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The economic cost of congenital CMV in the UK

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ABSTRACT

Objective: Congenital Cytomegalovirus (cCMV) is the most common infectious cause of congenital disability. It can disrupt neurodevelopment, causing lifelong impairments including sensori-neural hearing loss and developmental delay. This study aimed, for the first time, to estimate the annual economic burden of managing congenital cytomegalovirus (cCMV) and its sequelae in the UK.

Design: The study collated available secondary data to develop a static cost model.

Setting: The model aimed to estimate costs of cCMV in the UK for the year 2016.

Patients: Individuals of all ages with cCMV.

Main outcome measures: Direct (incurred by the public sector) and indirect (incurred personally or by society) costs associated with management of cCMV and its sequelae.

Results: The model estimated that the total cost of cCMV to the UK in 2016 was £732 million (lower and upper estimates were between £495 and £942 million). Approximately 40% of the costs were directly incurred by the public sector, with the remaining 60% being indirect costs, including lost productivity. Long-term impairments caused by the virus had a higher financial burden than the acute management of cCMV.

Conclusions: The cost of cCMV is substantial, predominantly stemming from long-term impairments. Costs should be compared against investment in educational strategies and vaccine development programmes that aim to prevent virus transmission, as well as the value of introducing universal screening for cCMV to both increase detection of children who would benefit from treatment, and to build a more robust evidence base for future research.

INTRODUCTION

Cytomegalovirus (CMV) is a herpesvirus, transmitted via bodily fluids. It is most commonly acquired through contact with saliva and urine of young children infected with CMV. In healthy children and adults, it is generally asymptomatic, but symptoms may include fever, pharyngitis and lymphadenopathy. When the virus is transmitted *in utero,* CMV can cause lifelong impairments in affected infants.

The seroprevalence of CMV in women of reproductive age is between 45% and 100% [1, 2]. Congenital CMV (cCMV) can occur in infants born to seronegative women who have primary CMV infection during pregnancy, as well as in infants born to seropositive women who experience either viral re-activation, or re-infection with a new viral strain, during pregnancy.

If cCMV produces symptoms at birth, treatment with ganciclovir, or its oral prodrug valganciclovir, may be initiated within the first 4 weeks of life [3]. Whether children with isolated sensorineural hearing loss (SNHL) should be treated is an area of current controversy [4]. The majority of infants (around 90% [3]) do not have clinical symptoms at birth and therefore are not diagnosed (or treated) in the neonatal period, but may be diagnosed retrospectively when SNHL or neurodevelopmental delay becomes apparent.

The most common neurodevelopmental impairment resulting from cCMV is SNHL, however, cerebral palsy, epilepsy, visual impairment, behavioural problems, feeding difficulties, sensory processing disorders, learning disability, balance disorders, attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) have also been associated with cCMV. As a result, children with cCMV may require extensive input from health and social care services, including audiology and audio-vestibular clinics, implant centres, paediatrics (including general paediatrics, neurology, gastroenterology, orthopaedics, community paediatrics, and infectious diseases specialists), physiotherapists, ophthalmologists, orthoptists, occupational therapists, dieticians, sensory integration therapists, speech and language therapists, psychologists and psychiatrists, teachers of the deaf, and special educational needs support and social workers. Children with

profound SNHL may be eligible for cochlear implantation, and children with motor impairments may require home modifications and wheelchairs to aid mobility. These impairments affect individuals throughout their life, especially in education, also impacting the level of productivity they are able to contribute to society when they reach adulthood. Of importance, due to missed opportunities for diagnosis of cCMV in routine clinical practice, cCMV may never be identified as the cause of subsequent impairment.

Given the missed diagnoses, lack of systematic testing for cCMV and heterogeneity in childhood impairments, there is considerable uncertainty around the disease burden. Each child is likely to follow a different care pathway dependent on the age of diagnosis (if, indeed, cCMV is ever diagnosed), the impairments a child acquires, and the degree of severity and combination of impairments. Following the acute management of cCMV (in cases where treatment is considered appropriate), management of subsequent impairments in the UK tends to involve interaction with impairment-specific services rather than relating to the cCMV per se.

