP in Denmark) as well as for a control group and estimated actual and incremental costs for people with CP over a lifetime (5). The authors shared the full Danish report with us, published in 2007, which provided the level of detail required for our modelling (6). The cost ratios compared to the reference group - those aged 0-4 years - were calculated for people with CP and controls from the Danish report and applied to the different cost categories in our model: The Danish cost ratios for hospitalization were applied to the hospitalization costs as well as other costs (mostly surgical procedures) in our study,; Danish primary health care cost ratios were applied to model specialized and non/specialized outpatient visits in our study, and finally the Danish cost ratio of drugs/tests was applied to model the costs of tests in our study. The age categories in the report and used in the modelling were 0-4 years (reference group), 5-9 years and 10-14 years. Unfortunately, the primary data needed to look at changes by year could not be made available. Our study provided cost estimates for year 1-3 (provider) and year 1-2 (household). The mean cost from year 1-3 (provider) and from year 1-2 (household) formed the baseline for the modelling if not indicated differently. The provider costs in year 4 and household cost in year 3 and 4 were assumed to be the mean cost from year 1-3 or year 1-2 respectively if not indicated differently (for detail of modelling parameters, see Table 3). From year 5 the cost ratios derived from the Danish cost estimates were used to model the costs into the future.

Additional cost and modelling parameters: The expected future health-related cost of providing the children with a wheelchair was not yet captured in this study due to the young age of the children. Hence, after consulting with experts, we added the costs of a wheelchair to the health care provider

costs (US$ 301) and the annual costs of adapting the wheelchair to the child's needs to the household costs (US$ 1253) to year 3,4,5,6,7 and 10 (7). After consulting with physicians and physiotherapists working with these children, we made the following assumptions: i) 99% of children with microcephaly will require a wheelchair, which was multiplied by 82.7%, the number of children with confirmed microcephaly in the "severe CZS" group (8); ii) 5% of children in the mild/moderate CZS group and iii) 0.1% of children in the control group needed a wheelchair. From the government perspective, costs incurred in addition of the health provider costs were the disability allowance of US$ 293.5 per month (equivalent to the minimum wage in Brazil, 2017 (9)) paid to families with a baby with confirmed microcephaly, as well as the additional cost of education. Children in both CZS groups are eligible to attend a special creche one year earlier than other children at an annual cost of US$ 1384.5 per pupil. Further, we assumed that the additional educational resources required by children in both CZSs groups were a conservative 20% higher than those of children in the control group (Table 2).

Results

Health burden in DALYs

In our analysis we also explored the incremental health burden, measured in DALYs, due to severe and moderate CZS (table S2). Over ten years the incremental health (10) burden for severe CZS versus no CZS varied between 23622 (confirmed cases) and 46755 (maximum) DALYs with Years lived with disability (YLDs) contributing 91% and Years of life lost (YLLs) only 9% to the incremental number of DALYs. Assuming 5x and a range of 2-10x the case burden of confirmed severe CZS, the health burden of moderate CZS versus no CZS was estimated to be 50065 (range 20026-100130) DALYs. For moderate CZS 100% of the incremental DALYs were attributed to YLDs, as the mortality for moderate CZS and no CZS was assumed the same in the absence of further evidence.

Tables and Figures

Table S1:

Table S1: Cost ratios for modelling costs beyond year 3 (provider) and year 2 (household)

		Years in model (costs discounted at 5% from year 3 (2018) as year of analysis was 2017									
		Measured in study			**Modelled**						
Modelling ratios (%) and costs per year (US$) by cost category	Baseline of modelling	1	2	3	4	5	6	7	8	9	10
Health provider costs per child per year											
Specialist/non-specialist visits severe & moderate CZS (Modelling cost ratio %)	Mean year 1-3	*Study data*			100%	128%					161%
Specialist/non-specialist visits severe CZS (US$)	*$286.6*	*$258.4*	*$275.4*	*$310.6*	$260.0	$317.3	$302.2	$287.8	$274.1	$261.0	$313.2
Specialist/non-specialist visits moderate CZS (US$)	*$137.9*	*$151.3*	*$135.7*	*$120.6*	$125.0	$152.6	$145.3	$138.4	$131.8	$125.5	$150.6
Specialist/non-specialist visits no CZS (Modelling cost ratio %)	Mean year 1-3	*Study data*			100%	58%					53%
Specialist/non-specialist visits no CZS (US$)	*$73.7*	*$128.3*	*$78.9*	*$13.3*	$66.9	$36.7	$35.0	$33.3	$31.7	$30.2	$26.7
Hospitalization CZS (Modelling cost ratio %)	Mean year 1-3	*Study data*			100%	31%					20%
Hospitalization severe CZS (US$)	*$794.9*	*$1,098.6*	*$3.3*	*$1,221.6*	$721.0	$215.7	$205.5	$195.7	$186.4	$177.5	$107.3
Hospitalization moderate CZS (US$)	*$280.6*	*$494.9*	*$0.0*	*$330.4*	$254.5	$76.2	$72.5	$69.1	$65.8	$62.7	$37.9
Hospitalization no CZS (Modelling cost ratio %)	Mean year 1-3	*Study data*			100%	30%					36%
Hospitalization no CZS (US$)	*$196.2*	*$189.1*	*$48.6*	*$334.2*	$178.0	$51.6	$49.1	$46.8	$44.6	$42.4	$47.9
Other services (e.g. orthesis, prothesis) CZS (Modelling cost ratio %)	Mean year 1-3	*Study data*			100%	31%					20%
Other services (e.g. orthesis, prothesis) severe CZS (US$)	*$1,109.2*	*$272.9*	*$256.0*	*$2,665.4*	$1,006.1	$301.0	$286.7	$273.1	$260.1	$247.7	$149.7
Other services (e.g. orthesis, prothesis) moderate CZS (US$)	*$41.5*	*$0.0*	*$0.0*	*$118.7*	$37.7	$11.3	$10.7	$10.2	$9.7	$9.3	$5.6
Other services (e.g. orthesis, prothesis) no CZS (Modelling cost ratio %)	Mean year 1-3	*Study data*			100%	30%					36%
Other services (e.g. orthesis, prothesis) no CZS (US$)	*$0.0*	*$0.0*	*$0.0*	*$0.0*	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Drugs and tests CZS (Modelling cost ratio %)	Year 3/ Mean year 1-3**	*Study data*			100%	119%					132%
Drugs and tests severe CZS (US$)	*$181.1*	*$638.7*	*$342.8*	*$172.5*	$164.3	$186.4	$177.6	$169.1	$161.1	$153.4	$162.2
Drugs and tests moderate CZS (US$)	*$202.5*	*$277.7*	*$325.6*	*$4.0*	$183.7	$208.5	$198.6	$189.1	$180.1	$171.5	$181.4
Drugs and tests no CZS (Modelling cost ratio %)	Year 3	*Study data*			100%	122%					222%
Drugs and tests no CZS (US$)	*$50.5*	*$304.5*	*$194.2*	*$48.1*	$45.8	$53.4	$50.9	$48.4	$46.1	$43.9	$76.0
		Modelled using cost from 2017									
Wheelchair all groups (Modelling cost ratio %)	cost estimate 2017	0%	0%	100%	100%	100%	100%	100%	0%	0%	100%
Wheelchair severe CZS, 81.9% require a wheelchair (US$)	$301.4	$0.0	$0.0	$235.2	$224.0	$213.3	$203.1	$193.5	$0.0	$0.0	$167.1

