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Economic assessments of the burden of congenital cytomegalovirus infection and the cost-effectiveness of prevention strategies

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Abstract

Objective: This is a critical review of published economic analyses on congenital cytomegalovirus infection and strategies for its detection and prevention.

Findings: The review identified four cost-of-illness studies and nine cost-effectiveness analyses: three of vaccination of young women, two of prenatal screening, and four of newborn screening. All reported either large economic costs or favorable cost-effectiveness of interventions. However, sensitivity analyses did not address some of the most critical assumptions.

Conclusions: Reviewed economic analyses overattributed certain adverse long-term outcomes to congenital cytomegalovirus infection, while other long-term costs were not included. Overall, limited conceptual frameworks, unrepresentative data sources, and unsupported or inadequately documented assumptions regarding outcomes and costs hinder the ability of policymakers to draw conclusions. A major challenge is the limited information on long-term outcomes and costs for representative cohorts of individuals with congenital cytomegalovirus, which further research could helpfully address.

Keywords

Congenital cytomegalovirus; Cost-effectiveness; Economic evaluation; Cost of illness

Introduction

Congenital cytomegalovirus (cCMV) infection occurs in an estimated 0.4–0.8% of 3.8 million US newborn infants each year.¹ It is an important cause of sensorineural hearing loss (SNHL), intellectual disability (historically referred to as mental retardation), cerebral palsy (CP), and epilepsy.^{2–4} Diagnosis of cCMV infection requires laboratory testing of specimens

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collected within the first 3 weeks of life, which is infrequently done.⁵ Consequently, few (<5%) children with cCMV infection are clinically diagnosed.⁶⁻⁸ Roughly 10% of CMV-infected infants have symptomatic cCMV disease with clinical signs, such as hepatosplenomegaly, petechiae, chorioretinitis, jaundice, microcephaly, and small-for-gestational-age.^{4,9,10}

Children with symptomatic cCMV disease often experience serious neurodevelopmental disabilities, SNHL, and ocular problems.^{2,11} Children with symptomatic cCMV disease have also been reported to be at elevated risk of autism spectrum disorder (ASD),¹² but conclusive evidence is lacking. In high-income countries, 50–70% of representative cohorts of symptomatic children develop permanent impairments, mostly SNHL or intellectual disability.^{2,13} In addition, infants with symptomatic cCMV disease have a 4–10% risk of neonatal death.^{2,14,15} That implies that at least 80 infants die each year in the United States due to cCMV, although few are recorded as having cCMV as cause of death.¹⁴ Children with asymptomatic cCMV infection are at elevated risk of SNHL,^{2,16} but for them, unlike children with symptomatic cCMV, there is no clear evidence of elevated risk of neurodevelopmental disability or vision impairment.^{12,17,18}

In this review, studies on cCMV-associated costs as well as economic evaluations of interventions focused on diagnosis or prevention are critically examined using a comprehensive conceptual framework. Along with studies published through 2011 identified in a 2013 book chapter,¹⁹ economic studies of cCMV published through 2019 were identified through literature scans. A search of PubMed using “congenital cytomegalovirus” and “cost” as keywords on June 3, 2020 found no additional economic analyses of cCMV. One additional analysis published online in December 2020 was included in a final update.²⁰

All cost estimates reported in the text are expressed in 2018 US dollars; the tables report both original costs, including other currencies, and converted to 2018 US dollar equivalents.

Economic assessments – overview of methods

Economic assessments are of two types – cost studies and economic evaluations of preventive or therapeutic interventions. Cost studies include both empirical analyses of data on healthcare costs and comprehensive cost-of-illness (COI) studies. The former often report gross healthcare costs for diagnosed patients, which do not show impact of the disease. The impact of disease is quantified as the incremental cost relative to costs of unaffected cohorts. COI studies assess the attributable economic burden of disease using incremental cost estimates and generally include medical and non-medical direct costs and productivity costs resulting from premature death, disability, or sickness.^{21,22}

COI studies commonly follow a prevalence approach to estimate costs associated with prevalent cases during a specified time period relative to expected costs in the absence of disease. Incidence-based COI studies project current and future-year incremental costs for a hypothetical cohort of incident cases relative to unaffected individuals.²³ Lifetime costs are discounted to a present value using a social discount rate. For example, an analysis of lifetime medical costs associated with preterm birth in the United States assessed costs

during the first 5 years by following a birth cohort and projected lifetime costs beyond age 5 by estimating attributable fractions of four disabling sequelae of prematurity (cerebral palsy, intellectual disability, hearing loss, and vision impairment) multiplied by incremental costs.^{24,25} The analysis adjusted for the frequency of overlapping diagnoses to avoid double-counting of costs.²⁴

