Consequences of congenital cytomegalovirus infection in early childhood

Korndewal, Marjolein

Chapter 6

Healthcare costs attributable to congenital cytomegalovirus infection

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Submitted

Abstract

Importance
Congenital cytomegalovirus infection (cCMV) is the most common congenital infection worldwide. It can cause symptoms at birth as well as long-term impairment, including sensorineural hearing loss and developmental delay.

Objective
This study estimates cCMV-related healthcare costs in the Netherlands in the first six years of life.

Design, Setting, and Participants
In a nation-wide retrospective cohort study 156 children with cCMV were identified by testing 31,484 stored neonatal dried blood spots using polymerase chain reaction. Use of healthcare resources in the first six years of life by children with cCMV and a matched cCMV-negative control group was analyzed. Mean costs per child were calculated from a healthcare perspective, by multiplying healthcare resource use by its reference prices.

Exposure
Children with cCMV (exposed) were compared with children without cCMV (unexposed).

Main Outcome and Measures
The average total healthcare costs per child were calculated. The total costs were based on the average costs for hospital admissions and consultations by medical specialists, general practitioners and other healthcare providers.

Results
Medical data of 133 cCMV-positive and 274 cCMV-negative children were analyzed. Mean healthcare costs of children with cCMV (€6,113) were higher than those of cCMV-negative children (€3,570). The additional healthcare costs of cCMV were €2,544 (95% CI -€451, €5,538) per child in the first six years of life. When cCMV-positive children had symptoms at birth (€15,922), costs were more than four times higher than in asymptomatic cCMV-positive children (€3,730). In the Netherlands a total of €2.3 million could be attributed to cCMV for the whole birth cohort (184,634 children) of 2008 in the first six years of life.

Conclusions and Relevance
Children with cCMV, especially those symptomatic at birth, accrue higher healthcare costs than cCMV negative children in the first six years of life, although this is not statistically significant. Costs of special needs education, psychological healthcare and non-healthcare costs such as productivity losses of parents will further increase costs. In addition to the health impact, the economic impact needs to be taken into account in preventive measures aiming to reduce the prevalence and burden of cCMV.

Trial Registration
Dutch Trial Register: Identifier: NTR 3582.

Introduction

Cytomegalovirus (CMV) infections are endemic worldwide and generally cause no harm in immunocompetent individuals. [1] Congenital CMV infection (cCMV) is caused by vertical transmission of CMV from mother to fetus. About 10 to 15% of children with cCMV have symptoms at birth including hepatosplenomegaly, microcephaly and intracranial calcifications. [2, 3] Children with cCMV, both with and without symptoms at birth, can develop long-term impairments such as sensorineural hearing loss [4, 5], cognitive and motor developmental delay [2, 6] and visual impairment [7, 8]. The birth prevalence of cCMV varies between 0.2% and 6% globally [3, 9] and is 0.5% in the Netherlands. [10, 11]

The economic impact of cCMV and its impact on the healthcare system may be substantial. The cCMV-related symptoms at birth and long-term impairment are expected to result in a significant demand on the healthcare system, both during childhood and later in life. Moreover, severe and permanent cCMV-related health problems may lead to reduced lifetime productivity. It has been estimated that four billion dollars of healthcare costs, for 40,000 children with cCMV and 2800 transplant patients, could be saved annually in the United States of America if a 100% effective vaccine against CMV would be available with a 100% uptake. [12]

Previously, we assessed the clinical consequences of cCMV in the Netherlands. [13] In this nation-wide retrospective cohort study, medical data of the first six years of life of children with cCMV and without cCMV were compared. We found that 19.6% of children with cCMV and 12.4% of children without cCMV had symptoms at birth. Long-term impairment was seen in 24.8% of children with cCMV compared to 12.0% in those without cCMV. [13]

This nation-wide cohort was used to investigate cCMV-related healthcare use and related costs in the first six years of life. This is the first study that directly estimates the costs of healthcare for children with cCMV. The retrospective design of this study allowed us to evaluate the care that was actually sought and provided, while generally parents and healthcare providers were unaware of the cCMV-status of the child. The information provided by this study can be used to estimate the impact of cCMV on the healthcare system and to support policy-makers in their ongoing discussions on cost-effectiveness of preventive strategies.

Methods

Study design and participants

The CROCUS-study is a nation-wide retrospective cohort study aimed to assess the prevalence of cCMV and its long-term consequences in the first six years of life in the Netherlands. The study design has been published elsewhere [11]. In short, parents of 73,693 children, born between January 1 and September 30 2008, living in the Netherlands were invited to participate in the study between October 2012 and January 2013. In the first part of this study neonatal dried blood spots of 31,484 children were tested retrospectively by polymerase chain reaction for CMV DNA and 156 children with cCMV were detected. Of these, only four children had been diagnosed with cCMV prior to this study. From the cCMV-negative children a control group was selected, matched for sex, month of birth and postal code region. Parents of 133 cCMV-positive children and 274 cCMV-negative children gave informed consent for collection of medical data from general practitioners, medical specialists and other healthcare providers. Parents were asked to list all healthcare providers who had seen their child. Between May 2014 and January 2015 requests for medical records or information concerning hospital admissions and outpatient clinic visits, sent to these healthcare providers and the requested information was received.