The financial cost of cCMV to the health service and wider society is not known in the UK. This is essential to understand in order to plan services, to be able to develop cost-effectiveness models for preventive interventions – such as educational strategies to reduce the risk of women acquiring infection in pregnancy and CMV vaccines in development – and screening to enable earlier diagnosis of cCMV and intervention for affected children.

This economic model aimed to provide a ‘snapshot’ of the estimated financial cost of cCMV to the UK in 2016 (the most recent complete year when the model was developed). Where possible, the model included estimates of the direct costs of cCMV to the health service and government, indirect wider societal costs, and personal costs to families.

METHODS

Data sources

A comprehensive literature review identified studies reporting epidemiological and economic data associated with cCMV and its sequelae (see Supplement C for details). Epidemiological, longitudinal and cross-sectional studies were selected to estimate the number of individuals for whom costs for management of cCMV and its sequelae would be incurred, with a preference for UK-based studies. All sequelae for which sufficient epidemiology and cost data were available were included, resulting in inclusion of SNHL, cerebral palsy, ASD and epilepsy. Where UK data were unavailable, agreement on the most appropriate source to use was sought from clinical experts (see Supplement A for further details).

Where available, costs were identified from published literature, with a preference for UK-based studies. Where no economic studies were available, clinical costs were estimated using recommended care guidelines and published data on NHS treatment costs. All costs identified in published literature were converted to British Pounds and updated to 2016 values using appropriate inflationary indices where required (the Hospital and Community Health Services Index for health and social care costs, and the Gross Domestic Product Deflator for all other costs). All epidemiological and cost inputs and their sources are detailed in Supplements A and B respectively.

Key assumptions

Despite differing definitions, for simplicity, the model assumed equivalence between cohorts described as ‘symptomatic’. Costs for each sequela were included separately, as it was assumed that management would require use of condition-specific services even in cases of multi-morbidity. Although anti-viral treatment (approved for clinical use for cCMV in 2001) can improve long-term outcomes for treated children, estimates of the proportion of children with specific long-term outcomes were not adjusted for treatment effects in the model as there is a lack of data on the long-term implications of the treatment. The cost of anti-viral treatment for neonates, however, was included.

Model structure

The model time-horizon was one year, estimating costs for 2016. The population of individuals with cCMV in any one year was separated into four age bands:

- Age-band 1: All incident cases of babies born in 2016 up to the age of one year, including costs associated with acute management of babies diagnosed with cCMV.
- Age-band 2: Children aged one to five years, including costs associated with follow-up care for babies diagnosed with cCMV, as well as diagnoses and pre-school treatment costs for all infants with cCMV (with and without a cCMV diagnosis) developing any sequelae emerging in that time period (e.g. SNHL, cerebral palsy, ASD).
- Age-band 3: Children and adolescents aged between five and 18 years, including costs associated with management of ongoing and newly diagnosed sequelae, as well as educational support for all children and adolescents with cCMV (with and without a cCMV diagnosis).
- Age-band 4: Adults aged 18 to 81 (average UK life expectancy), including costs associated with ongoing management of sequelae and lost productivity for individuals with limited work capacity due to sequelae, for all adults with cCMV (with and without a cCMV diagnosis).

Where reported by secondary sources, costs associated with any time off work and/or changes to the working patterns of caregivers to allow them to care for their child were also included.

Sensitivity analysis

To explore uncertainty in some of the core epidemiological inputs, results are presented for three scenarios. The ‘base case’ scenario used inputs we consider most appropriate based on the evidence available and clinical expert opinion, while the impact of using lower and higher inputs was assessed using alternative inputs, as summarised in Table 1.

***Table 1*: Summary of variable model inputs used for different scenarios**

Input	Base case	Lower estimates	Upper estimates
% of live births born with cCMV	0.49% (Average of lower and higher estimates)	0.33% (Griffiths et al., 1991)	0.64% (Kenneson and Cannon, 2007)
% of those with cCMV born 'symptomatic'	11.00% (Griffiths et al., 1991)	4.80% (Peckham et al., 1983)	12.70% (Dollard et al., 2007)
% of live births with confirmed cCMV diagnosed at ≤21 days	0.030% (Average of lower and higher estimates [a])	0.006% (Townsend et al., 2011)	0.081% (All born 'symptomatic' [b])

[a] As calculated using base case inputs; [b] As calculated using upper estimate inputs.