Full economic evaluations of interventions project changes in health outcomes and costs.²⁶ Study types include cost-effectiveness analyses (CEAs) and cost-benefit analyses (CBAs). In a CBA conducted from the societal perspective, both costs and improvements in health outcomes, notably avoided deaths, are expressed in monetary terms. A CBA differs from a partial economic evaluation that reports changes in costs but does not assess health outcomes. Partial economic evaluations can report estimates of how much money might be saved if cases were avoided, either from a payer perspective (i.e., budget impact analysis) or a healthcare sector perspective. In a full CEA, analysts separately calculate both monetary costs and health outcomes. If health is improved and costs are lower with the intervention, it is cost-saving relative to the comparator. If net costs are positive, an incremental cost-effectiveness ratio (ICER) is calculated by dividing net costs by change in health outcomes. Health outcomes can be in “natural” units, e.g., deaths or cases averted or quality-adjusted life-years (QALYs), which calculate the loss of healthy life-years from both morbidity and mortality using health-state “utilities”; a CEA that uses QALYs is a cost-utility analysis (CUA).

Economic assessments include different types of costs depending on the study perspective. Analyses from a healthcare perspective focus on healthcare costs. Societal perspective analyses also include non-medical direct costs, such as costs of special education services for children with disabilities and costs of personal care, as well as “indirect” costs of productivity lost due to premature death or disability.²⁷ Personal care can be paid or unpaid, with informal care time valued using imputed costs.²⁸ Because of differences in methods it is difficult to compare productivity cost estimates from different studies.²² Most CEAs do not include productivity costs, consistent with 1996 CUA guidelines by a non-official US panel.²⁹ A second guideline in 2016 suggested that societal perspective analyses include both productivity and consumption costs.^{22,30} In economic studies, costs are defined as the opportunity cost of resources used up in producing a good or service, which may differ substantially from the prices charged by sellers or negotiated payments, which can be influenced by market power.

The reliability of economic estimates is dependent on the completeness and accuracy of the data underlying the estimates. Estimates from healthcare cost studies are limited by the accuracy of records of diagnoses, encounters and costs. If per-person cost estimates for a condition are based on data for a subset of individuals, such as individuals with epilepsy who have frequent seizures, cost estimates cannot be extrapolated to all individuals with that condition.³¹ Generalizing from data on individuals with relatively severe disease to all persons with a disorder is a common source of overstatement of the economic burden of disease.^{32,33}

Assessments of healthcare costs associated with cCMV

Two recent studies examined data on healthcare expenditures associated with diagnoses of cCMV (Tables 1A and 1B).^{6,34} U.S. health services research studies have generally relied on billing codes in administrative data to ascertain cCMV cases.^{5,34-38} Meyers et al. reported expenditures for pooled private and public health insurance claims databases for infants with diagnosis codes for CMV infection or cCMV disease.³⁴ However, few infants are diagnosed with cCMV infection or disease; just 2-3 per 10,000 infants have cCMV diagnosis codes in administrative data,^{5,34,38} which is 1/20 the prevalence of cCMV infection and roughly half the prevalence of symptomatic cCMV disease. Laboratory testing for CMV in the neonatal period, although typically prompted by clinical recognition of complications,⁵ can also follow suspicion of maternal infection or a failed newborn hearing screen.³⁹ Clinical ascertainment bias is likely to result in the most severely affected individuals with cCMV infections receiving diagnoses for cCMV or CMV.⁶ In particular, healthcare costs for infants or children with cCMV ascertained using diagnosis codes in healthcare databases are likely to be substantially higher than for all children with cCMV or even those with symptomatic cCMV disease.

The other empirical healthcare cost study retrieved a representative sample of stored neonatal dried blood spots, tested for CMV DNA, and linked to healthcare data to generate unbiased estimates of healthcare costs associated with cCMV infection.⁶ The nationwide CROCUS cohort study in the Netherlands identified 156 children aged 4 years with cCMV by testing 31,484 stored neonatal specimens from Dutch children born during 2008, a prevalence of 0.5%.^{6,12,40} Korndewal et al. assessed clinician-reported use of healthcare resources in the first 6 years of life for 133 (85%) children with cCMV and a matched control group of 274 children. They calculated costs per child by multiplying reported numbers of healthcare encounters by Dutch reference prices for each encounter type.⁶ Mean cost was 70% higher for 133 children with cCMV than for 274 children without cCMV. Of the cCMV children, 19.5% were classified as symptomatic based on newborn diagnosis codes, such as preterm birth or small for gestational age, compared with 12.4% of controls who had the same diagnosis codes. Mean cost for 107 children with asymptomatic cCMV was similar to 274 CMV-negative controls but 49% higher than 240 “asymptomatic” controls. Mean cost for 26 children with symptomatic cCMV was 350% higher than all CMV-negative controls and 46% higher than for 34 “symptomatic” controls.