Collection of data on healthcare resource use

All collected medical data were entered in the study database without knowing whether the child in question had cCMV or not. The number of consultations with the various healthcare providers were recorded. Additionally, the number of inpatients days and number of specific diagnostic procedures and interventions during hospital admissions or at the outpatient clinic were registered. Afterwards the cCMV-status and categorization of patients as being symptomatic or asymptomatic at birth and as having long-term impairments or not, were added to the database for analysis. Being symptomatic at birth was defined as having one or more specific signs or symptoms in the first four weeks of life. These were preterm birth, being small for gestational age, microcephaly, hepatomegaly or splenomegaly, generalized petechiae or purpura, seizures and hypotonia, thrombocytopenia, neutropenia, elevated alanine transaminase, conjugated hyperbilirubinemia, neonatal sensorineural hearing loss, cranial ultrasound abnormalities and ophthalmological abnormalities. Long-term impairments included sensorineural hearing loss, permanent visual impairment, neurological impairment (epilepsy, cerebral palsy, microcephaly, attention deficit-hyperactivity disorder and autism spectrum disorder) and moderate to severe motor, cognitive or speech-language developmental delay.

Healthcare reference prices

This study was carried out from a healthcare perspective. Reference prices for consultations with healthcare providers, hospital admissions and outpatient visits were obtained from the “Dutch Manual for Costing: Methods and Reference Prices for Economic Evaluations in Healthcare" (from here on referred to as the manual) [14]. These reference prices from 2009 were converted into 2013 Euros according to the consumer price index [15]. Medication costs were not included in our analyses because no expensive medicines had been prescribed and medication costs in this study were generally low. In those cases where the manual did not provide reference prices, other references were used, the reference prices of

similar activities were extrapolated, or prices were obtained from the previous version of the manual [16] or from the financial department of a University Medical Center.
Reference prices of outpatient clinic visits and inpatient days, as provided by the manual [14], included costs of medical personnel, materials, building maintenance, overheads and equipment and also nutrition and medication in the case of hospital admissions. However, diagnostic procedures and interventions were not included in these reference prices. Separate reference prices of diagnostic procedures, as determined for January 2013, were obtained from the website of The Dutch Healthcare Authority [17]. Simple laboratory tests, such as hematology and biochemistry tests, were not taken into account because costs were generally low. Reference prices for individual healthcare providers were added up to calculate the costs of multidisciplinary consultations. Further details on the reference healthcare prices are displayed in Supplement 6.1.

Data analysis and missing data handling

Healthcare costs were calculated per child by multiplying the healthcare resource use by their reference prices.
It was assumed that all children who needed healthcare were first seen by the general practitioner, since referral by a general practitioner is required for appointments with medical specialists or other healthcare providers in the Netherlands. If the exact number of consultations with the physical therapist or speech therapist was not clear from the medical data, this was estimated on the basis of the condition and severity of the disorder. These estimates were provided by a healthcare provider working in this specific field and are shown in supplement 6.2. When no data were available concerning visits to the general practitioner or other healthcare providers mentioned by parents, multiple imputation (25 imputations) was used to estimate the number of visits. This was based on sex, date of birth, cCMV-status and the recorded number of visits to healthcare providers, number of days of hospital admissions and costs of diagnostic procedures and interventions.
The mean healthcare costs in the first six life years of the cCMV-positive and cCMV-negative children were compared using a t-test, which is an appropriate statistical method for comparing cost data [18]. A pooled t-test analysis was performed on the data estimated by multiple imputation. Furthermore, analyses were performed to investigate the healthcare costs for children who were symptomatic or asymptomatic at birth and those with and without long-term impairments.
To assess the impact of cCMV on the Dutch healthcare system, the additional healthcare costs per child attributable to cCMV were extrapolated to the Dutch birth cohort of 2008, comprising 184,634 live-born children [19]. All statistical analyses were performed using SAS version 9.3.

Ethical and legal issues

This study is registered in the “Dutch Trial Register” (NTR 3582). It was approved by the medical ethics committee of the Leiden University Medical Center in Leiden. The authors declare compliance with the Helsinki Declaration of 1975, as revised in 2008, regarding all procedures during this study.

Results

Baseline data and collected data

Parents of 133 children with cCMV and 274 children without cCMV gave informed consent for collection of their children's medical data. Baseline data of these children are presented in Table 6.1.

Detailed clinical consequences were described elsewhere. [13] The collected medical data included general practitioner files of 95% of the participating children. Data were available for 100% of children whose parents indicated that they had attended a medical specialist. Data were obtained of 96% of children attending a speech therapist or a physical therapist. Data were available of 89% of children whose parents noted that they had attended a speech and hearing center. The amount of missing data did not differ between the cCMV-positive and cCMV-negative groups.

Table 6.1 - Baseline characteristics of children with and without cCMV

	cCMV-positive (n = 133)	**cCMV-negative** (n = 274)
Age on 1-1-2014 (years)	5.6 ± 0.2	5.6 ± 0.2
Female sex	58 (43.6%)	125 (45.6%)
Symptomatic at birth*	26 (19.5%)	34 (12.4%)
- With long-term impairment	14 (53.8%)	3 (8.8%)
- Without long-term impairment	12 (46.2%)	31 (93.4%)
Long-term impairment**	33 (24.8%)	33 (12.0%)
- With symptoms at birth	14 (42.4%)	3 (9.1%)
- Without symptoms at birth	19 (57.6%)	30 (90.9%)

Data are presented as number (%) or mean ± standard deviation

* Any of the following in the first four weeks of life:
preterm birth, being small for gestational age, microcephaly, hepatomegaly or splenomegaly, generalized petechiae or purpura, seizures and hypotonia, thrombocytopenia, neutropenia, elevated alanine transaminase, conjugated hyperbilirubinemia, neonatal sensorineural hearing loss, cranial ultrasound abnormalities or ophthalmological abnormalities.