RESULTS

Our model estimated that the cost of cCMV in 2016 was £732 million, with upper and lower estimates of £495 and £942 million pounds (see *Table 2***Error! Reference source not found.**). Of these costs, approximately 40% were 'direct' costs, incurred by the government for health, social, and educational services. The remaining 60% of costs were 'indirect' costs, including the cost of lost productivity to society, as well as the personal costs paid by families.

Acute cCMV management was only a small proportion of the overall costs, with estimates between approximately £198,000 and £4.1 million. This was driven by the combination of reasonably small costs per patient that are all incurred in early life (approximately £6,000 in the first year for diagnosed and treated infants, plus around £600 per year until age 5), and the small number of children diagnosed (between 46 and 630 live births per year).

The cost of managing long-term impairments was far higher. SNHL, the most common outcome following cCMV, was estimated to cost between £72 million and £181 million, while the greatest

costs were associated with the management of ASD. Estimated costs for ASD were between £241 million and £565 million, equating to around 50% to 60% of the total costs, despite the relatively low numbers of children affected (7.7% individuals born 'symptomatic' and 1.9% babies born 'asymptomatic'). While indirect costs comprised around 60% of the total ASD costs; around 30% in lost productivity and around 30% in other costs likely incurred by families (such as specialised accommodation and respite care for carers), direct costs for hospital care, (non-hospital) health and social care, and education were also high.

We estimated the total cost of cerebral palsy caused by cCMV to be £180.3 million, of which approximately 30% were direct non-clinical costs such as specialised education and social care, and another 30% were indirect societal costs of lost productivity. Direct clinical costs were a relatively small proportion of the total costs, at less than 10%. Aside from costs associated with acute management of cCMV, those associated with epilepsy were the lowest, at between £2.5 million and £12.7 million, and in line with other sequelae, many of these costs were indirect.

***Table 2*:** **Cost estimates for each scenario, stratified by impairment**

Type of costs	**Base case**	**Lower estimates**	**Upper estimates**
Acute management of cCMV [a]			
Direct clinical costs	£1,243,715	£251,467	£3,406,543
SNHL costs			
Direct clinical costs	£15,445,364	£8,328,804	£21,504,708
Direct non-clinical costs	£77,211,738	£42,596,089	£107,174,950
Indirect societal costs	£30,950,955	£17,132,678	£42,930,673
Indirect non-societal costs	£6,719,932	£3,710,426	£9,325,908
All SNHL costs	*£130,327,989*	*£71,767,997*	*£180,972,238*
Cerebral Palsy [b]			
Direct clinical costs	£15,179,159	£15,179,159	£15,179,159

Direct non-clinical costs	£75,138,349	£75,138,349	£75,138,349
Indirect societal costs	£69,614,061	£69,614,061	£69,614,061
Indirect non-societal costs	£20,331,864	£20,331,864	£20,331,864
All cerebral palsy costs	*£180,263,434*	*£180,263,434*	*£180,263,434*
ASD			
Direct hospital costs	£78,329,358	£45,744,806	£107,378,242
Direct non-hospital costs	£57,849,782	£33,784,900	£79,304,406
Indirect societal costs	£137,255,148	£80,157,812	£188,156,987
Indirect non-societal costs	£138,694,653	£80,998,527	£190,130,427
All ASD costs	*£412,128,940*	*£240,686,046*	*£564,970,062*
Epilepsy			
Direct clinical costs	£739,407	£219,529	£1,126,527
Direct non-clinical costs	£2,651,883	£787,341	£4,040,289
Indirect costs	£4,919,097	£1,460,475	£7,494,514
All epilepsy costs	*£8,310,386*	*£2,467,346*	*£12,661,329*
Aggregated costs			
Direct costs	£323,788,754	£222,030,445	£414,289,172
Indirect costs	£408,485,710	£273,405,445	£527,984,434
Total costs	**£732,274,464**	**£495,436,289**	**£942,273,606**

[a] For acute management of cCMV, all costs are direct clinical costs.