Cost-of-illness estimates for cCMV

This section summarizes stand-alone COI estimates for cCMV based on projections of medical and non-medical costs. In 2004 Arvin et al. stated that the economic impact of cCMV in the United States was \$1.86 billion in the 1990s,⁴¹ but the source of that widely cited estimate was not documented.⁴²⁻⁴⁴ Other authors have misattributed that cost estimate.²⁰ The US Institute of Medicine (IOM) Committee to Study Priorities for Vaccine Development in 2001 estimated the societal cost of cCMV as \$4 billion per year,⁴⁵ in 1995 dollars, equivalent to \$6.6 billion in 2018 dollars. The IOM cost estimate assumed that 90% of surviving children with symptomatic cCMV develop severe intellectual disability and require institutional care. However, the true risk of severe disability in symptomatic cCMV disease appears to be much lower.² For example, a Swedish cohort study found that 1 of 11

(9%) children with symptomatic cCMV detected through screening ultimately developed severe intellectual disability.⁴⁶ Also, institutional care is not inevitable; only a minority of individuals with severe intellectual disability in the United States receive institutional care.⁴⁷

Two incidence-based COI studies were published in recent years (Tables 1A-1B), both of which included assumptions that warrant critical scrutiny.^{44,48}

First, Walter et al. estimated the annual economic burden of cCMV in Germany to be US \$416 million and the lifetime cost per affected child using a 5% discount rate to be US \$1,312,543 (Table 1B).⁴⁴ According to the authors, 6500 (0.93%) of 700,000 annual births have cCMV infection, of whom 1,431 (22%) were considered affected, although the rate of cCMV infection in Europe was listed as 0.04-0.49%. Also, the aggregate cost was 317 times the cost per affected child, not 1,431 times as required for internal consistency.

Walter et al. projected lifetime direct costs for sequelae, including blindness, hearing loss, and intellectual disability based on cumulative incidence estimates, expert judgment of the frequencies of required services, and unit costs. For example, the excess of hearing loss as a sequela relative to baseline was 22% (listed as 0.22% in Table 7.3 of Walter et al.), and children who are deaf or hard of hearing were assumed to receive one cochlear implant, one hearing device every 6 years, and speech therapy once every 2 weeks until age 18 years. The incremental incidence of intellectual disability and CP were assumed to be 22% and 4%, respectively. The source listed for the CP estimate was a 1991 article, which in fact reported CP in 21.5% (14/65) of children with symptomatic cCMV infections.⁴⁹

Walter et al. also assessed the “indirect” costs of cCMV, which included the loss of parental employment and earnings, cost to employers of sick leave by employees to care for dependents, loss of human capital associated with premature mortality, and costs of schooling for children with disabilities (a direct cost). For example, the authors assumed that employed parents of children affected by cCMV all take 20 days of annual family leave and that 4% of fathers and 31% of mothers stop or reduce paid employment. The latter was based on published data for families with children treated for type 1 diabetes.

Second, Retzler et al. estimated the economic burden of cCMV in the United Kingdom as US\$700-1,300 million for each year’s birth cohort, assuming birth prevalence of 0.33–0.64%.⁴⁸ The authors reported that direct and indirect costs accounted for roughly 40% and 60% of total costs, respectively. Most costs in the base-case analysis were reportedly associated with four disorders, ASD (56%), CP (25%), SNHL (18%), and epilepsy (1%); no costs were estimated for intellectual disability. For ASD and epilepsy, Retzler et al. derived prevalence estimates from the CROCUS study. Korndewal et al. reported that ASD was diagnosed in 3.0% of children with cCMV (7.7% symptomatic and 1.7% asymptomatic) and 1.8% of children without cCMV in that study; epilepsy was diagnosed in 1.5% of children with cCMV (7.7% asymptomatic and 0.0% asymptomatic) and 1.1% of children without cCMV.¹² Retzler et al. assumed all cases of ASD and epilepsy among children with cCMV in the CROCUS study were due to cCMV. However, since both conditions are also found in children without cCMV, that study’s failure to subtract the prevalence in unaffected children overestimates the costs of cCMV. In addition, Retzler et al. assumed a 5% prevalence of CP,

⁴⁸ based on an Australian study that tested stored DBS of 323 children with CP,⁵⁰ more than three times the 1.5% prevalence in the CROCUS study.¹²

The Retzler et al. COI estimates presume that each of the four outcomes is caused by cCMV (which is not confirmed for ASD) independent of other outcomes. In fact, children frequently have co-occurring sequelae.² For example, children with cCMV disease are commonly reported to have both CP and seizures or both ASD and epilepsy.^{51,52} Adding together costs associated with ASD, epilepsy, and CP can result in overestimation of costs if the per-person cost estimates do not exclude individuals with co-occurring conditions.