** Any of the following impairments in the first six years of life:
sensorineural hearing loss, permanent visual impairment, neurological impairment (epilepsy, cerebral palsy, microcephaly, attention deficit-hyperactivity disorder, and autism spectrum disorder) and moderate to severe motor, cognitive or speech-language developmental delay

Healthcare costs

Mean healthcare costs during the first six years of life of children with and without cCMV are presented in Table 6.2. Mean healthcare costs per child were €6,113 for children with cCMV compared to €3,546 for cCMV-negative children, a difference of €2,568 with a 95% confidence interval (CI) from -€418 to €5,553. Especially physical therapists and speech therapists were attended more often by cCMV-positive children, and the mean healthcare costs for these types of care were statistically significantly higher in the cCMV-positive group compared to the cCMV-negative children.

Table 6.2a - Overview of healthcare costs of cCMV-positive and cCMV-negative children in the first six years of life (in 2013 €)

	cCMV-positive (n = 133)				cCMV-negative (n = 274)			
	% children[a]	mean visits/ days[b]	mean costs/ child[c]	SD mean costs	% children[a]	mean visits/ days[b]	mean costs/ child[c]	SD mean costs
Hospital admissions								
- Pediatric admissions[1]	45,9%	8,1 d	€1,901	€5183	36,5%	6,8 d	€1,283	€4295
- Neonatal admissions[2]	13,5%	9,1 d	€1,693	€10298	16,8%	8,5 d	€941	€3742
Medical specialists								
- Outpatient clinic visits[3]	75,2%	9,7	€701	€1300	71,9%	7,8	€492	€1093
General practitioner								
- All GP-visits[4]	100%	15,9	€575	€504	100%	16,4	€606	€573
Healthcare providers								
- Physical therapy	22,6%	31,2	€275	€942	11,3%	12,3	€55	€177
- Speech therapy	24,8%	55,9	€498	€1887	16,1%	21,3	€123	€453
Healthcare facilities								
- Speech/hearing center	12,8%	7,5	€82	€338	3,3%	9,8	€45	€362
- Rehabilitation center	3,0%	346,8	€391	€3091	0,7%	4,5	€2	€28
Total costs	**100%**		**€6,113**	**16678**	**100%**		**€3,546**	**€7376**

1) hospital admission to a pediatric ward; 2) hospital admission to a neonatal ward or neonatal intensive care unit; 3) visits to outpatient clinic and hospital emergency room, mean costs also include diagnostic procedures and medical interventions; 4) visits to general practitioner (GP) including out-of-hours visits to a general practitioner clinic.
a) % children: percentage of children of the whole group visiting a specific healthcare provider; b) mean visits or days: average number of visits by the children visiting the specific healthcare provider or the average number of days (d) of hospital admission; c) mean cost per child: average cost of specific healthcare based on the total costs divided by the total number of children in the whole group (cCMV+ or cCMV-); SD: standard deviation

Table 6.2b - Overview of healthcare costs of cCMV-positive and cCMV-negative children in the first six years of life (in 2013 €)

	cCMV+ vs cCMV- Mean difference	95% CI
Pediatric admissions	€618	-€408, €1644
Neonatal admissions	€752	-€1075, €2578
Outpatient clinic visits	€209	-€49, €466
All GP-visits	-€32	-€148, €85
Physical therapy	€220*	€56, €384
Speech therapy	€375*	€48, €703
Speech/hearing center	€37	-€37, €111
Rehabilitation center	€389	-€143, €921
Total costs	**€2,568**	**-€418, €5553**

95% CI: 95% confidence interval;* Statistically significant ($p < 0.05$)

Children with and without symptoms at birth

In both the cCMV-positive and cCMV-negative children, the healthcare costs were much higher in children with symptoms at birth compared to children who were asymptomatic at birth (Figure 6.1, Table 6.3, Supplement 6.3). As to be expected, a large part of the average total healthcare costs, more than €5,000, in these children with symptoms at birth was due to hospital admissions for neonatal care. In cCMV-positive children with symptoms at birth costs for physical therapy, speech therapy and rehabilitation center visits were noticeably higher compared to children without cCMV who had symptoms at birth. However, these differences were not statistically significant. In children without symptoms at birth, the costs for physical therapy were significantly higher for children with cCMV than for their cCMV-negative counterparts (mean difference: €110, 95% CI €8-€212).