Wheelchair moderate CZS, 5% require a wheelchair (US$)	$301.4	$0.0	$0.0	$14.4	$13.7	$13.0	$12.4	$11.8	$0.0	$0.0	$10.2
Wheelchair no CZS, 0.1% require a wheelchair (US$)	$301.4	$0.0	$0.0	$0.3	$0.3	$0.3	$0.2	$0.2	$0.0	$0.0	$0.2
Additional costs to government per child and year		**Modelled using cost from 2017**									
Education CZS (Modelling cost ratio %)	cost estimate 2017	n/a	n/a	n/a	120%	120%	120%	120%	120%	120%	120%
Education severe/moderate CZS (US$)	see table 2	$0.0	$0.0	$0.0	$1,255.8	$1,324.8	$1,261.7	$1,201.6	$1,144.4	$1,089.9	$1,038.0
Education no CZS (Modelling cost ratio %)	cost estimate 2017	n/a	n/a	n/a	n/a	100%	100%	100%	100%	100%	100%
Education no CZS (US$)	see table 2	$0.0	$0.0	$0.0	$0.0	$1,104.0	$1,051.4	$1,001.4	$953.7	$908.3	$865.0
Disability allowance severe CZS (only 82.7% of children receive allowance) (Modelling cost ratio %)	cost estimate 2017	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Disability allowance severe CZS (US$)	$3,521.5	$2,913.7	$2,913.7	$2,774.9	$2,642.8	$2,517.0	$2,397.1	$2,283.0	$2,174.2	$2,070.7	$1,972.1
Household costs per child and year											
Irregular household costs per child and year		***Measured in study***		**Modelled (where applicable)**							
Modelling ratios (%) where applicable and costs per year (US$) by cost category		1	2	3	4	5	6	7	8	9	10
Moving, altering house and coping (Modelling cost ratios %)		Study data		not modelled further							
Moving, altering house and coping severe CZS (US$)	*n/a*	*$309.3*	*$250.5*	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Moving, altering house and coping moderate CZS (US$)	*n/a*	*$122.3*	*$177.5*	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Moving, altering house and coping no CZS (US$)	*n/a*	*$0.0*	*$0.0*	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Special food for child (mostly special formula milk) (modelling cost ratios %)		Study data		not modelled further							
Special food for child (mostly special formula milk) severe CZS (US$)	*n/a*	*$475.6*	*$563.6*	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Special food for child (mostly special formula milk) moderate CZS (US$)	*n/a*	*$124.1*	*$261.1*	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Special food for child (mostly special formula milk) no CZS (US$)	*n/a*	*$0.0*	*$0.0*	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Regular costs											
Wheelchair adaptation (WA) and visual aids (VA) (Modelling cost ratios %)		Study data		VA modelled at 100% for years 3-5, 7 and 9; WA modelled at 100% for years 3-7 and 10.							
Wheelchair adaptation and visual aids severe CZS	*n/a*	*$55.5*	*$76.9*	$1040.4	$990.8	$943.6	$844.2	$855.9	$0.0	$47.1	$694.6
Wheelchair adaptation and visual aids moderate CZS	*n/a*	*$0.0*	*$9.1*	$64.0	$60.9	$58.0	$51.5	$52.6	$0.0	$3.2	$42.4
Wheelchair adaptation and visual aids no CZS	*n/a*	*$0.0*	*$0.0*	$1.2	$1.1	$1.1	$1.0	$1.0	$0.0	$0.0	$0.8
Visits (includes transport, fuel) CZS (Modelling cost ratio %)	Mean year 1-2	Study data		100%	100%	128%					161%
Visits severe CZS (US$)	*$992.6*	*$1124.2*	*$860.9*	$945.3	$900.3	$1098.6	$1046.3	$996.5	$949.0	$903.9	$1084.5
Visits moderate CZS (US$)	*$793.6*	*$1202.8*	*$384.5*	$755.9	$719.9	$878.5	$836.6	$796.8	$758.9	$722.7	$867.2

Visits (includes transport, fuel) no CZS (Modelling cost ratio %)	Mean year 1-2	Study data		100%	100%	58%					53%
Visits no CZS (US$)	$*189.7*	*$186.2*	*$193.2*	$180.7	$172.1	$94.5	$90.0	$85.7	$81.6	$77.8	$68.7
Income lost CZS (Modelling cost ratio %)	Year 2	Study data		100%	100%	140%					141%
Income lost severe CZS (US$)	$*132.5*	*$722.2*	*$132.5*	$126.2	$120.2	$146.7	$139.7	$133.1	$126.7	$120.7	$144.8
Income lost moderate CZS (US$)	$*239.5*	*$766.5*	*$239.5*	$228.1	$217.3	$265.1	$252.5	$240.5	$229.0	$218.1	$261.7
Income lost no CZS (Modelling cost ratio %)	$Year 2	Study data		100%	100%	108%					110%
Income lost no CZS (US$)	$*163.9*	*$222.2*	*$163.9*	$156.1	$148.7	$81.7	$77.8	$74.1	$70.6	$67.2	$59.3
Health Care Plan CZS (Modelling cost ratio %)	Mean year 1-2	Study data		100%	100%						
Health Care Plan severe CZS (US$)	$*195.4*	*$218.3*	*$172.4*	$186.1	$177.2	$168.8	$160.7	$153.1	$145.8	$138.8	$132.2
Health Care Plan moderate CZS (US$)	$*229.0*	*$94.0*	*$364.0*	$218.1	$207.7	$197.9	$188.4	$179.5	$170.9	$162.8	$155.0
Health Care Plan no CZS (Modelling cost ratio %)	Mean year 1-2	Study data		100%	100%						
Health Care Plan no CZS (US$)	*$117.7*	*$80.3*	*$155.1*	$112.1	$106.7	$101.7	$96.8	$92.2	$87.8	$83.6	$79.6
Hospitalization CZS (Modelling cost ratio %)	Mean year 1-2	Study data		100%	100%	31%					20%
Hospitalization severe CZS (US$)	*$116.9*	*$85.7*	*$148.0*	$111.3	$106.0	$31.7	$30.2	$28.8	$27.4	$26.1	$15.8
Hospitalization moderate CZS (US$)	*$30.5*	*$31.3*	*$29.6*	$29.0	$27.6	$8.3	$7.9	$7.5	$7.1	$6.8	$4.1
Hospitalization no CZS (Modelling cost ratio %)	Mean year 1-2	Study data		100%	100%	30%					36%
Hospitalization no CZS (US$)	*$125.8*	*$241.5*	*$10.1*	$119.8	$114.1	$33.1	$31.5	$30.0	$28.6	$27.2	$30.7
Drugs/ vitamins CZS (Modelling cost ratio %)	Mean year 1-2	Study data		100%	100%	119%					132%
Drugs/ vitamins severe CZS (US$)	*$484.9*	*$374.7*	*$595.2*	$461.8	$439.8	$499.2	$475.5	$452.8	$431.3	$410.7	$434.3
Drugs/ vitamins moderate CZS (US$)	*$206.7*	*$205.0*	*$208.4*	$196.8	$187.5	$212.8	$202.6	$193.0	$183.8	$175.1	$185.1
Drugs/ vitamins no CZS (Modelling cost ratio %)	Mean year 1-2	Study data		100%	100%	122%					222%
Drugs/ vitamins no CZS (US$)	*$0.0*	*$0.0*	*$0.0*	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tests CZS (Modelling cost ratio %)	Mean year 1-2	Study data		100%	100%	119%					132%
Tests severe CZS (US$)	*$13.0*	*$13.7*	*$12.2*	$12.3	$11.7	$13.3	$12.7	$12.1	$11.5	$11.0	$11.6
Tests moderate CZS (US$)	*$0.0*	*$0.0*	*$0.0*	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tests no CZS (Modelling cost ratio %)	Mean year 1-2	Study data		100%	100%	122%					222%
Tests no CZS (US$)	*$0.0*	*$0.0*	*$0.0*	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0

Actual and modelled costs up to 10 years of age with a 5% annual discount rate from year 3 (2018) as the year of analysis was 2017.
Cost measured in our study are shown in italic, modelled costs are shown in normal font.
Sources: Provider and household costs data from study and cost ratios from Danish report on the costs of Cerebral Palsy

* make note that both CZS groups were modelled using the same prediction parameters here.
** Year 3 for severe CZS, as there seemed to be a downwards trend it seemed to be inappropriate to use average of year 1-3, and sample size for the third year in group 2 was so small, that this was not possible hence average of year 1-3 was used.