Economic evaluations of preventive interventions for cCMV

The serious public health burden of cCMV infection has provided the impetus for prevention strategies, notably vaccination, prenatal screening and behavioral education, and newborn screening. Although the development of a CMV vaccine was identified as a research priority two decades ago,^{41,45,53} no vaccine candidate has yet shown acceptable efficacy nor is there consensus on the optimal target population for vaccination.^{54,55} The effectiveness of screening, whether prenatal or neonatal, is a function of the effectiveness of interventions facilitated by screening, such as antiviral treatments and behavioral modification. Published guidelines do not recommend routine prenatal screening of pregnant women for CMV.^{56,57} Newly published real-world evidence indicates that oral valganciclovir after primary maternal infection in pregnancy substantially reduces the risk of vertical transmission to the fetus.^{58,59} Although behavioral counseling of seronegative pregnant women on hygiene practices has been shown to reduce risk of CMV infection in research studies conducted in conjunction with prenatal screening,^{56,60} it is not known whether that is true outside of a research setting.

Newborn screening (NBS) for cCMV can take the form of either universal testing or targeted testing of infants who do not pass newborn hearing screening (NBHS). Several US jurisdictions have enacted policies to offer targeted testing.⁶¹⁻⁶⁴ Universal CMV NBS would enable timely diagnosis and treatment of infants with symptomatic cCMV infections.⁵⁶ Treatment of symptomatic infants who have central nervous system involvement with valganciclovir has been demonstrated to result in better hearing and neurodevelopmental test scores at age 24 months.^{56,65,66} Although many CMV experts recommend that infants identified with cCMV infection and isolated SNHL be prescribed valganciclovir,⁶⁷ this is not yet supported by definitive research findings although one observational study has reported substantially improved hearing.⁶⁸ A number of clinical studies are underway, the findings of which will inform clinical guidelines for infants with cCMV infection and isolated SNHL.^{56,64,66,69,70}

Immunization—Several evaluations of the economic benefit of a hypothetical CMV vaccine have been published (Tables 2A-2B),^{43,45,71,72} each of which included assumptions that could be questioned.

In 1990, Porath et al. assessed the “cost-benefit” of a hypothetical CMV vaccine, but this was a partial (cost-only) CEA. Medical “costs” were based on healthcare charges submitted to insurance companies,⁷¹ not amounts actually paid. Moreover, the authors assumed that 50% of children with symptomatic cCMV attend special schools for the blind or deaf and

that “30% of those severely retarded children will need special education and institutionalization for an estimated duration of 40 years.”⁷¹

In 2012, Dempsey et al. projected that vaccinating adolescent females with a CMV vaccine that was 95% effective would likely be cost-saving.⁴³ The authors did not define their analytic perspective. The implied prevalence of cCMV infection, 1.1%, was above the accepted range, whereas the baseline symptomatic percentage, 4.5%, was low (Table 2A). Avoided costs were projected from prevented cCMV-related cases with SNHL, vision loss, and intellectual disability, the baseline frequencies of which were mostly conservative. Lifetime cost estimates for the sequelae were taken from an analysis of direct and productivity costs for specific disabilities.^{47,73} The case definition for SNHL in the cost study was permanent bilateral hearing loss of moderate or greater severity, unlike the estimated prevalence of SNHL in published reviews, which included mild and unilateral losses.^{2,3,9,13-16} The cited sources did not provide estimates. The productivity cost estimates used by Dempsey et al., which accounted for up to 80% of lifetime costs,^{47,73} reflect substantial premature mortality among individuals with intellectual disability, which is inconsistent with the assumption by Dempsey et al. of no reduction in life expectancy.⁴³ Individuals who experience multiple sequelae, e.g., hearing loss and intellectual disability, were assumed by Dempsey et al. to incur the costs associated with each sequela (see Discussion).

In 2018, N’Diaye et al. projected that vaccination against CMV of 14-year-old females would be cost-effective from the French national health insurance perspective.⁷² Owing to the complicated modeling assumptions, it is unclear what proportion of live births were assumed to have cCMV in the absence of vaccination; 13% of those infected were assumed symptomatic (Table 2A). The investigators modeled neonatal deaths, intellectual disability, hearing loss, and vision impairment separately for symptomatic and asymptomatic cCMV cases. They assessed direct costs of sequelae and modeled lower life expectancy for persons with intellectual disability. The analysis had a mismatch of case definitions for prevalence and costs of sequelae, with prevalence reflecting any level of impairment and costs restricted to individuals who received services. The assumed prevalence of some sequelae of asymptomatic cCMV appears implausibly high, e. g., 8% with intellectual disability.⁷² A long-term assessment of a screened cohort found that children with asymptomatic cCMV infection were no more likely to have intellectual disability than uninfected children.¹⁷ Although the source for that estimate reported a pooled frequency of 8% with cognitive deficits,² many fewer had intellectual disability.^{2,46} N’Diaye et al. also assumed that 1% of children with asymptomatic cCMV develop vision impairment as a complication,⁷² which is not consistent with published evidence.^{12,18,74}