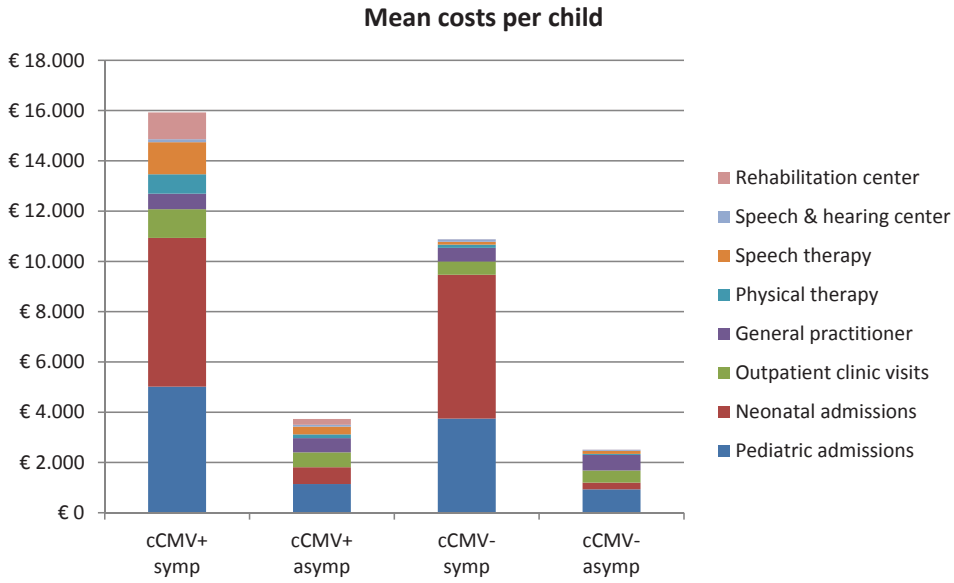

Figure 6.1 - Mean costs per child (in 2013 €) for children with (cCMV+) and without cCMV (cCMV-) who were symptomatic (symp) or symptomatic (asymp) at birth.

About half of the total costs of children with cCMV were attributable to the small group (20%) of children with symptoms at birth, while the other half was accounted for by the 80% asymptomatic children. In children without cCMV the 12% symptomatic children incurred almost 40% of the total costs (Supplement 6.5).

Children with and without long-term impairment

The average healthcare costs of children with long-term impairment were seven times higher in cCMV-positive children and three times higher in cCMV-negative children compared to children without long-term impairments (Figure 6.2, Table 6.3, Supplement 6.4). Children with long-term impairment and cCMV had higher costs for physical therapy compared to children with long-term impairment without cCMV (mean difference: €801, 95% CI €178-€1423). Also the costs for neonatal hospital admissions and attending a rehabilitation center and speech therapy were higher in these cCMV-positive children, but this was not statistically significant.

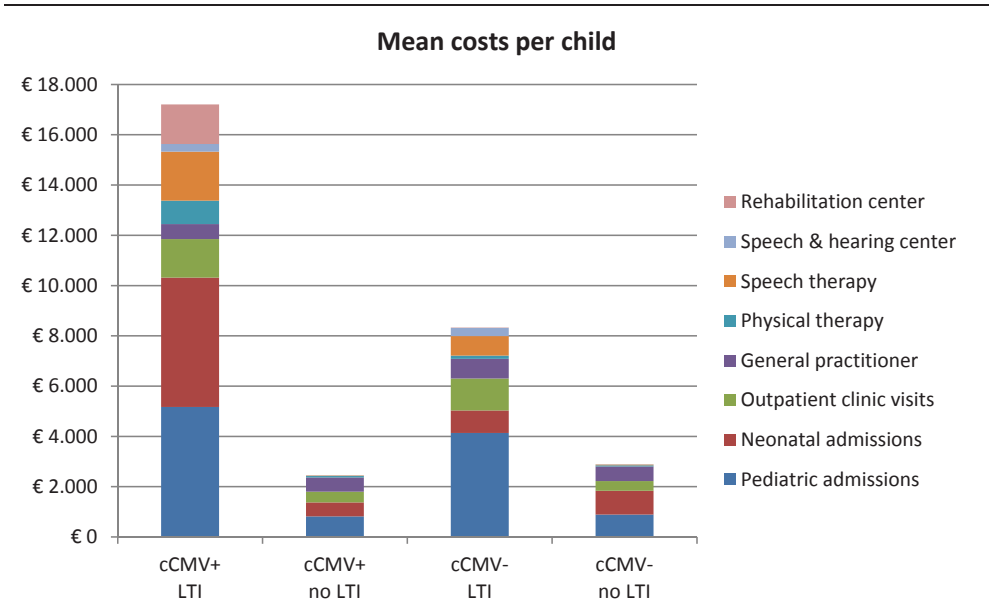

Figure 6.2 - Mean costs per child (in 2013 €) for children with (cCMV+) and without cCMV (cCMV-) who developed long-term impairment (LTI) or did not develop long-term impairment (no LTI).

In cCMV-positive children, 70% of the total costs were incurred by the 25% of children with long-term impairment in this group. In children without cCMV, the 12% children with long-term impairment accounted for approximately 30% of the total costs. An important part (43%) of the costs of cCMV-positive children were incurred by the 11% of children who were symptomatic at birth and had long-term impairments (Supplement 6.5).

Table 6.3 - Mean difference in mean total costs per child in 2013 € for children with and without cCMV

	cCMV-positive (n = 133)		**cCMV-negative** (n=274)		**Mean difference**	95% CI
	Mean	SD	Mean	SD		
Symptomatic at birth	€15,922	€32,530	€10,878	€16,697	€5,044	-9,213, 19,302
Asymptomatic at birth	€3,730	€7,739	€2,507	€3,736	€1,223	-330, 2,777
Long-term impairment	€17,205	€30,034	€8,332	€14,652	€5,044	-2,924, 20,671
No long-term impairment	€2,453	€4,307	€2,890	€5,378	-€437	-1,529, 655

SD: standard deviation, 95% CI: 95% confidence interval

Costs of congenital cytomegalovirus infection

Based on the birth rate of 184,634 live-born children in 2008 and the birth prevalence of cCMV of 0.5% in the Netherlands, an estimated 915 children were born with cCMV in that year in the Netherlands. The total healthcare costs of children with cCMV during the first six years of life would add up to approximately 5.6 million euro (3.0 million euro/100,000 children). Approximately half of these costs would be attributable to the approximately 80% children with cCMV who are asymptomatic at birth. The additional national healthcare costs during the first six years of life, attributable to cCMV, for this year cohort were estimated at 2.3 million euro (1.3 million euro/100,000 children).