[b] The cost of cerebral palsy caused by cCMV does not vary across our scenarios as the calculations were based on the proportion of children with cerebral palsy (inputs that were not variable in the model), rather than those with cCMV.

DISCUSSION

Model findings and implications

The model base case estimated that the cost of cCMV to the UK in 2016 was £732 million (lower and upper estimates of £495 and £942 million respectively), of which approximately 40% of the costs were direct and 60% indirect. To put this in perspective, the total NHS 2015-16 budget was £116 billion, indicating our projections of the direct costs to the government of managing cCMV (including non-healthcare costs) equate to just under 0.3% the total NHS budget. For a virus that is rarely discussed in routine antenatal care, and about which there is a lack of awareness among parents and medical professionals alike [5-7], this is a considerable economic impact.

Acute management of cCMV was the lowest contributing cost (estimated at £1.2 million), with costs for management of long-term sequelae being orders of magnitude greater. Accordingly, further research assessing how far anti-viral treatment, administered pre- or post-natally, can be efficacious in reducing long-term impairment should be prioritised. Evidence shows that post-natal administration of valganciclovir is efficacious at stabilising and improving affected hearing, as well as a modest improvement in neurodevelopment in the 24 months following birth [8, 9]. Currently, treatment is only advised for 'symptomatic' babies with central nervous system involvement, with controversy remaining over whether babies with only SNHL should be treated [4]. Moreover, evidence indicates that a high proportion of cCMV positive babies who develop sequelae receive neither a diagnosis, nor anti-viral intervention [10]. In addition to research into the cost and effectiveness of administering treatment to a wider group of cCMV-positive babies, consideration of new diagnostic techniques, such as foetal MRI or blood sampling, is an essential component for early identification of babies who may benefit from anti-viral treatment.

A recent cost-effectiveness study indicated that both universal and targeted newborn screening would be cost-effective options for detecting and reducing hearing loss caused by cCMV in the USA under a wide range of assumptions [11]. Despite differences between the US and UK healthcare systems, this suggests that there is potential for a similar impact of universal screening on the UK, while a more

narrowly focussed UK study has predicted that CMV screening at least for babies who fail their national hearing screen would be cost-effective [12]. The introduction of universal screening would have additional research benefits, with identification of infected and affected infants providing more robust epidemiological and cost data, and helping us to understand more about the aetiology, prognosis and epidemiology of cCMV in the UK. The current model demonstrates how scarce robust literature specific to the UK is, with prevalence and incidence rates over 20 years old, and few large-scale longitudinal follow-up studies. Consequently uncertainty in our cost estimates can be observed in the wide range between our upper and lower estimates. Robust data are essential for decision-making to assess the cost-effectiveness of screening, preventative interventions such as educational strategies to modify behaviours to reduce the risk of acquiring CMV infection in pregnancy, CMV vaccines (currently in development [13]), and anti-viral treatment.

Limitations

The modelling approach taken is limited by the validity and availability of the inputs chosen and we anticipate that these costs underestimate the 'true' cost of cCMV. Use of primary data was not possible due to resource constraints and the low rate of diagnosis (demonstrated in Korndewal et al., 2017 [10]). Reliance on secondary data resulted in several limitations.

Firstly, it was not possible to include all cost-incurring outcomes that may be attributable to cCMV. Cost-incurring outcomes that have been linked to cCMV but were not included in the cost model include foetal loss and stillbirth, ADHD, visual impairment, vestibular dysfunction (which limited evidence suggests is particularly common among diagnosed children [14]), speech and language impairment, motor impairment, and intellectual impairment. Exclusion was primarily due to insufficient epidemiological data. In some instances, poor clarity of clinical pathways (e.g. vestibular dysfunction) limited our ability to estimate the costs of disease management, while overlap between study definitions of some impairments and sequelae included in the model meant the risk of double-counting was too high for inclusion of both (e.g. speech and language impairment and SNHL).