Prenatal screening—Two CEAs of prenatal screening for CMV have been published (Tables 3A-3B).^{75,76} In 2009, Cahill et al. projected that screening at 20 weeks’ gestation followed by intravenous hyperimmune globulin (HIG) treatment of seronegative women would be highly cost-effective relative to no screening.⁷⁵ That study assumed that HIG is highly effective and overstated preventable CMV-related health outcomes and costs. For example, it assumed that more than 2,000 infants die each year and more than 8,300

experience severe disability due to cCMV in the United States, both of which were an order of magnitude greater than population-based estimates.²

Albright et al. (2019) published a decision analysis of universal and risk-based CMV screening and treatment of pregnant women.⁷⁶ They assumed that brief behavioral counseling of seronegative pregnant women would reduce primary maternal CMV infections by 85%, based on findings from a small controlled study in Italy.⁶⁰ Albright et al. assumed that 5% of all children with cCMV infection die as neonates, which is true for symptomatic cases. The authors took maximal estimates from the literature of the prevalence of complications among survivors, 90% for children with symptomatic cCMV and 14% of those with asymptomatic infections and assumed that all complications result in severe disability. In particular, all cases of SNHL were assumed to result in profound bilateral SNHL,⁷⁶ which is incorrect.^{3,16}

Newborn screening—Five economic evaluations of NBHS-targeted CMV NBS have been published to date;^{20,77-80} two also assessed the cost-effectiveness of universal CMV NBS (Tables 3A-3B).^{20,79} All of these studies focused on potential improvements in hearing-related outcomes from NBS. In 2015, Williams et al. provided detailed, comprehensive cost accounting estimates of targeted saliva-based screening in the National Health Service in England and Wales.⁷⁸ The cost of the screening process, including administration costs, was US\$102 per infant referred for testing and US\$1,020 per infant with cCMV. The per-infant cost of screening was 4.9 times the unit cost of the PCR assay, US\$20.8. The cost per infant identified with cCMV and “protected” by treatment with valganciclovir was said to be consistent with other NBS tests, and the authors called for full economic evaluations to assess the cost-effectiveness of screening for cCMV.

In 2015, Bergevin et al. published a budget impact analysis of NBHS-targeted screening in Utah.⁷⁷ The authors reported variable screening costs, i.e., costs that vary in proportion to numbers screened, of US\$70 per infant screened. Including a fixed program administration cost, which averaged US\$134 per infant screened, the per-infant cost of screening was US\$204, yet the analysis implausibly assumed a screening cost of just US\$33 per infant. Finally, the analysis assumed that administering valganciclovir would eliminate cochlear implants, which is not consistent with evidence.⁸¹

In 2016, Gantt et al. modeled the cost-effectiveness of universal and targeted cCMV screening in Canada.⁷⁹ The authors assumed that antiviral treatment improves hearing loss by one level among 50% of treated infants with cCMV (e.g., from severe to moderate loss).⁷⁹ The cost of saliva screening for CMV was assumed to be US\$10.50-52.50 per infant for the oral swab and CMV PCR analysis and a confirmatory urine PCR analysis, if needed, with no costs for administration or specimen collection and transport.⁷⁹

Universal screening was calculated by Gantt et al. to be cost-saving in analyses that assumed a screening cost of roughly US\$10 per infant and reduced education and productivity costs (Table 3B).⁷⁹ Those analyses assumed that each adult with bilateral severe to profound hearing loss loses roughly \$1 million in lifetime productivity, which exceeds the expected lifetime earnings for an unselected infant.^{82,83} Additionally, the inclusion by Gantt et al. of

human capital costs was inconsistent with Canadian CEA guidance calling for friction cost estimates of productivity losses.²² Finally, Gantt et al. attributed the cost of special education for hearing loss to cCMV, ignoring the cost of regular schooling.⁷⁹

In 2019, Beswick et al. projected cost savings with NBHS-targeted CMV screening in Queensland, Australia.⁸⁰ A detailed cost accounting found the average cost per infant tested was US\$313, of which just over one-tenth was the laboratory cost of the PCR assay, US \$32.4. Beswick et al. assumed a 40% reduction in the number of children who develop severe/profound SNHL with screening and treatment. In the absence of screening, 43% of children with cCMV and SNHL were assumed to develop severe/profound SNHL, of whom 50% would receive cochlear implants. However, a study that followed 92 children with asymptomatic cCMV found that although 12 of the children developed SNHL by age 5 years, just two (17%) were candidates for cochlear implants with bilateral severe/profound SNHL.¹⁶