Discussion

This is the first cost-of-illness study on cCMV using real-life data from a cCMV-positive cohort and a matched cCMV-negative control group to estimate the attributable costs of cCMV. It demonstrated that children with cCMV have higher average healthcare costs in the first six years of life than cCMV-negative children. The difference in total healthcare costs between these groups, although statistically not significant, is more than €2,500 per child. When extrapolated to the Dutch birth cohort of 2008 this means that 2.3 million euro healthcare costs in the first six years of life could be attributed to cCMV in the Netherlands. The total costs of children with cCMV in this birth cohort would add up to 5.6 million euro for the first six years of life. Although the costs in cCMV-positive children are highest in children with long-term impairment (70% of the total costs), especially in those who also had symptoms at birth (43% of the total costs), the large and usually unrecognized group of children with cCMV who are asymptomatic at birth are responsible for half of the costs

Estimates of costs of cCMV are scarce and up to now these were all based on assumptions of the prevalence of impairments and the costs associated with these impairments. For example the estimated costs of cCMV and CMV-related morbidity of 4 billion United States dollars per year, calculated on an expected 40,000 cCMV-positive newborn infants (assuming a 1% birth prevalence) and 2800 transplant patients per year in the United States were based on general assumptions concerning hospitalization, outpatient visits and special schooling expenses. [12] The few other studies that have been conducted on the costs of cCMV, were mostly cost-effectiveness studies on the effect of preventive measures such as targeted neonatal screening [20, 21] and vaccination [22]. These studies did not aim to estimate the total costs of cCMV and most of these cost-effectiveness studies focused primarily on the costs of hearing loss, since sensorineural hearing loss is frequently seen in children with cCMV. [4]

Costs of illness studies are difficult to compare, due to differences in design and calculation methods. However, a rough indication of the costs of different illnesses in the Netherlands can be obtained from the Cost of illness tool. [23] To put our results into perspective, the results of this study were compared to the costs for congenital disorders of the central nervous system in children 0 to 6 years in the Netherlands in 2011. These costs are estimated to be around 3.5 million euro (in 2011 euros), which is noticeably lower than the estimated costs of cCMV. [24]
It is important to realize that costs are now estimated for the first six years of life, in one birth cohort. These figures will generally be applicable to the other birth cohorts as well. The total healthcare cost of cCMV for children up to six years of age are therefore assumed to be around 5.6 million euro every year and the costs are presumably even higher when older children and adults are taken into account.

Even though the difference in average healthcare costs between the cCMV-positive and cCMV-negative children is quite large (€2,500), it is statistically not significant. This is due to the large variance in costs, which is probably the result of differences in disease severity and the relatively small number of children availing of specific care types (e.g. rehabilitation center).

Moreover, there are several reasons to presume that the actual difference in healthcare costs between the cCMV-positive and cCMV-negative children is larger than found in this study. First of all, children who died of cCMV in the first five years of life were not included in this study as inclusion started at five years of age. The healthcare costs of these children before they died could have been substantial.
Second, this study estimated the healthcare costs only up to six years of age. When this cohort will be followed-up for longer the difference between cCMV- positive and cCMV-negative children might become even larger. The onset of some cCMV-related sequelae, such as sensorineural hearing loss can occur up to, or even after, the age of six years. [25] Consequently, more healthcare costs can be incurred later in these children's lives. For example, the cost of a pediatric cochlear implant is considerable (estimated lifetime cost: €82,000 - €108,000). [26]
Importantly, cCMV-related sequelae are often permanent, leading to ongoing healthcare costs, while in the general population most healthcare costs in children are usually made in the first five years of life. [27]

Moreover, specific data about visits to, for example, dieticians and psychosocial care centers, were often not available because they were not mentioned by the parents and consequently no medical data was collected, even though it was clear from other medical records that this type of care had been provided. As cCMV is associated with poorer cognitive development [2] and potentially with neuro-behavioral problems such as autism, [28, 29] lack of detailed data on psychological healthcare in this study means that the overall health costs, specifically of cCMV-positive children, would probably be higher. All in all, it is likely that the total healthcare costs of children with cCMV are underestimated in this study.

Finally, it should be noted that this study only looked at healthcare costs. Other costs related to the impairment of children with cCMV, such as special needs education, [30] future reduced productivity and potential productivity loss of parents, were not taken into account.

Conclusion

This study shows that healthcare costs are higher in children with cCMV, albeit not statistically significantly, compared to cCMV-negative children. In cCMV-positive children, the highest costs were incurred by the 11% of children with long-term impairment and symptoms at birth, who are responsible for 43% of the total costs. However, half of the total costs in children with cCMV are caused by children who are asymptomatic at birth. Moreover, the real healthcare and other costs are probably even higher in the cCMV-positive group, because costs for psychosocial healthcare and special needs education were not taken into account in this study. This study provides crucial information essential for discussions on the necessity of programs to reduce or prevent the burden of cCMV.