Table S2:

Table S2: Costs (US$ 2017) per child modelled to 5 and 10 years of age (probabilistic sensitivity analysis)

	Severe CZS	Moderate CZS	No CZS
	Cost per child (US$ 2017) Mean (95% CI) *Median*	**Cost per child (US$ 2017)** Mean (95% CI) *Median*	**Cost per child (US$ 2017)** Mean (95% CI) *Median*
Costs per child to the health provider/ government			
Cost of specialist/non-specialist visits to the health provider			
Modelled to 5 years of ageto 5 years of age	1422 (1093-1883) *1398*	685 (476-1023) *660*	324 (291-358) *324*
Modelled to 10 years of age	2861 (2189-3800) *2815*	1376 (952 - 2061) *1376*	481 (431-533) *480*
Cost of hospitalization to the health provider			
Modelled to 5 years of ageto 5 years of age	3253 (1603-6058) *3039*	1168 (310 - 2602) *1061*	800 (357-1559) *746*
Modelled to 10 years of age	4124 (2022-7672) *3849*	1479 (391-3309) *1343*	1030 (458-2013) *958*
Cost of other services to the health provider (e.g. orthesis, prosthetis)			
Modelled to 5 years of ageto 5 years of age	4499 (4068-4972) *4493*	168 (136-202) *167*	0.00
Modelled to 10 years of age	5715 (5139-6352) *5707*	213 (173-257) *212*	0.00
Cost of diagnostic tests, physical examinations and drugs to the health provider			
Modelled to 5 years of ageto 5 years of age	1507 (1099-2120) *1470*	1000 (773-1254) *994*	646 (501-878) *630*
Modelled to 10 years of age	2335 (1346-3893) 2233	1920 (1483-2412) *1910*	911 (557-1548) *864*
Cost of wheelchair to the health provider			
Modelled to 5 years of ageto 5 years of age	672 (629-711) 673	27 (10-53) *25*	1 (1-1) *1*
Modelled to 10 years of age	1236 (1157-1307) 1237	61 (22-121) *58*	1 (1-1) *1*
Cost of education to the government			
Modelled to 5 years of ageto 5 years of age	2582 (2168-3053) 2572	2582 (2168-3053) *2572*	1104 (900-1328) *1100*
Modelled to 10 years of age	8317 (6524-10424) 8260	8317 (6524-10424) *8260*	5883 (4794-7077) *5860*
Cost of disability allowance to the government			
Modelled to 5 years of ageto 5 years of age	13763 (12832-14578) 13786	n/a	n/a
Modelled to 10 years of age	24661 (22993-26121) 24703	n/a	n/a
Total costs per child to the health provider/ government			
Total cost per child to the health provider			
Modelled to 5 years of ageto 5 years of age	11354 (9475-14265) 11185	3047 (2100-4534) *2949*	1770 (1283-2537) *1722*
Modelled to 10 years of age	16271 (13558-20234) 16068	5050 (3721-6993) *4939*	2422 (1680-3536) *2359*
Total cost per child to the government (incl. disability allowance if appl. and education)			
Modelled to 5 years of ageto 5 years of age	27699 (25494-30764) 27551	5629 (4564-7162) *5553*	2874 (2325-3672) *2829*
Modelled to 10 years of age	49249 (45449-53864) 49092	13367 (10996-16093) *13289*	8305 (6930-9893) *8274*

Costs per child to the household			
Out of pocket costs of visits (and other)			
Modelled to 5 years of ageto 5 years of age	4930 [3747- 6274] *4895*	3942 (2273-6024) *3870*	825 (611-1066) *819*
Modelled to 10 years of age	9910 (7536-12609) *9841*	7924 (4580-12,137) *7778*	1228 (910-1589) *1221*
Out of pocket costs of hospitalization			
Modelled to 5 years of ageto 5 years of age	483 (236-832) *465*	127 (31-317) *111*	516 (38-1729) *379*
Modelled to 10 years of age	612 (298-1049) *588*	160 (39-402) *140*	664 (49-2215) *486*
Out of pocket costs of drugs/ vitamins			
Modelled to 5 years of ageto 5 years of age	2368 (1884-2916) *2357*	1009 (574-1577) *987*	0
Modelled to 10 years of age	4570 (3635-5630) *4549*	1947 (1108-3036) *1902*	0
Out of pocket costs of tests			
Modelled to 5 years of ageto 5 years of age	63 (31-108) *61*	0	0
Modelled to 10 years of age	122 (60-209) *118*	0	0
Out of pocket cost of Health Care Plan			
Modelled to 5 years of ageto 5 years of age	921 (653-1237) *913*	1083 (532-1868) *1042*	556 (387-758) *549*
Modelled to 10 years of age	1650 (1170-2217) *1636*	1941 (953-3348) *1867*	996 (694-1358) *984*
Out of pocket cost of moving and altering house as well as cost of coping			
Modelled to 5 years of ageto 5 years of age	560 (331-917) *537*	299 (115-580) *282*	0
Modelled to 10 years of age	560 (331-917) *537*	299 (115-580) *282*	0
Out of pocket cost of wheelchair (adaptation) and visual aids			
Modelled to 5 years of age	3106 (2914-3283) *3108*	192 (81-359) *183*	3 (3-3) *3*
Modelled to 10 years of age	5547 (5207-5857) *5550*	346 (142-652) *329*	3 (3-3) *3*
Out of pocket cost of special food			
Modelled to 5 years of age	1039 (847-1256) *1035*	386 (162-717) *369*	0.00
Modelled to 10 years of age	1039 (847-1256) *1035*	386 (162-717) *369*	0.00
Cost of income forgone			
Modelled to 5 years of age	1241 (641-2031) *1209*	1718 (609-3479) *1615*	773 (501-1116) *760*
Modelled to 10 years of age	1902 (927-3289) *1832*	2916 (1028-5949) *2736*	1122 (701-1661) *1102*

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Total costs per child to the household			
Total cost per child to the household			
Modelled to 5 years of age	14712 (13157-16451) *14674*	8761 (6471-11549) *8667*	2685 (1961-2994) *2585*
Modelled to 10 years of age	25915 (22972-29254) *25827*	15928 (11608-21213) *15737*	4031 (3004-5747) *3915*
Total net cost per child to the household (disability benefit deducted)			
Modelled to 5 years of age	956 (-859-2924) *924*	8761 (6471-11549) *8667*	2685 (1961-2994) *2585*
Modelled to 10 years of age	1266 (-2103-4952) *1201*	15928 (11608-21213) *15737*	4031 (3004-5747) *3915*
Total cost per child to the household excluding income forgone			
Modelled to 5 years of age	13471 (12055-15055) *13435*	7043 (5127-9334) *6957*	1912 (1283-3163) *1790*
Modelled to 10 years of age	24013 (21318-27097) *23940*	13012 (9303-17532) *12847*	2909 (2030-4553) *2763*
Total costs per child to the society			
Total cost per child to society			
Modelled to 5 years of age	28660 (26059-32047) *28514*	14378 (11799-17608) *14275*	5557 (4559-7043) *5467*
Modelled to 10 years of age	50521 (45982-56020) *50362*	29288 (24303-35364) *29116*	12332 (10511-14614) *12262*

Table S2: **The costs per child** (US$ 2017) (note: not the incremental costs) for severe CZS, moderate CZS and no CZS by time horizon (to 5 and 10 years of age) are shown in this table using the results from the **probabilistic sensitivity analysis (PSA)** using 10,000 iterations. The first number represents the mean, the second and third number the 95% confidence interval based on percentiles and the last number the median. Detailed cost per child by cost category as well as total cost by perspective (health provider, government, household, societal) are shown. The net cost to the household means that the disability benefit provided by the government to families of children with severe CZS was deducted from the household cost. This net cost to the household was used when estimating the societal cost to avoid double counting. It only applies to children with severe CZS, since for moderate CZS and no CZS children the net cost to the household is the same as the cost to the household, as they do not receive a disability benefit.