Most recently, Chen et al. assessed the cost-effectiveness of targeted and universal NBS strategies from the perspective of the healthcare system in China.²⁰ The cost of screening was assumed to be US\$15 for a CMV PCR test; no implementation or operational costs were included in the analysis. The authors assumed that all infants with either cCMV and hearing loss at birth or symptomatic cCMV regardless of hearing loss would receive treatment with intravenous ganciclovir, which is contrary to current guidelines; a sensitivity analysis modeled use of oral valganciclovir at twice the cost per infant. It was also assumed that treatment would greatly reduce the risk of progressive or late-onset SNHL and would lead to substantial improvement in hearing loss for infants with symptomatic cCMV. Chen et al. projected averted costs and QALY gains associated with projected reductions in numbers of children with mild-to-moderate and severe-to-profound hearing losses, especially through avoidance of cochlear implants. The authors calculated ICERs of US\$79 per QALY for NBHS-targeted screening and US\$2,087 for universal NBS and concluded that both types of screening would be cost-effective and possibly cost-saving.

Several key assumptions in the analysis by Chen et al. do not appear to be consistent with available evidence. Although the assumptions made about the prevalence of SNHL in infants with cCMV appear conservative relative to the peerreviewed international literature, they appear to overstate the risk of SNHL, particularly severe-to-profound hearing loss, for Chinese infants with cCMV. A study that screened 18,796 infants at 5 birthing hospitals across Shandong province serving economically diverse populations found 155 (0.8%) infants with cCMV, none of whom were symptomatic and none had hearing loss detected by NBHS.⁸⁴ A screening study from Beijing likewise reported no infants with cCMV were symptomatic at birth, cited in a report of preliminary findings from the Shandong study.⁸⁵ If the assumptions of the Chen model were accurate, 22 of the 155 infants in the Shandong study would have been symptomatic at birth and between 4 and 5 would have had hearing loss diagnosed at birth. Among 141 infants who received audiologic monitoring for 1–4 years, four (2.8%) were identified with late-onset mild to moderate hearing loss and none had severe-to-profound hearing loss.⁸⁴ Therefore, the assumed benefits of prevention of cochlear implants by Chen et al. are likely substantially overstated. The mild clinical manifestations of cCMV observed in the China study were attributed to the high maternal

seroprevalence (96.2%) combined with much less exposure to young children (<7%) than other populations as a result of China's unique 1-child policy.⁸⁵

Chen et al. applied published estimates of health-related quality of life for adults with bilateral deafness, with and without cochlear implants, to children with both unilateral and bilateral hearing loss, which is not necessarily valid. More critically, the assumed gain in quality of life for adults with cochlear implants was several times larger than reported in a study of children who had received cochlear implants.⁸⁶ Finally, Chen et al. assumed no net improvement in hearing among treated infants with asymptomatic cCMV and hearing loss at birth.²⁰ One study recently reported that a large proportion of asymptomatic infants with isolated hearing loss who received oral valganciclovir subsequently experienced improved hearing.⁶⁸

Discussion

Published estimates have frequently depended on unrealistic assumptions that led to biased estimation of costs. For example, one study assumed that almost all children with symptomatic cCMV develop severe intellectual disability and require institutionalization.⁴⁵ Although 90% of children with symptomatic cCMV disease referred to academic centers are reported to have disabilities,⁸⁷ roughly 60% of representative samples of children with symptomatic cCMV do so, many with moderate impairments.² Another study assumed that all cases of cCMV-attributable SNHL result in profound hearing loss.⁷⁶ Some studies used estimates of prevalence of sequelae based on broad case definitions, e.g., inclusive of unilateral and mild SNHL, and applied per-person cost estimates based on narrower case definitions, e.g., bilateral moderate to profound hearing losses.⁷²

Multiple authors have assumed that disabling outcomes observed among children with cCMV infections are attributable to cCMV without regard to the corresponding risk among children without cCMV. For example, Retzler et al. took CROCUS estimates of frequencies of ASD and epilepsy among children with cCMV and did not subtract the prevalence among uninfected children in the same study.⁴⁸ In addition, although Retzler et al. assumed that 5% of children with cCMV develop CP,⁴⁸ the pooled prevalence of CP from four studies with >2 years follow-up of screened cohorts with cCMV (range 1.5–5.3%) is 3% (9/300);^{12,46,88,89} the population prevalence of CP is 0.3%.⁴⁸ Other researchers have assumed that children with asymptomatic cCMV can develop vision impairment,⁷² whereas impaired visual acuity is not more frequent among such children than children without infection.^{12,18,74}

Reliable economic estimates of the burden of cCMV associated with sequelae require analysts to subtract the frequencies of each endpoint in representative cohorts of children without cCMV infections from that observed in children with cCMV. The only cCMV economic study which has done so to date is the CROCUS study;⁶ medical costs during the first 6 years of life were found to be 70% higher for children with cCMV infection and 350% higher for children with symptomatic cCMV infection.