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Conflict of Interest Disclosures:

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Supplement 6.1 - Reference prices of Consultations per Healthcare Provider (in 2013 €)

Reference prices of consultations with healthcare professionals	Reference price	Reference
Reference prices of General Practitioners consultations		
General Practitioner's visit (10 minutes)	30.48	[14]
General Practitioner's house call	46.81	[14]
General Practitioner's consultation by telephone	15.24	[14]
Out-of-hours GP visit	151.97	a
Out-of-hours GP consultation by telephone	75.90	a
Reference prices of outpatient-clinic visits		
Outpatient clinic visit (general hospital)	69.67	[14]
Outpatient clinic visit (university hospital)	140.42	[14]
Outpatient clinic visit (unknown type of hospital)	78.37	[14]
Outpatient clinic telephone consultation (general hospital)	34.84	b
Outpatient clinic telephone consultation (university hospital)	70.21	b
Outpatient clinic telephone consultation (unknown type hospital)	39.69	b
Outpatient treatment (one-day admission)	320.18	[14] c
Emergency room visit	164.37	[14]
Emergency room telephone consultation	82.19	b
Specialized Skeletal dysplasia team (university hospital)	460.45	d
Reference prices of hospital admissions – per day		
Inpatient day (general hospital)	473.51	[14]
Inpatient day (university hospital)	625.91	[14]
Inpatient day (unknown type of hospital)	497.46	[14]
Inpatient day (Burn Center)	971.81	[31]
Neonatal or pediatric Intensive Care Unit (university hospital)	2376.28	[14]
Reference prices per visit to an allied health professional		
Physiotherapist (30 minutes)	39.19	[14] e
Speech therapist (30 minutes)	35.92	[14] e
Remedial therapist (30 minutes)	38.10	[14] e
Occupational therapist (30 minutes)	11.98	[14]
Orthoptist (30 minutes)	27.98	f
Reference prices per discipline in speech and hearing center		
Audiologist (15 minutes)	78.37	g
Clinical linguist (15 minutes)	78.37	g
Speech-language pathologist (15 minutes)	78.37	g
Ear. Nose and Throat specialist (15 minutes)	78.37	[14]
Cochlear Implant coordinator/physician (15 minutes)	78.37	[14]
Speech therapist (30 minutes)	35.92	[14]
Acoupedist (30 minutes)	35.92	h
Rehabilitation therapist (30 minutes)	35.92	h
Physiotherapist (30 minutes)	39.19	[14]
Occupational therapist (30 minutes)	11.98	[14]
Audiology assistant (30 minutes)	11.98	i
Reference prices rehabilitation center		
Visit to a rehabilitation specialist	69.67	[14]
Visit to rehabilitation center therapists. such as physiotherapist, occupational therapist. speech therapist (60 minutes)	119.74	[14]

a No reference prices were available for out-of-hours GP consultations. The Dutch Healthcare Authority states tariffs of €8.67 and of €43.15, for standard GP consultations and out-of-hours consultation [32], respectively, indicating that out-of-hour consultations are 4.98 times higher than standard GP consultations. Therefore reference prices for GP consultations as stated in Hakkaart et al. [14] were multiplied by 4.98, resulting in an assumed reference price of €151.97 for out-of-hours GP visits and of €75.90 for out-of-hours GP consultation by telephone.
b In line with GP reference prices of general practitioners, telephone consultations by the outpatient clinic and emergency room were assumed to cost half of the reference price of outpatient clinic and emergency room visits.
c The reference price for outpatients' treatment is based on the reference price as provided by the Dutch Manual for Costing in Healthcare Economic Evaluations. This reference price does not include fees for physicians, therefore additional weighted reference prices for time spent by the medical specialist and residents are added.
d One child had visited a specialized team in a University hospital because of skeletal dysplasia. This team consists of an orthopedic surgeon, a medical revalidation specialist, a physiotherapist and a pediatrician. The reference price of per consultation was calculated by adding reference prices of these medical specialists and the physical therapist, resulting in a reference price of (3*140.42) + (1*39.19) = 460.45 per consultation.
e Reference prices were stated in the manual per session for physical therapist, speech therapists, and remedial therapists. After contacting the Institute for Medical Technology Assessment, who had developed the Manual, we were informed that duration of an average session with these therapists is half an hour.
f No reference prices were available for consultations with an orthoptist. Since the level of education is equal to other allied health professionals, we assumed the mean reference prices per half hour for physical therapist , speech therapist, remedial therapist, occupation therapist and dietician. In addition, we assumed the duration of consultations with an orthoptists to be half an hour.
g No reference prices were available for consultations with audiologists, clinical linguists and speech-language pathologists. Since the education level of these professions is similar to the education level of medical specialists, the same rate has been assumed for these professions. Following personal communication with a speech and hearing center the duration of an audiologist's consultation was calculated as lasting fifteen minutes, hearing diagnostics as one hour and diagnostics by a speech therapist as two and a half hours.
h No reference price was available for consultations of an acoupedist and rehabilitation therapist, however, these professionals are all specialized speech therapists and therefore the reference price of a speech therapist is applied here.
i No reference price was available for a consultation with an audiologist assistant. Since this profession has a lower education level than the professions of the allied health professionals, we assumed the lowest reference price of allied health professionals, the reference price of an occupational therapist, which is €11.98 per half an hour.