Table S3:

Table S3: Incremental costs per child modelled to 5 and 10 years of age
Base case and probabilistic sensitivity analysis results

	Severe CZS vs no CZS		Moderate CZS vs no CZS	
	Incremental cost per child (US$ 2017) Base case	**Incremental cost per child (US$ 2017) PSA** Mean (95% CI); *Median*	**Incremental cost per child (US$ 2017) Base case**	**Incremental cost per child (US$ 2017) PSA** Mean (95% CI); *Median*
Incremental costs per child to the health provider/ government				
Incremental cost per child to the health provider				
Modelled to 5 years of age	9,587.9	9571.2 (7533.9 - 12465.2); *9404.0*	1,276.9	1266.3 (31.2 - 2885.4); *1198.3*
Modelled to 10 years of age	13,848.6	13830.8 (10881.3 - 17814.3); *13638.4*	2,623.4	2612.3 (860.8 - 4770.5); *2544.3*
Incremental cost per child to the government (incl. disability allowance if appl. and eduation)				
Modelled to 5 years of age	24,826.5	24814.6 (22498.7 - 27890.7); *24670.6*	2,753.5	2746.2 (1471.2 - 4360.2); *2685.7*
Modelled to 10 years of age	40,940.3	40931.6 (37202.2 - 45438.4); *40815.1*	5,056.0	5051.4 (2822.8 - 7651.4); *4991.8*
Incremental costs per child to the household				
Incremental cost per child to the household				
Modelled to 5 years of age	12,045.8	12048.3 (10023.8 - 13983.3); *12049.2*	6,076.1	6071.1 (3425.7 - 9002.2); *6012.6*
Modelled to 10 years of age	21,911.4	21919.0 (18557.5 - 25431.9); *21897.9*	11,895.9	11892.3 (7208.7 - 17276.3); *11747.3*
Incremental net cost per child to the household (disability benefit deducted)				
Modelled to 5 years of age	-1,716.3	-1715.2 (-3885.5 - 437.5); *-1724.5*	6,076.10	6071.1 (3425.7 - 9002.2); *6012.6*
Modelled to 10 years of age	-2,747.8	-2742.7 (-6476.1 - 1156.5); *-2768.6*	11,895.92	11892.3 (7208.7 - 17276.3); *11747.3*

Incremental cost per child to the household excluding income forgone				
Modelled to 5 years of age	11,570.5	11567.9 (9721.2 - 13305.4); *11588.2*	5,132.1	5122.5 (2809.8 - 7581.5); *5084.7*
Modelled to 10 years of age	21,120.1	21117.5 (18014.6 - 24289.8); *21100.6*	10,099.0	10085.8 (6007.6 - 14792.2); *9983.8*
Incremental costs per child to the society				
Incremental cost per child to society				
Modelled to 5 years of age	23,110.3	23099.4 (20174.7 - 26587.2); *22997.7*	8,829.6	8817.3 (5800.5 - 12071.1); *8760.1*
Modelled to 10 years of age	38,192.5	38188.9 (33434.2 - 43703.7); *38069.5*	16,951.87	16943.7 (11635.5 - 22821.6); *16822.3*

Table S3: **The incremental costs per child** (US$ 2017) for severe CZS and moderate CZS versus no CZS by time horizon (to 5 and 10 years of age) and perspective (health provider, government, household, society) are shown in this table using the results from both the **base case analysis** and the **probabilistic sensitivity analysis (PSA),** the latter using 10,000 iterations. Amongst the PSA results, the first number represents the mean, the second and third number the 95% confidence interval based on percentiles and the last number the median. The incremental net cost to the household means that the disability benefit provided by the government to families of children with severe CZS was deducted from the household cost. This incremental net cost to the household was used when estimating the societal cost to avoid double counting. It only applies to children with severe CZS since for children with moderate CZS and no CZS children the net cost to the household is the same as the cost to the household, as they do not receive a disability benefit.

Table S4:

Table S4: Incremental economic burden of confirmed cases of severe CZS – base case and probabilistic sensitivity analysis		
	Incremental burden of confirmed cases (US$ 2017)	
	Base case	Mean (95% CI); Median
Severe CZS health provider burden		
To 5 years of age	$30,971,018	30,916,227 (24,128,666 - 40,422,748); 30,406,316
To 10 years of age	$44,048,809	43,995,253 (34,238,123 - 56,915,800); 43,435,727
Severe CZS government burden		
To 5 years of age	$80,444,866	80,406,895 (72,135,566 - 90,922,177); 80,086,395
To 10 years of age	$128,989,648	128,983,850 (114,817,744 - 144,949,860); 128,826,658
Severe CZS household burden		
To 5 years of age	$39,031,649	39,040,672 (31,998,491 - 45,683,731); 39,095,620
To 10 years of age	$69,359,667	69,396,060 (57,629,926 - 81,232,501); 69,421,921
Severe CZS net household burden		
To 5 years of age	-$6,028,589	-6,025,249 (-13,300,053 - 1,143,797); -6,043,817
To 10 years of age	-$9,650,686	-9,635,119 (-21,659,644 - 2,967,486); -9,708,246
Severe CZS societal burden		
To 5 years of age	$74,416,277	74,381,646 (64,141,960 - 86,286,547); 74,093,441
To 10 years of age	$119,338,962	119,348,731 (102,336,468 - 138,062,305); 119,085,971
Moderate CZS health provider burden [b]		
To 5 years of age	$21,940,335	21,759,739 (555,698 - 49,572,046); 20,595,911
To 10 years of age	$44,973,913	44,785,652 (14,767,265 - 81,857,572); 43,591,502
Moderate CZS government burden [b]		
To 5 years of age	$47,220,232	47,097,279 (25,114,620 - 74,925,391); 46,015,466
To 10 years of age	$86,606,422	86,532,557 (48,278,865 - 130,995,827); 85,488,592
Moderate CZS household burden [b]		
To 5 years of age	$104,506,556	104,422,684 (58,945,110 - 154,860,326); 103,467,751
To 10 years of age	$204,061,260	204,003,270 (123,704,941 - 296,637,334); 201,487,678
Moderate CZS societal burden [b]		
To 5 years of age	$151,726,788	151,519,963 (99,692,753 - 207,842,810); 150,523,906
To 10 years of age	$290,667,682	290,535,828 (199,615,289 - 391,615,465); 288,418,847

Table S4 shows the **incremental economic burden** of Brazil (US$ 2017) for severe CZS and moderate CZS versus no CZS by time horizon (to 5 and 10 years of age) and perspective (health provider, government, household, society)

using the results from both the **base case analysis** and the **probabilistic sensitivity analysis (PSA),** the latter using 10,000 iterations. Amongst the PSA results, the first number represents the mean, the second and third number the 95% confidence interval based on percentiles and the last number the median. The incremental net burden to the household means that the disability benefit provided by the government to families of children with severe CZS was deducted from the household cost when calculating their economic burden. This incremental net burden to the household was used when estimating the societal burden to avoid double counting. It only applies to severe CZS since for moderate CZS and no CZS the net burden to the household is the same as the cost to the household, as they do not receive a disability benefit.

[a] confirmed = confirmed severe CZS cases only, total N=3474

[b] clinical burden for moderate CZS was assumed to be 5 times the confirmed clinical burden of severe CZS

Table S5:

Table S5: Total and incremental economic burden (US$ 2017) deterministic scenario analysis

	Total economic burden			Incremental burden severe or moderate versus no CZS		
	Confirmed cases[a]	Likely cases[b]	Maximum cases[c]	Confirmed cases[a]	Likely cases[b]	Maximum cases[c]
Severe CZS health provider						
To 5 years of age	$37,073,291	$55,225,758	$73,378,224	$30,971,018	$46,135,584	$61,300,150
To 10 years of age	$52,388,010	$78,039,134	$103,690,258	$44,048,809	$65,616,750	$87,184,690
Severe CZS government						
To 5 years of age	$90,326,239	$134,553,335	$178,780,432	$80,444,866	$119,833,674	$159,222,481
To 10 years of age	$157,460,561	$234,559,125	$311,657,690	$128,989,648	$192,147,791	$255,305,935
Severe CZS household						
To 5 years of age	$48,237,780	$71,856,797	$95,475,814	$39,031,649	$58,143,001	$77,254,352
To 10 years of age	$83,163,015	$123,882,730	$164,602,444	$69,359,667	$103,320,747	$137,281,827
Severe CZS net household						
To 5 years of age	$3,177,542	$4,733,385	$6,289,228	-$6,028,589	-$8,980,411	-$11,932,233
To 10 years of age	$4,152,663	$6,185,961	$8,219,260	-$9,650,686	-$14,376,022	-$19,101,358
Severe CZS societal						
To 5 years of age	$93,503,781	$139,286,720	$185,069,660	$74,416,277	$110,853,263	$147,290,248
To 10 years of age	$161,613,223	$240,745,086	$319,876,949	$119,338,962	$177,771,770	$236,204,577
Moderate CZS health provider [d]						
To 5 years of age	$52,451,702	$78,134,011	$103,816,321	$21,940,335	$32,683,142	$43,425,949
To 10 years of age	$86,669,916	$129,106,740	$171,543,564	$44,973,913	$66,994,818	$89,015,724
Moderate CZS government [d]						
To 5 years of age	$96,627,096	$143,939,327	$191,251,558	$47,220,232	$70,341,019	$93,461,806
To 10 years of age	$228,960,986	$341,068,826	$453,176,666	$86,606,422	$129,012,157	$171,417,892
Moderate CZS household [d]						
To 5 years of age	$150,537,212	$224,245,847	$297,954,481	$104,506,556	$155,676,865	$206,847,174
To 10 years of age	$273,078,002	$406,787,179	$540,496,356	$204,061,260	$303,977,265	$403,893,271
Moderate CZS societal [d]						
To 5 years of age	$247,164,308	$368,185,173	$489,206,039	$151,726,788	$226,017,884	$300,308,980
To 10 years of age	$502,038,988	$747,856,005	$993,673,022	$290,667,682	$432,989,422	$575,311,163