Secondly, where impairments were included in the model, accuracy and comprehensiveness was limited by the data available. In particular, it is likely that the costs associated with SNHL were

underestimated. A recent paper by Lanzieri et al. (2017) suggests SNHL may be more common among children with 'asymptomatic' cCMV than the previous literature indicates [15]. If replicable, the number of children with cCMV-related SNHL, and, therefore, incurring associated costs, will be higher than our model estimates. Similarly, some costs, particularly non-healthcare costs, were unavailable for some SNHL subgroups. Despite our model estimating unilateral hearing loss in almost 50% of the cases of SNHL attributed to cCMV, few management costs were included (aside from the relatively low costs of fitting and replacing hearing aids) due to lack of data. Other potentially substantial costs of unilateral hearing loss may include support from speech and language therapists and teachers of the deaf, provision of which varies with severity and geographical location, and lost productivity due to reduced academic performance [16]. Further, the model includes only cochlear implants and hearing aids, but alternative (and costly) hearing devices such as radio aids and bone-conduction hearing aids are also commonly used in cases of both unilateral and bilateral SNHL. In particular, bone-conduction hearing aids, which have an approximately 40% uptake where audiologically appropriate [17], cost around £5,000 for fixing and fitting, with additional ongoing maintenance costs [18]. Due to the scarcity of cost studies in the UK, it is also possible that there is uncertainty around the cost inputs which would have been propagated through the model.

Finally, although we consider it appropriate that many of the costs are likely to be sustained on the basis of each impairment separately, there is a risk the model may overestimate some costs due to double-counting in cases of multi-morbidity. In particular, lost productivity in adulthood may be double-counted in some cases. However, we are confident that this is outweighed by productivity losses associated with impairments not included.

Key knowledge gaps

There are a number of key knowledge gaps that were identified in the development of this cost model. To begin with, we are uncertain about the prevalence of cCMV in the UK, with the most recent UK-specific estimates from small-scale studies over 25 years ago [19]. Similarly, because of the problem of low diagnosis rates (particularly in asymptomatic babies), estimates of risk for long-term

impairments are uncertain. Further, we do not know what proportion of babies are likely to undergo investigations for cCMV, nor the proportion of diagnosed babies likely to receive anti-viral treatment.

Other knowledge gaps were identified relating to the management of long-term impairments. With regard to hearing loss, we do not know how common hearing amplification and rehabilitation is in unilateral SNHL, nor the proportion of cases of cCMV-related SNHL that are candidates for cochlear implantation. Given the high prevalence of SNHL in children impaired following cCMV, and the high costs of technologies used in the management of the condition, these clarifications could have a large impact on estimates of the cost of cCMV. Similarly, there is a lack of evidence on the severity of ASD in children with cCMV. This too has important cost implications, due to the high lifetime cost of supporting low-functioning individuals with ASD and the fact that the costs of ASD contributed most to the overall cost of cCMV in this model.

In the absence of systematic screening for cCMV in the UK, large-scale longitudinal prospective cohort studies would be important in helping to clarify these figures. Further, studies looking specifically at costs and resource use in subgroups of children with confirmed cCMV and high-cost impairments (SNHL and ASD) would provide better quality evidence from which to estimate impairment-specific costs. Retrospective identification of individuals with cCMV in large cohorts using analysis of Guthrie cards, as used in a recent costing study conducted in the Netherlands [20]), may provide an alternative approach to gathering data to help fill these knowledge gaps.

Conclusion

The cost of cCMV to the UK is substantial, predominantly stemming from long-term impairments caused by the virus. This study provides a preliminary figure against which the cost of new interventions can be compared. Due to the scarcity of robust data preventing inclusion of many expected costs, it is likely that this model underestimates the ‘true’ cost. Further research is needed into the efficacy of measures that aim to prevent virus transmission, including both educational campaigns and immunisation (should a vaccine become available), as well as pre- and post-natal treatment to prevent long-term impairments. The introduction of universal screening for cCMV may

be valuable for detecting children for whom treatment may be beneficial, and building a more robust evidence base for future research.

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What is known about this topic

- Congenital cytomegalovirus is the most common infectious cause of congenital disability.
- When transmitted *in utero* cytomegalovirus can disrupt neurodevelopment, causing lifelong impairments including sensori-neural hearing loss, cerebral palsy and autism spectrum disorder.

What this study adds

- For the first time, this study estimates the economic cost of managing congenital cytomegalovirus and its sequelae in the UK.
- These estimated costs provide values against which investment in preventative measures and screening programmes can be evaluated.

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