Supplement 6.2 - Assumed numbers of consultations per diagnosis for speech therapy and physical therapy

Physical therapist	**Assumed number consultations**
Behavioral and movement disorders (e.g. developmental coordination disorder, attention deficit-hyperactivity disorder, autism spectrum disorder)	20
Balance disorders	20
Hypermobility	20
Hypertonicity	20
Urine or fecal Incontinence	10
KISS Syndrome (Kinematic Imbalances due to Suboccipital Strain)	9
Mild restraint of abduction upper arm	18
Hypertonicity (newborn)	12
Proprioceptive problems	18
Scoliosis	18
Sensory processing disorder - not otherwise specified	18
Developmental delay - fine motor skills	18
Developmental delay - gross motor skills	18
Urge incontinence	10
Positional plagiocephaly	10

Speech therapist	**Assumed number consultations**		
	Mild	**Moderate**	**Severe**
Articulation disorder - not otherwise specified	8	20	40
Lisping	8	16	24
Stuttering or speech dysfluency	12	20	40
Auditory processing disorder	12	16	24
Expressive language disorder	12	24	40
Hearing impairment		16	
Hyper salivation		8	

A disorder was classified as mild, moderate or severe based on the medical information from the speech therapist; when no statements were made about disease severity it was assumed to be moderate. All medical data were classified by one author (MK) and checked by a second author (AO).

Supplement 6.3 - Overview of healthcare costs (in 2013 €) in the first six years of life of cCMV-positive and cCMV-negative children with or without symptoms at birth

	cCMV-positive (n = 133)							
	Symptomatic at birth (n = 26)				Asymptomatic at birth (n = 107)			
		mean	mean costs			mean	mean costs	
	% [a]	visits [b]	mean [c]	SD [d]	% [a]	visits [b]	mean [c]	SD [d]
Hospital admission								
- Pediatric admissions 1	65,4	14,8 d	€ 5,016	9,956	41,1	5,5 d	€ 1,144	2,531
- Neonatal admissions 2	30,8	11,8 d	€ 5,918	20,792	9,3	7,0 d	€ 666	4,638
Medical specialists								
- Outpatient clinic visits 3	84,6	14,1	€ 1,140	2,175	72,9	8,4	€ 594	946
General practitioner								
- All GP visits 4	100	16,6	€ 619	521	100	15,8	€ 564	500
Healthcare providers								
- Physical therapy	42,3	46,6	€ 772	1,769	17,8	22,2	€ 154	519
- Speech therapy	42,3	84,0	€ 1,277	3,607	20,6	41,8	€ 309	1,043
Healthcare facilities								
- Speech & hearing center	19,2	7,6	€ 120	372	11,2	7,4	€ 72	328
- Rehabilitation center	3,8	737,0	€ 1,060	5,306	2,8	216,7	€ 228	2,215
Total costs			**€ 15,922**	**32,530**			**€ 3,730**	**7,739**
	cCMV-negative (n = 274)							
	Symptomatic at birth (n = 34)				**Symptomatic at birth (n = 34)**			
		mean	mean costs			mean	mean costs	
	% [a]	visits [b]	mean [c]	SD [d]	% [a]	visits [b]	mean [c]	SD [d]
Hospital admission								
- Pediatric admissions 1	44,1	18,5 d	€ 3,942	10,850	35,4	4,9 d	€ 934	2,524
- Neonatal admissions 2	52,9	16,3 d	€ 5,719	8,824	11,7	3,4 d	€ 264	1,129
Medical specialists								
- Outpatient clinic visits 3	85,3	8,5	€ 534	733	70,0	7,7	€ 486	1,135
General practitioner								
- All GP visits 4	100	14,1	€ 537	423	100	16,7	€ 616	591
Healthcare providers								
- Physical therapy	26,5	12,3	€ 128	255	9,2	12,3	€ 44	160
- Speech therapy	17,6	18,2	€ 115	313	15,8	21,7	€ 124	470
Healthcare facilities								
- Speech & hearing center	5,9	17,5	€ 95	513	2,9	7,5	€ 38	335
- Rehabilitation center	2,9	1,0	€ 2	13	0,4	8,0	€ 2	30
Total costs			**€ 10,878**	**16,697**			**€ 2,507**	**3,736**

1) hospital admission to a pediatric ward; 2) hospital admission to a neonatal ward or neonatal intensive care unit; 3) visits to outpatient clinic and hospital emergency room, mean costs also include diagnostic procedures and medical interventions, 4) visits to general practitioner including out-of-hours general practitioner clinic visits. a) %: percentage of children of the whole group visiting a specific healthcare provider; b) mean visits: average number of visits by the children visiting the specific healthcare provider or the average number of days (d) of hospital admission; c) mean costs: average costs of specific healthcare based on the total costs divided by the total number of children in the whole group; d) SD: standard deviation of average cost of specific type of healthcare.