Using burden numbers from severe CZS						
No CZS health provider						
To 5 years of age	**$6,102,273**	**$9,090,174**	**$12,078,074**	-	-	-
To 10 years of age	**$8,339,201**	**$12,422,384**	**$16,505,568**	-	-	-
No CZS government						
To 5 years of age	**$9,881,373**	**$14,719,662**	**$19,557,950**	-	-	-
To 10 years of age	**$28,470,913**	**$42,411,334**	**$56,351,755**	-	-	-
No CZS household						
To 5 years of age	**$9,206,131**	**$13,713,796**	**$18,221,462**	-	-	-
To 10 years of age	**$13,803,348**	**$20,561,983**	**$27,320,617**	-	-	-
No CZS societal						
To 5 years of age	**$19,087,504**	**$28,433,458**	**$37,779,412**	-	-	-
To 10 years of age	**$42,274,261**	**$62,973,317**	**$83,672,372**	-	-	-
Using burden numbers from moderate CZS						
No CZS health provider						
To 5 years of age	**$30,511,366**	**$45,450,869**	**$60,390,372**	-	-	-
To 10 years of age	**$41,696,003**	**$62,111,922**	**$82,527,841**	-	-	-
No CZS government						
To 5 years of age	**$49,406,864**	**$73,598,308**	**$97,789,752**	-	-	-
To 10 years of age	**$142,354,564**	**$212,056,669**	**$281,758,775**	-	-	-
No CZS household						
To 5 years of age	**$46,030,655**	**$68,568,981**	**$91,107,308**	-	-	-
To 10 years of age	**$69,016,742**	**$102,809,914**	**$136,603,085**	-	-	-
No CZS societal						
To 5 years of age	**$95,437,519**	**$142,167,289**	**$188,897,059**	-	-	-
To 10 years of age	**$211,371,306**	**$314,866,583**	**$418,361,860**	-	-	-

Table S5 shows a scenario analysis for the total and incremental economic burden in Brazil where the number of cases of severe and moderate CZS was varied. The results show the total economic burden (left) for severe, moderate and no CZS and the incremental economic burden (right) comparing severe CZS or moderate CZS with no CZS by perspective (health provider, government, household, societal), time horizon (to 5 and 10 years of age) and case numbers (confirmed, likely, maximum). The total and incremental net burden to the household for severe CZS means that the disability benefit provided by the government to families of children with severe CZS was deducted from the household cost when calculating their total and incremental economic burden. This incremental net burden to the household was used when estimating the societal burden to avoid double counting. It only applies to severe CZS since for moderate CZS and no CZS the net burden to the household is the same as the burden to the household, as they do not receive a disability benefit.

[a] confirmed = confirmed severe CZS cases only, total N=3474

[b] likely = confirmed severe CZS cases + 50% of severe CZS cases under investigation (N=2659) + 50% of probable severe CZS cases (N=743), total N=5175

[c] maximum = confirmed severe CZS cases + severe CZS cases under investigation + probable severe CZS cases, total N=6876

[d] clinical burden for moderate CZS was assumed to be 5 times the clinical burden of severe CZS in either of the three scenarios (confirmed, likely and maximum)

Table S6:

Table S6: Incremental DALY health burden of CZS

		Incremental **YLLs** CZS vs no CZS [a]		Incremental **YLDs** CZS vs no CZS		Incremental **DALYs** CZS vs no CZS	
	Assumed number of cases in year 1	To 5 years	To 10 years	To 5 years	To10 years	To 5 years	To 10 years
Severe CZS							
Confirmed cases	3474	914	2019	12193	21603	**13107**	**23622**
Confirmed + 50% probable + 50% under investigation cases	5175	1362	3007	18164	32181	**19525**	**35188**
Confirmed + probable + under investigation cases	6876	1809	3996	24134	42759	**25943**	**46755**
Moderate CZS (assuming confirmed cases)							
Severe CZS cases x 5	17370	0	0	28078	50065	**28078**	**50065**
Severe CZS cases x 2	6948	0	0	11231	20026	**11231**	**20026**
Severe CZS cases x 10	34740	0	0	56156	100130	**56156**	**100130**
Moderate CZS (assuming confirmed + 50% probable+ 50% under investigation cases)							
Severe CZS cases x 5	25875	0	0	41826	74579	41826	74579
Severe CZS cases x 2	10350	0	0	16730	29831	16730	29831
Severe CZS cases x 10	51750	0	0	83652	149157	83652	149157
Moderate CZS (assuming confirmed + probable+ under investigation cases)							
Severe CZS cases x 5	34380	0	0	55574	99092	55574	99092
Severe CZS cases x 2	13752	0	0	22230	39637	22230	39637
Severe CZS cases x 10	68760	0	0	111148	198185	111148	198185

Table S1 shows the health burden measured in Disability adjusted life years (DALYs) in detail for severe CZS and moderate CZS using different assumptions of the number of cases. Results are presented in Years of life lost (YLLs), Years lived with disability (YLDs) and DALYs. The burden was modelled to 5 and 10 years of age. Mortality rates applied to children with severe CZS were 4.9% for year 1, 2.6% for year 2, 0.9% for year 3,4&5 and 0.3% for year 6-10 (See table 2). Mortality estimates for the first 3 years were based on observed death of children with severe CZS in the Rio de Janeiro Cohort and thereafter based on estimates and assumptions. Mortality of children with moderate CZS were assumed to be no different from the general population and national mortality rates were used: 1.3% for year 1, 0.1% for year 2, 0.03% for year 3, 4 &5 and 0.01% for year 6-10. Mortality rates up to age 5 were based on infant and <5 mortality rates and mortality for from age 5-10 was assumed to be 1/3 of mortality when aged 2-4.

Figure S1:

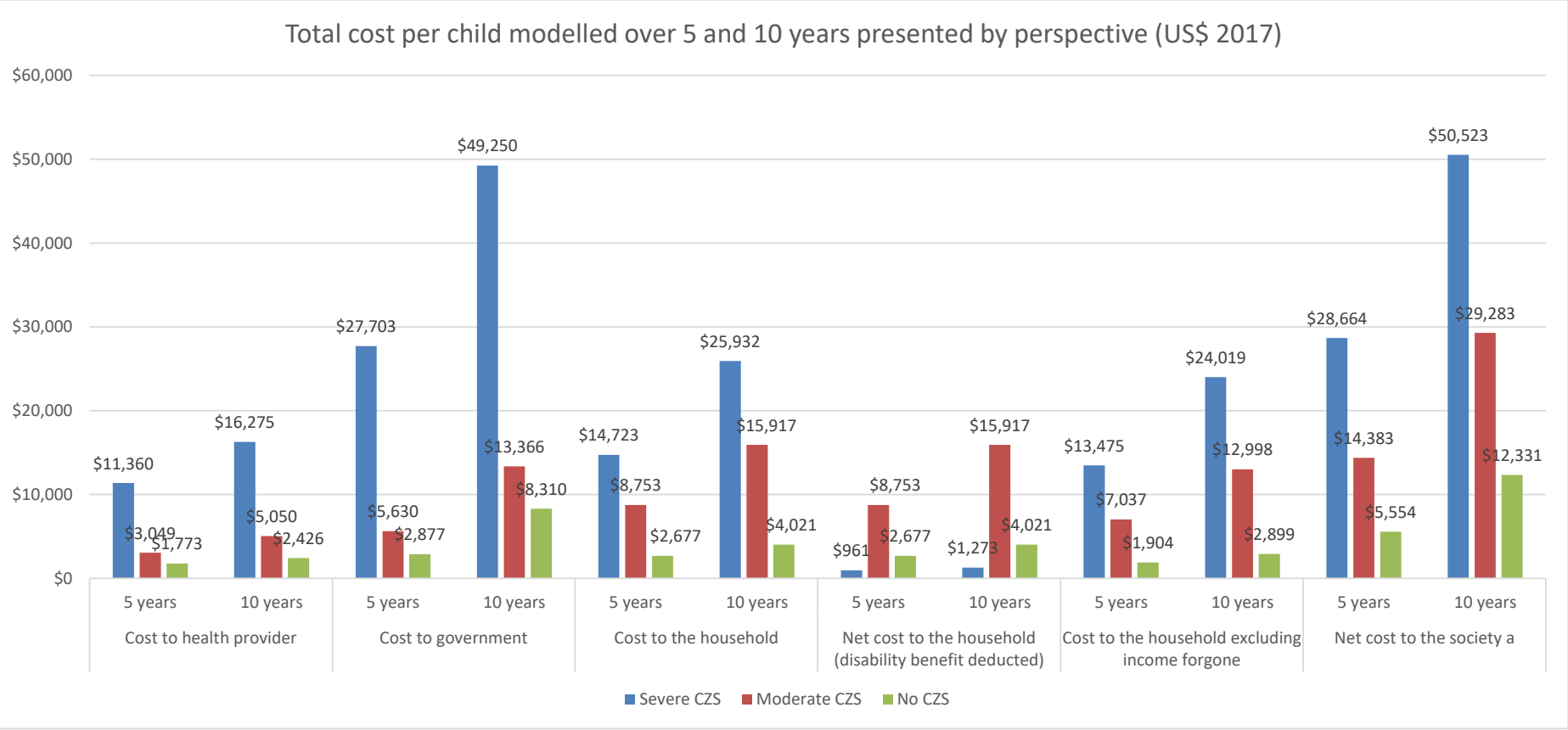
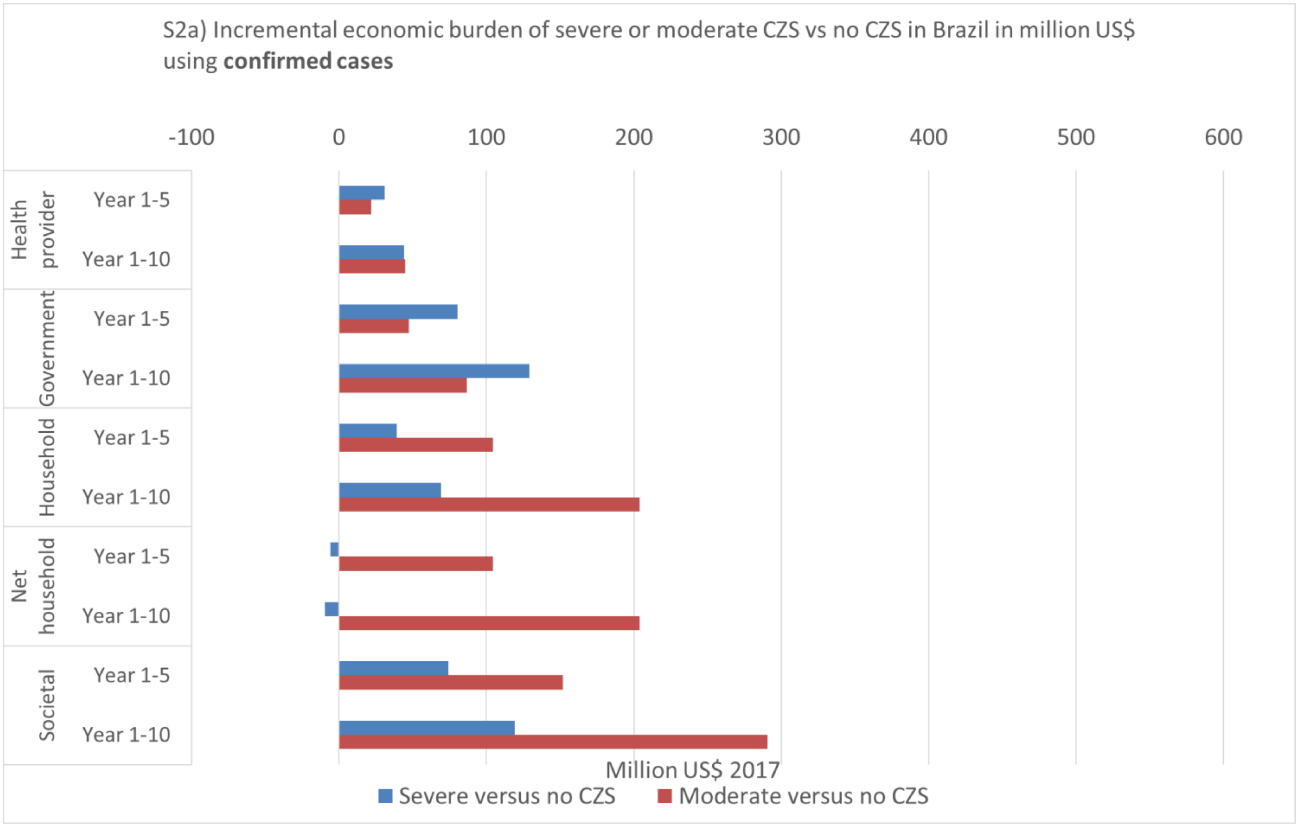
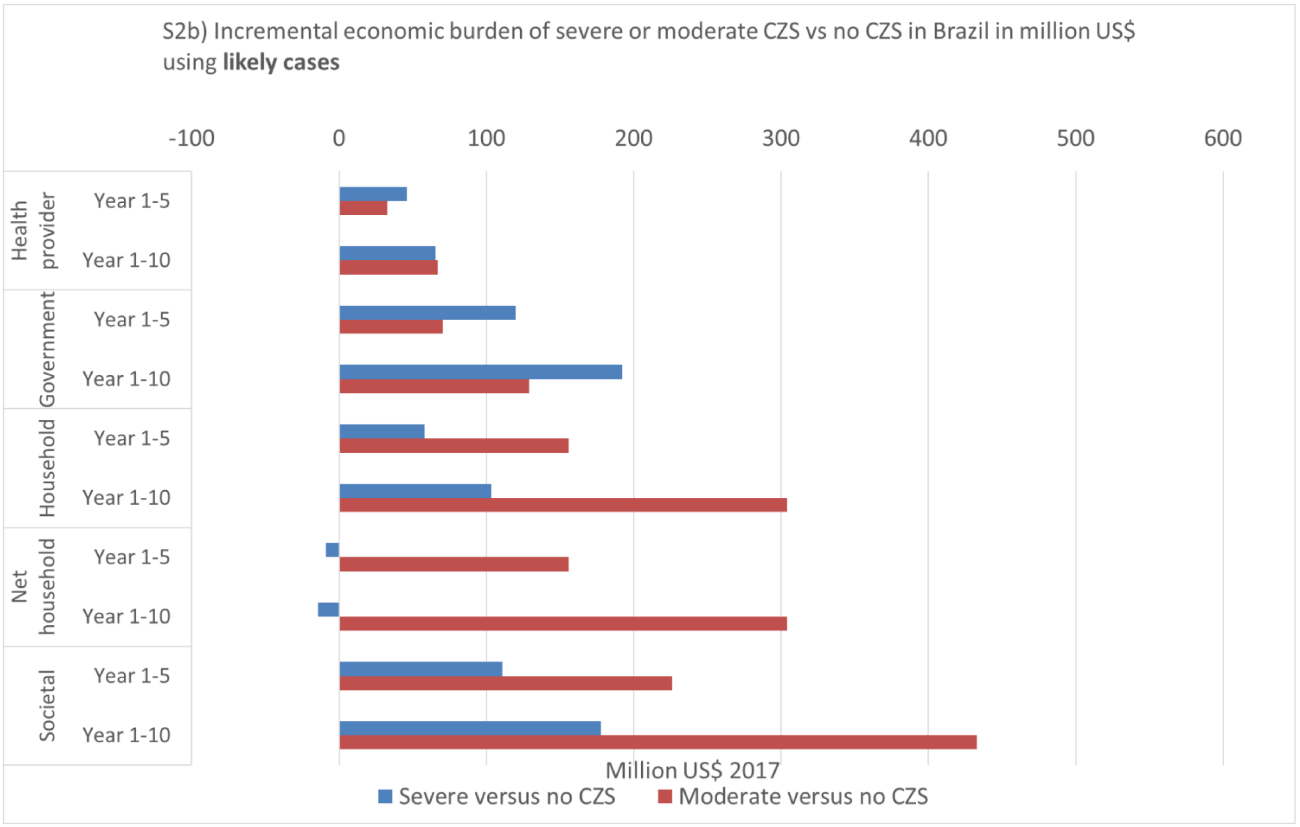


Figure S1: **The total costs per child** (US$ 2017) (note: not the incremental cost) for severe CZS (blue), moderate CZS (red) and no CZS (green) by time horizon (to 5 and 10 years of age) are shown by perspective (health provider, government, household, societal) in this table using the results from the **base case analysis**. The net cost to the household means that the disability benefit provided by the government to families of children with severe CZS was deducted from the household cost. This net cost to the

household was used when estimating the societal cost to avoid double counting. It only applies to children with severe CZS, since for moderate CZS and no CZS children the net cost to the household is the same as the cost to the household, as they do not receive a disability benefit.