Most reviewed studies ignored the co-occurrence of outcomes, e.g., SNHL, CP, and intellectual disability in the same individual, which can result in double-counting of costs if

the estimated costs included data on individuals with multiple conditions.^{47,73} Dempsey et al. assumed individuals with both SNHL and intellectual disability incur the average costs for each, despite overlapping costs for special education and productivity loss in the original cost study.^{47,73} In contrast, a preterm birth study used a hierarchical algorithm to eliminate potential double-counting of costs, for example, counting costs for individuals with SNHL excluding those who also had CP or intellectual disability.²⁴

The CEAs of vaccination against CMV likely understated cost-effectiveness by not modeling the indirect impact of vaccine-derived herd immunity on protection to susceptible individuals.^{90,91} The indirect protective effect of a CMV vaccine is expected to be key to its population-level effectiveness.^{55,92} N'Diaye et al. acknowledged that this exclusion made their estimates of CMV vaccine cost-effectiveness conservative.⁷²

The two CEAs of prenatal screening addressed different interventions. One relied on speculative assumptions about the effectiveness of HIG.⁷⁵ The other study assumed brief behavioral counseling seronegative women would result in an 85% reduction in cCMV cases, citing a controlled trial that found a 64% reduction in cCMV infections among infants of seronegative participants.^{60,76}

Although some assert that cCMV newborn screening has been shown to be cost-effective,^{1,93,94} others note that cost-effectiveness calculations depend on the long-term effectiveness of valganciclovir, which has yet to be demonstrated.^{66,77,79,80} Observational studies have reported mixed findings on longterm hearing outcomes, and the short-term hearing benefits of antiviral therapy do not necessarily persist.^{51,81,95}

A widely-cited cost-effectiveness study by Gantt et al. made several questionable assumptions. First, the estimate of productivity loss per child exceeds the expected value of lifetime earnings for a typical infant. Second, the authors did not subtract the cost of regular schooling from special education costs for children who are deaf or hard of hearing; special education costs attributable to hearing loss are considerably lower.^{73,96} Finally, Gantt et al. only modeled the laboratory cost of screening,⁷⁹ even though the bulk of NBHS-targeted screening costs occur outside laboratories.^{62,77,78,80} A recent cost-effectiveness study from China likewise only modeled the laboratory cost of screening and assumed a low cost test.²⁰ That study did not consider societal costs but may have overstated the health gains and avoided costs from the prevention of severe-to-profound SNHL and avoidance of cochlear implants.

Conclusions

With one exception, all published economic assessments of cCMV presented several limitations and biases, associated with a lack of data on representative cohorts of children with cCMV. Many children who have severely symptomatic cCMV disease experience serious and costly neurological conditions. Because such children may be overrepresented in administrative records with cCMV diagnoses, it could be misleading to assess costs based on such data. Almost nothing is known about the overall economic impact of cCMV on families

and societies, including parental time use.⁹⁷ Altogether, these limitations complicate the economic assessment of any intervention, such as a hypothetical vaccination program.

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Table 1A -
Elements and Input Variables in Cost Studies of Congenital Cytomegalovirus (cCMV) Infection

Study	Country	Perspective (s)	Study design	Sensitivity analyses	Targeted population	cCMV cases	Comparator group	Incidence or birth prevalence of cCMV and percentage classified as symptomatic or affected	Cumulative Incidence of sequelae
Meyers J, et al. Clin Ther. 2019 ³⁴	USA	Societal	Retrospective cost analysis of empirical data	None	Infants aged <1 year enrolled in health plans contributing claims data	Infants with cCMV ICD-9-CM diagnosis codes in claims data	Infants with no cCMV diagnosis code	1.9–3.8 per 10,000 100% symptomatic	
Korndewal MJ, et al. Arch Dis Child. 2018 ⁶	Netherlands	Healthcare payer	Statistical retrospective analysis of empirical data on resource utilization and costs for 156 cCMV positive children and 365 matched cCMV negative children	None	Cohort followed from birth through age 6 years, CMV status based on PCR for CMV DNA in neonatal dry blood spots	Children who tested positive for cCMV in stored dried blood spot specimens	Children negative for cCMV in stored dried blood spot specimens	0.5% (156/31,484) 19.5% symptomatic	
Reizler J, et al. Arch Dis Child. 2019 ⁴⁸	UK	Societal, Healthcare, NHS, payer, Government	Incidence-based COI model based on inputs from various sources	Deterministic 1-way analyses using ranges of direct and indirect costs	UK birth cohort	Derived from various sources	No comparator group	0.49% (range, 0.33–0.64%) 11.0% symptomatic (range 4.8–12.7%)	<ul style="list-style-type: none"> Autism spectrum disorder—7.7% of symptomatic and 1.7% of asymptomatic cases Cerebral palsy—9.6% of cases attributed to cCMV Epilepsy – 7.7% of symptomatic cases Hearing loss – 32.8% of symptomatic and 9.9% of asymptomatic cases
Walter et al. 2018 ⁴⁴	Germany	Societal	Incidence-based COI model based on inputs from various sources	Deterministic 1-way analyses	German birth cohort	Uncertain	Children without cCMV infection	0.93% (6500/700,000) 7.6% symptomatic 22.0% affected (symptomatic or	<ul style="list-style-type: none"> Proportions of affected children with Hearing loss 0.22 Intellectual disability 0.22

