Supplementary appendix

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

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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*

.. table continues next page

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:

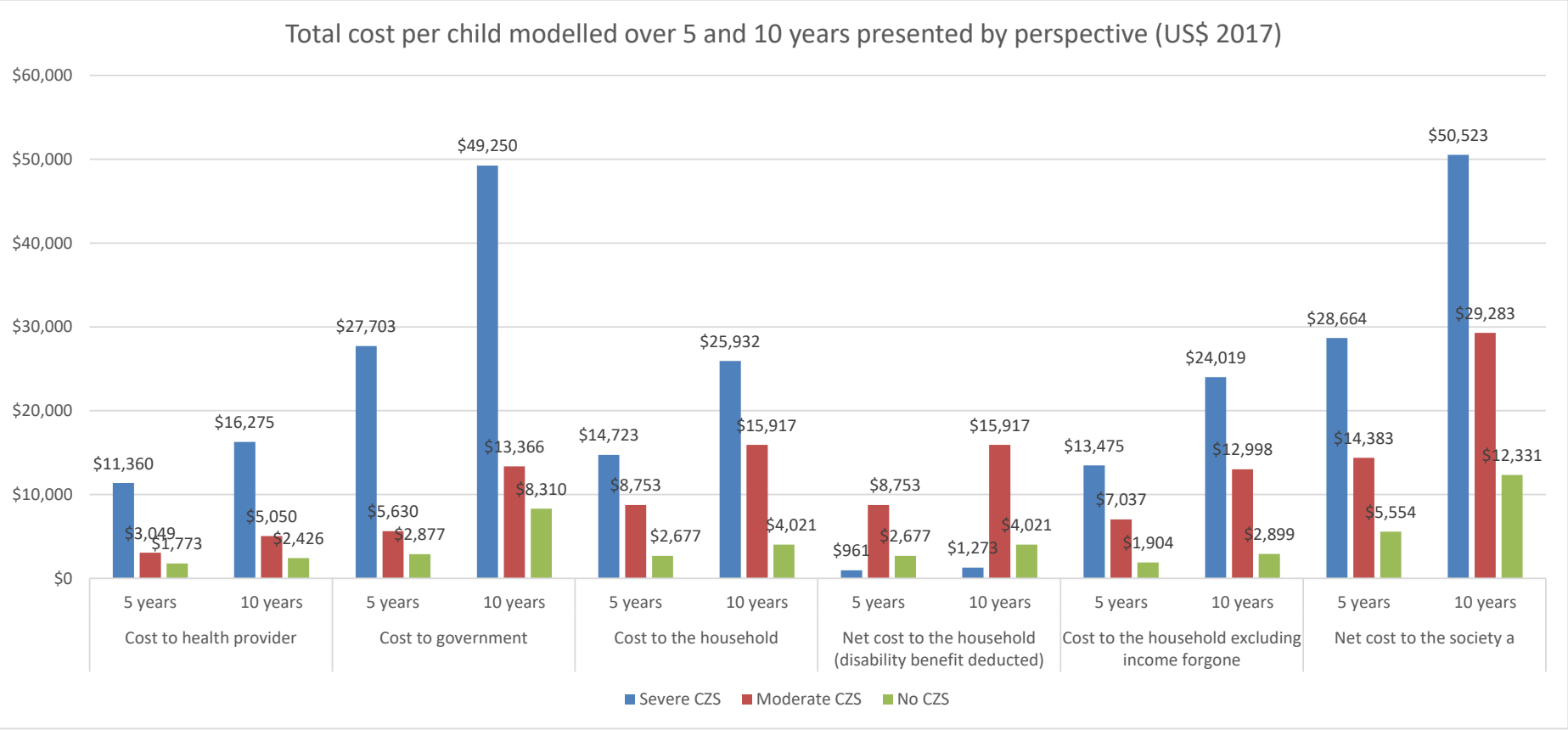
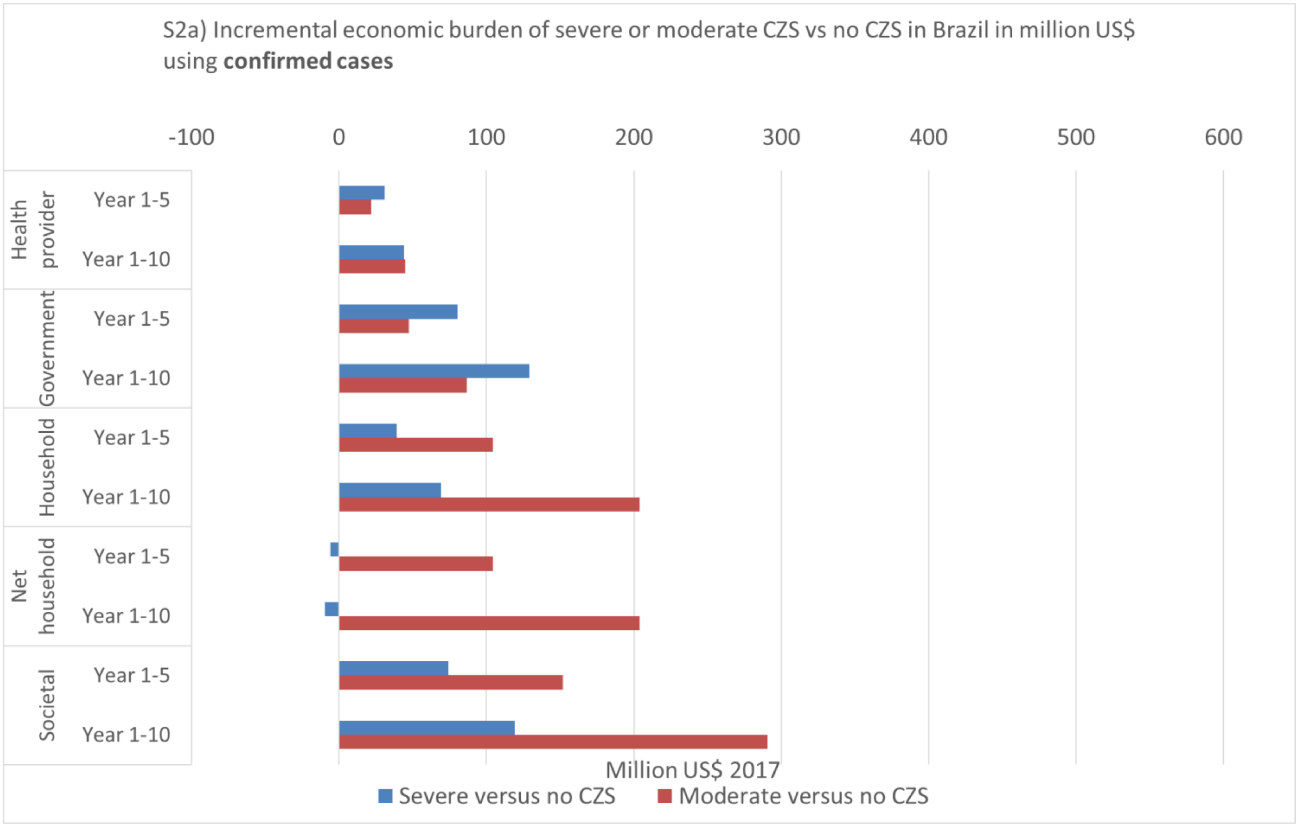
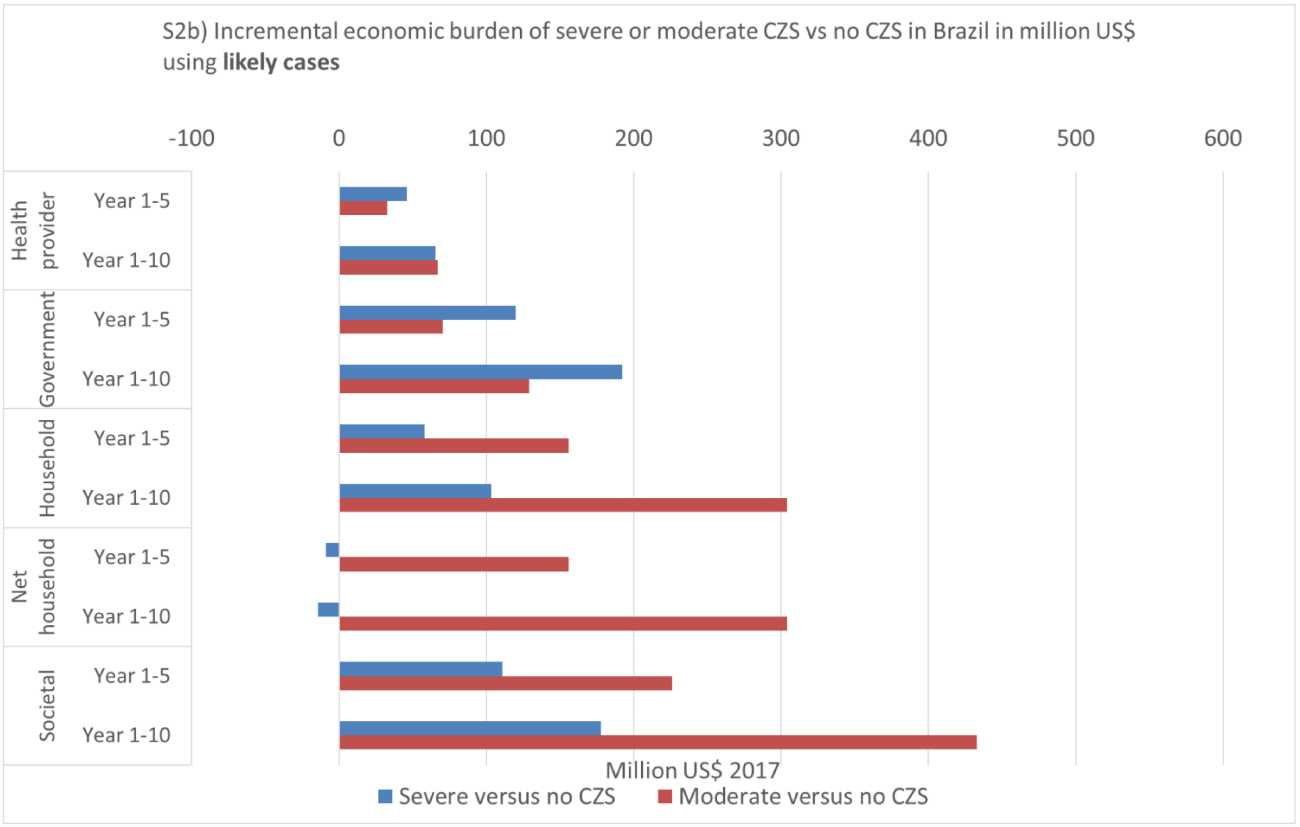