Figure S2:


S2a) Incremental economic burden of severe or moderate CZS vs no CZS in Brazil in million US$ using **confirmed cases**
-100
0
100
200
300
400
500
600
Health provider
Year 1-5
Year 1-10
Government
Year 1-5
Year 1-10
Household
Year 1-5
Year 1-10
Net household
Year 1-5
Year 1-10
Societal
Year 1-5
Year 1-10
Million US$ 2017
Severe versus no CZS
Moderate versus no CZS



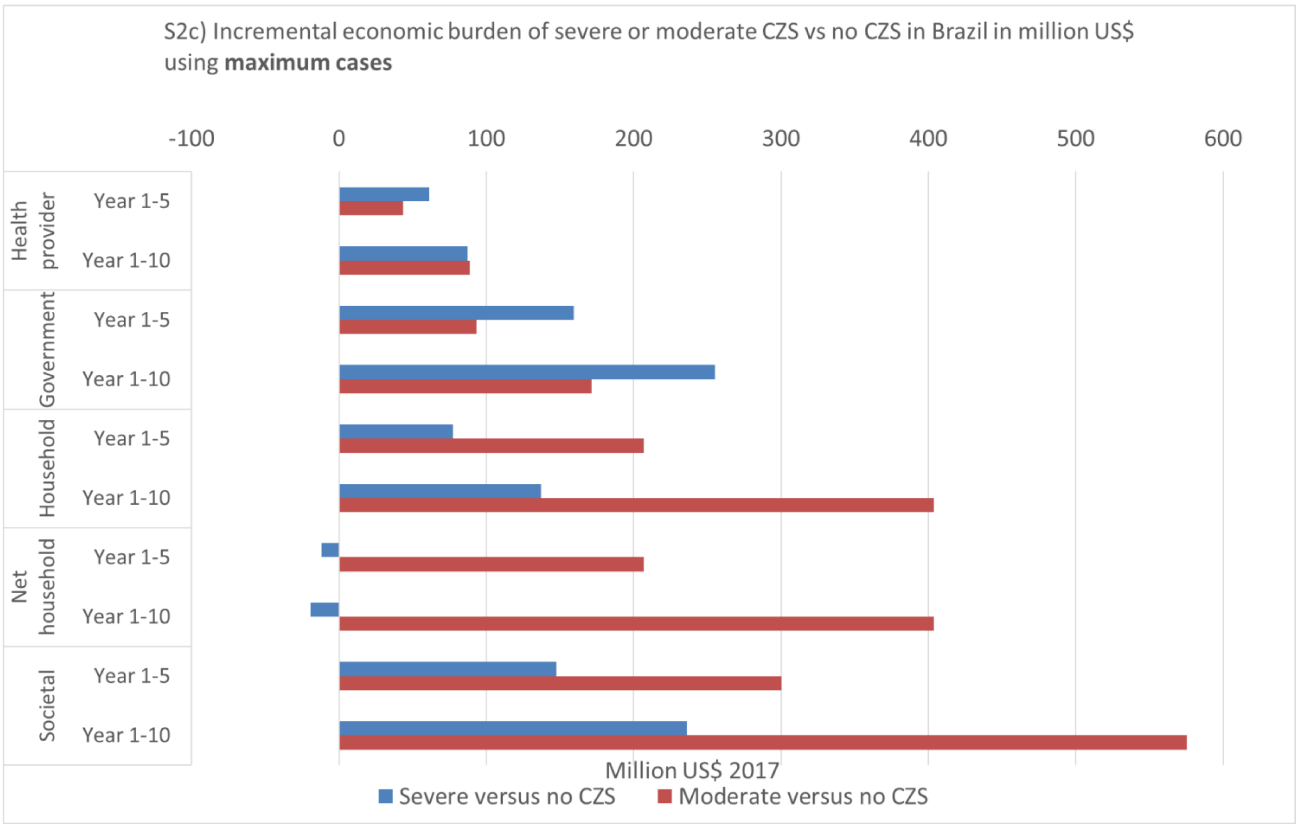


Figure S2 shows a **scenario analysis for incremental economic burden in Brazil** in million US$ 2017 where the number of cases of severe and moderate CZS was varied. The results show the incremental economic burden

comparing severe CZS (blue) or moderate CZS (red) with no CZS by perspective (health provider, government, household, societal), time horizon (to 5 and 10 years of age) and case numbers (confirmed, likely, maximum). The incremental net burden to the household for severe CZS means that the disability benefit provided by the government to families of children with severe CZS was deducted from the household cost when calculating their economic burden. This incremental net burden to the household was used when estimating the societal burden to avoid double counting. It only applies to severe CZS since for moderate CZS and no CZS the net burden to the household is the same as the burden to the household, as they do not receive a disability benefit.

[a] confirmed = confirmed severe CZS cases only, total N=3474
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[c] maximum = confirmed severe CZS cases + severe CZS cases under investigation + probable severe CZS cases, total N=6876
[d] clinical burden for moderate CZS was assumed to be 5 times the clinical burden of severe CZS in either of the three scenarios (confirmed, likely and maximum

References

1. Sperhac AM, Salzer JL. A new developmental screening test. The Denver II. J Am Acad Nurse Pract. 1991;3(4):152-7.
2. Kuper H, Lyra T, Moreira M, de Albuquerque M, de Araújo T, Fernandes S, et al. Social and economic impacts of congenital Zika syndrome in Brazil: Study protocol and rationale for a mixed-methods study [version 1; referees: 1 approved]. Wellcome Open Research. 2018;3(127).
3. Moreira M, Vasconcelos Z. Vertical Exposure to Zika Virus and Its Consequences for Child Neurodevelopment: Cohort Study in Fiocruz/IFF; ClinicalTrials.gov Identifier: NCT03255369. US. National Library of Medicine.
4. Bayley N. Bayley scales of infant and toddler development. 3 ed. SAn Antonio, TX: Pearson; 2006.
5. Kruse M, Michelsen SI, Flachs EM, Bronnum-Hansen H, Madsen M, Uldall P. Lifetime costs of cerebral palsy. Developmental medicine and child neurology. 2009;51(8):622-8.
6. Kruse M, Michelsen SI, Flachs EM. Livstidsomkostminger ved Cerebral Parese. 2007.
7. Ministry of Health Brazil. SIGTAP - Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS.
8. Study physicians and physiotherapists at IFF Fiocruz, Rio de Janeiro. 2018.
9. Government of Brazil. Benefício de Prestação Continuada 2019 [Available from: http://www.antigo.previdencia.gov.br/wp-content/uploads/2019/05/Relatorio-Avaliacao-BPC-Fasico_31_05_2019.pdf.
10. UNICEF. Infant and under 5 mortality [Available from: https://data.unicef.org/country/bra/.

Reflexivity statement

1. **How does this study address local research and policy priorities?**

Almost all the children affected by Congenital Zika Syndrome were born in Brazil. Consequently, the care of these children became an important concern of the Brazilian government. However, there was a lack of information on the needs of these children, given that the condition was new. This project sought to understand the social and economic impacts of Congenital Zika Syndrome, to help inform the response of the government and to maximise support to families. This study is therefore clearly focussed on addressing local research and policy priorities.