Supplement 6.4 - Overview of healthcare costs (in 2013 €) in the first six years of life of cCMV-positive and cCMV-negative children with or without long-term impairment

	cCMV-positive (n = 133)							
	Any long-term impairment (33)				No long-term impairment (100)			
	% [a]	mean visits [b]	mean costs mean [c]	SD d	% [a]	mean visits [b]	mean costs mean [c]	SD [d]
Hospital admission								
- Pediatric admissions	66,7	15,5d	€ 5.173	€ 8.905	39,0	3,9d	€ 821	€ 2.211
- Neonatal admission	21,2	14,3d	€ 5.143	€ 19.515	11,0	5,8d	€ 554	€ 3.203
Medical specialists								
- Outpatient clinic visits	87,9	17,8	€ 1.536	€ 2.169	71,0	6,3	€ 425	€ 625
General practitioner								
- All GP visit	100	15,8	€ 595	€ 568	100	16,0	€ 568	€ 481
Healthcare providers								
- Physical therapy	51,5	46,1	€ 928	€ 1,712	13,0	11,6	€ 59	€ 166
- Speech therapy	72,7	74,8	€ 1,954	€ 3,392	9,0	5,4	€ 17	€ 111
Healthcare facilities								
- Speech & hearing center	39,4	8,9	€ 301	€ 615	4,0	2,8	€ 9	€ 76
- Rehabilitation center	12,1	346,8	€ 1,575	€ 6,056	0		€ 0	€ 0
Total costs			**€ 17,205**	**€ 30,034**			**€ 2,453**	**€ 4,307**
	cCMV-negative (n = 274)							
	Any long-term impairment (33)				Any long-term impairment (33)			
	% [a]	mean visits [b]	mean costs mean [c]	SD [d]	% [a]	mean visits [b]	mean costs mean [c]	SD [d]
Hospital admission								
- Pediatric admissions	63,6	63,6	63,6	63,6	63,6	63,6	63,6	63,6
- Neonatal admission	12,1	12,1	12,1	12,1	12,1	12,1	12,1	12,1
Medical specialists								
- Outpatient clinic visits	78,8	78,8	78,8	78,8	78,8	78,8	78,8	78,8
General practitioner								
- All GP visit	100	100	100	100	100	100	100	100
Healthcare providers								
- Physical therapy	30,3	30,3	30,3	30,3	30,3	30,3	30,3	30,3
- Speech therapy	63,6	63,6	63,6	63,6	63,6	63,6	63,6	63,6
Healthcare facilities								
- Speech & hearing center	15,2	14,0	€ 325	€ 975	1,7	4,4	€ 6	€ 84
- Rehabilitation center	6,1	4,5	€ 16	€ 80	0		€ 0	€ 0
Total costs			**€ 8.332**	**€ 14.652**			**€ 2,890**	**€ 5,378**

1) hospital admission to a pediatric ward; 2) hospital admission to a neonatal ward or neonatal intensive care unit; 3) visits to outpatient clinic and hospital emergency room, mean costs also include diagnostic procedures and medical interventions, 4) visits to general practitioner including out-of-hours general practitioner clinic visits. a) %: percentage of children of the whole group visiting a specific healthcare provider; b) mean visits: average number of visits by the children visiting the specific healthcare provider or the average number of days (d) of hospital admission; c) mean costs: average costs of specific healthcare based on the total costs divided by the total number of children in the whole group;
d) SD: standard deviation of average cost of specific type of healthcare.

Supplement 6.5 -Total healthcare costs for children with and without cCMV and the relative contribution of the different subgroups

cCMV-positive (n = 133)							
		number children	% of total number	total costs	% of total costs	mean cost	standard deviation
Symptomatic	Total	26	20%	€ 413,967	51%	€ 15,922	€ 32,530
Asymptomatic	Total	107	80%	€ 399,109	49%	€ 3,730	€ 7,739
Long-term imp.	Total	33	25%	€ 567,759	70%	€ 17,205	€ 30,034
No long-term imp.	Total	100	75%	€ 245,317	30%	€ 2,453	€ 4,307
Long-term imp.	Sympt.	14	11%	€ 347,927	43%	€ 24,852	€ 41,550
	Asympt.	19	14%	€ 219,833	27%	€ 11,570	€ 14,898
No long-term imp.	Sympt.	12	9%	€ 66,040	8%	€ 5,503	€ 8,913
	Asympt.	88	66%	€ 179,277	22%	€ 2,037	€ 2,972
Total		**133**		**€ 813,076**			
cCMV-negative (n = 274)							
		number children	% of total number	total costs	% of total costs	mean cost	standard deviation
Symptomatic	Total	34	12%	€ 369,843	38%	€ 10,878	€ 16,697
Asymptomatic	Total	240	88%	€ 601,634	62%	€ 2,507	€ 3,736
Long-term imp.	Total	33	12%	€ 274,942	28%	€ 8,332	€ 14,652
No long-term imp.	Total	241	88%	€ 696,536	72%	€ 2,890	€ 5,378
Long-term imp.	Sympt.	3	1%	€ 97,069	10%	€ 32,356	€ 34,448
	Asympt.	30	11%	€ 177,873	18%	€ 5,929	€ 7,440
No long-term imp.	Sympt.	31	11%	€ 272,774	28%	€ 8,799	€ 11,972
	Asympt.	210	77%	€ 423,761	44%	€ 2,018	€ 2,478
Total		**274**		**€ 971,478**			

The total number and percentage of children, the total costs and percentage of total cost and the mean costs and standard deviations are displayed for the subgroups with and without symptoms at birth, the children with and without long-term impairment and for the subgroups of children with or without symptoms at birth who develop long-term impairment or those who do not develop long-term impairment. Sympt: symptomatic, Asympt: asymptomatic, imp.: impairment