Figure S1: **The total costs per child** (US$ 2017) (note: not the incremental cost) for severe CZS (blue), moderate CZS (red) and no CZS (green) by time horizon (to 5 and 10 years of age) are shown by perspective (health provider, government, household, societal) in this table using the results from 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



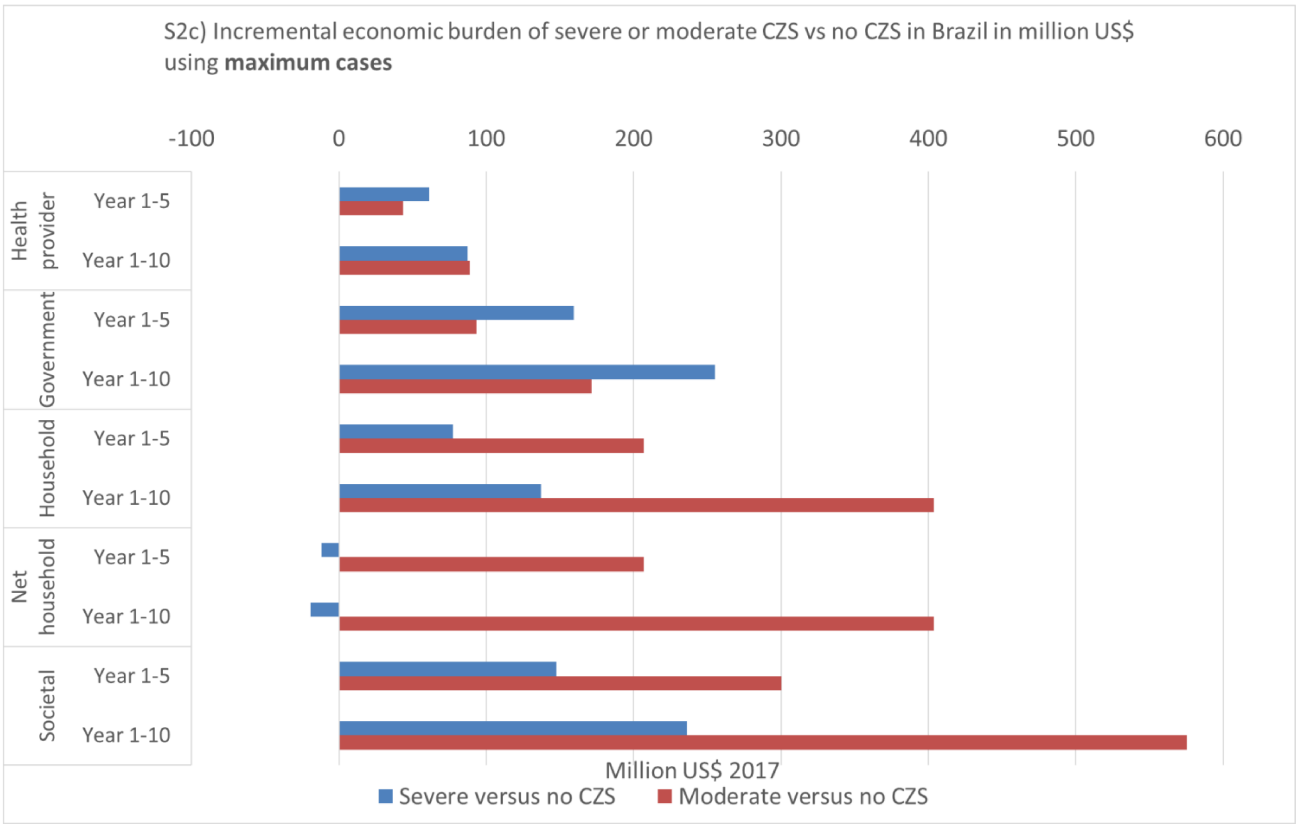


Figure S2 shows a **scenario analysis for incremental economic burden in Brazil** in million US$ 2017 where the number of cases of severe and moderate CZS was varied. The results show the incremental economic burden

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
[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

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