2. **How were local researchers involved in study design?**

Three research teams from three settings were involved in the study: Fiocruz in Rio de Janeiro, Fiocruz and affiliated organizations in Recife, The London School of Hygiene & Tropical Medicine. The current study built upon two existing studies, which had been designed and implemented by the two Brazilian research teams. Moreover, the local researchers determined the current study design, by contributing to decisions on the research questions, developing the data collection tools, and defining the approach for achieving the study sample. A one-week planning workshop was held in Recife with all research partners to facilitate agreement on the study design. Most notably, MP is an economist and guided the development and pilot-tested the collection of costing data for the current paper.

3. **How has funding been used to support the local research team(s)?**

Approximately £300,000 in funding was given by Wellcome for the project. This amount was divided into three equal parts, for the three research settings (Rio de Janeiro, Recife, London) with a principal investigator (EM, TL, HK) from each setting responsible for the funding decisions and reporting for her setting. The Brazilian funding was mostly spent on supporting research staff and for the collection of data.

4. **How are research staff who conducted data collection acknowledged?**

All research staff who contributed towards data collection and interpretation are included as authors. They all contributed during the writing process and reviewed and agreed the final draft.

5. **How have members of the research partnership been provided with access to study data?**

All members of the research partnership have access to the study data.

6. **How were data used to develop analytical skills within the partnership?**

Presentations on economic analysis and our plans for modelling were presented during a group workshop, to improve the knowledge and awareness of researchers within the partnership. The economists from Rio de Janeiro (MP) and London (SF) worked closely with a professor of economics (MJB) to guide the analysis of the project, including through a one week visit by MP to London.

7. How have research partners collaborated in interpreting study data?

A workshop was held in Rio de Janeiro with all the research partners to present preliminary findings and agree the interpretation of the study data.

8. How were research partners supported to develop writing skills?

The overall study led to the publication of 9 papers (given below), with two further in submission. Seven of these papers have a local researcher as first author and all of which included local researchers as authors. For each paper, British academics support local researchers in identifying appropriate journals, structuring the paper, revising the English language and improving the presentation to be more appropriate for international journals. The writing skills of the research partners were supported through these steps.

9. How will research products be shared to address local needs?

A dissemination meeting was held in Recife to share the main findings of the research, with the audience including other researchers, policy makers and mothers of children with Congenital Zika Syndrome. Information presented at that meeting was tailored to help inform practice and policy and therefore address local needs.

10. How is the leadership, contribution and ownership of this work by LMIC researchers recognised within the authorship?

Two previous publications on the economic data have been submitted (Cad SAude Publica, and Wellcome Open), led by a local researcher (MP). The authorship of the current paper includes 9 authors, 6 of whom are from Brazil. We acknowledge that in this publication the first and last author are from a high income setting. However, of the 9 published papers, 7 have a Brazilian first author and 5 have a Brazilian senior author (see list below). On all the publications, the majority of the authors are Brazilian.

11. How have early career researchers across the partnership been included within the authorship team?

We have included early career researchers (SF, LB) in the research team including as first author.

12. How has gender balance been addressed within the authorship?

All authors are female.

13. How has the project contributed to training of LMIC researchers?

Two workshops were held with all the researchers to agree research methods and to validate the main findings. These workshops were instructive to all researchers. The LMIC researchers were generally highly experienced and required little training in the conduct of research. However, they received support to publish papers in international journals.

14. How has the project contributed to improvements in local infrastructure?

This project has not directly contributed to improvements in local infrastructure.

15. What safeguarding procedures were used to protect local study participants and researchers?

Ethical approval was received for this study from the relevant agencies in Brazil and in the UK. Informed consent was achieved from all participants. We were committed to keeping information confidential and anonymised. We have not made data openly available as we are concerned that individual participants could be identified. The subject matter was distressing and the researchers formed a support group and met regularly to discuss the research and issues that arose.

Further information. The full list of papers published through this study, to provide context:

1: Pinto M, Moreira MEL, Barros LBP, Costa ACCD, Fernandes S, Kuper H. Gasto catastrófico na síndrome congênita do vírus Zika: resultados de um estudo transversal com cuidadores de crianças no Rio de Janeiro, Brasil [Catastrophic expenditure on congenital Zika syndrome: results of a cross-sectional study of caregivers of children in Rio de Janeiro, Brazil]. Cad Saude Publica. 2021 Nov 22;37(11):e00007021. Portuguese. doi: 10.1590/0102-311X00007021. PMID: 34816948.

2: de Melo APL, Lyra T, de Araújo TVB, de Albuquerque MDSV, Valongueiro S, Kuper H, Penn-Kekana L. "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 Dec 8;12(12):1410. doi: 10.3390/v12121410. PMID: 33302536; PMCID: PMC7763975.

3: Simas C, Penn-Kekana L, Kuper H, Lyra TM, Moreira MEL, de Albuquerque MDSV, de Araújo TVB, de Melo APL, Figueira Mendes CH, Nunes Moreira MC, Ferreira do Nascimento MA, Pimentel C, Pinto M, Valongueiro S, Larson H. Hope and trust in times of Zika: the views of caregivers and healthcare workers at the forefront of the epidemic in Brazil. Health Policy Plan. 2020 Oct 1;35(8):953-961. doi: 10.1093/heapol/czaa042. PMID: 32681164; PMCID: PMC7553755.

4: Passos MJ, Matta G, Lyra TM, Moreira MEL, Kuper H, Penn-Kekana L, Mendonça M. The promise and pitfalls of social science research in an emergency: lessons from studying the Zika epidemic in Brazil, 2015-2016. BMJ Glob Health. 2020 Apr;5(4):e002307. doi: 10.1136/bmjgh-2020-002307. PMID: 32345582; PMCID: PMC7213811.

5: Sá MRC, Vieira ACD, Castro BSM, Agostini O, Smythe T, Kuper H, Moreira MEL, Moreira MCN. De toda maneira tem que andar junto: ações intersetoriais entre saúde e educação para crianças vivendo com a síndrome congênita do vírus Zika [The need to act together in every way possible: inter-sector action in health and education for children living with the congenital Zika syndrome]. Cad Saude Publica. 2019 Nov 28;35(12):e00233718. Portuguese. doi: 10.1590/0102-311X00233718. PMID: 31800795; PMCID: PMC7612576.

6: Kuper H, Lyra TM, Moreira MEL, de Albuquerque MDSV, de Araújo TVB, Fernandes S, Jofre-Bonet M, Larson H, Lopes de Melo AP, Mendes CHF, Moreira MCN, do Nascimento

MAF, Penn-Kekana L, Pimentel C, Pinto M, Simas C, Valongueiro S. Social and economic impacts of congenital Zika syndrome in Brazil: Study protocol and rationale for a mixed-methods study. Wellcome Open Res. 2019 Sep 11;3:127. doi: 10.12688/wellcomeopenres.14838.2. PMID: 31667356; PMCID: PMC6807146.

7: Kuper H, Lopes Moreira ME, Barreto de Araújo TV, Valongueiro S, Fernandes S, Pinto M, Lyra TM. The association of depression, anxiety, and stress with caring for a child with Congenital Zika Syndrome in Brazil; Results of a cross- sectional study. PLoS Negl Trop Dis. 2019 Sep 30;13(9):e0007768. doi: 10.1371/journal.pntd.0007768. PMID: 31568478; PMCID: PMC6786834.

8: Albuquerque MSV, Lyra TM, Melo APL, Valongueiro SA, Araújo TVB, Pimentel C, Moreira MCN, Mendes CHF, Nascimento M, Kuper H, Penn-Kekana L. Access to healthcare for children with Congenital Zika Syndrome in Brazil: perspectives of mothers and health professionals. Health Policy Plan. 2019 Sep 1;34(7):499-507. doi: 10.1093/heapol/czz059. PMID: 31369667; PMCID: PMC6788207.

9: Moreira MCN, Nascimento M, Mendes CHF, Pinto M, Valongueiro S, Moreira MEL, Lyra TM, Kuper H; SEIZ Research Group. Emergency and permanence of the Zika virus epidemic: an agenda connecting research and policy. Cad Saude Publica. 2018 Aug 20;34(8):e00075718. doi: 10.1590/0102-311X00075718. PMID: 30133655.