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Study	Country	Perspective (s)	Study design	Sensitivity analyses	Targeted population	cCMV cases	Comparator group	Incidence or birth prevalence of cCMV and percentage classified as symptomatic or affected	Cumulative Incidence of sequelae
								with sequelae) (1431/6500)	<ul style="list-style-type: none"> • Cerebral palsy 0.04 • Convulsions 0.02 • Developmental disorder 0.06

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; COI, cost of illness; ICD-9, International Classification of Diseases, 9th revision; NHS, National Health Service; PCR, polymerase chain reaction.

Table 1B -

Cost Estimates in Cost Studies of Congenital Cytomegalovirus (cCMV) Infection*

Study	Sources of direct cost estimates	Methods of calculating direct medical costs	Productivity costs	Costs Reported
Meyers J, et al. Clin Ther. 2019 ³⁴	MarketScan Commercial and Encounters and Multi-State Medicaid data	Regression-adjusted incremental per-child mean medical expenditure (sum of insurer and out-of-pocket payments) relative to infants without cCMV codes adjusted for covariates	Not included	Birth hospitalization: \$15,568 with a vaginal delivery ($p < 0.001$) and \$37,199 with a cesarean delivery ($p < 0.001$) Post-birth: \$39,091 ($p < 0.001$), 4 times non-cCMV infants, in 2016 US dollars (adjusted using medical care component of the Consumer Price
Korndewal MJ, et al. Arch Dis Child. 2018 ⁶	Encounters and procedures were reported by healthcare providers and unit costs of services were taken from a database of national reference prices	Mean cumulative costs to age 6 years were calculated for both cCMV positive and negative children stratified by presence of diagnosis codes as infants consistent with cCMV neonatal symptoms	Not included	Mean per-child cost to age 6 years: <ul style="list-style-type: none"> Children with cCMV (n = 133): €6113 (US \$7671) Children without cCMV (n = 274): €570 (US \$4480) Symptomatic cCMV (n = 26): €15,922 (US \$20,067) Asymptomatic cCMV (n = 107): €730 (US \$4680)
Reizler J, et al. Arch Dis Child. 2019 ⁴⁸	Data sources for unit cost estimates for children with sequelae were derived from published UK sources for ASD, epilepsy, and SNHL and a Danish source for CP	Lifetime cost estimates for sequelae were multiplied by numbers of cases of sequelae assumed related to cCMV	Productivity loss due to permanent sequelae in adults and to parents caring for children with severe sequelae	Absolute and percentage differences in mean cost between cCMV positive and cCMV negative children: <ul style="list-style-type: none"> All children: €543 (US \$3191), 70% higher Symptomatic at birth: €044 (US\$6329), 46% higher Asymptomatic at birth: €223 (US\$ 1536), 49% higher With long-term impairment: €8873 (US \$11,133) Without long-term impairment: €-437 (US\$-548)
Walter et al. 2018 ⁴⁴	<ul style="list-style-type: none"> Outpatient unit costs from EBM catalogue (not defined) Medication prices from health insurance 	Lifetime direct medical and non-medical costs of sequelae calculated by multiplying assumed numbers of encounters or procedures by unit costs	Loss of parental employment and earnings through age 18 were based on a published survey of German families of children with type 1 diabetes — 31%	Total cost for a year's birth cohort in base-case analysis assuming 0.46% birth prevalence: £732 million (US \$1,046 million) Range: £495 to £942 million (US\$707 to US\$1,346 million). Annual economic burden €42.9 million in 2008 Euros (US\$416 million) Lifetime cost per affected child €66,444 in 2008 Euros (US \$1,312,543) for 1,431 affected children, calculated using a 5% discount rate

Study	Sources of direct cost estimates	Methods of calculating direct medical costs	Productivity costs	Costs Reported
	<ul style="list-style-type: none"> Inpatient unit costs from G-DRG catalogue (not defined) “Cost of schools for blind, deaf and handicapped people (Halwachs-Baumann, Pre-uss et al., BMI Deutschland)” “Cost of nursing homes for severe handicapped people (AOK 2009)” 		of mothers and 4% of fathers reduced or stopped working. This was multiplied by sex-specific gross salaries. Parents who remained employed were assumed to take family leave of 20 days per year. Deaths were multiplied by the present value of lifetime earnings.	
	Other costs based on assumptions			
	<ul style="list-style-type: none"> Impact on parental employment (<age 18) Short-term family leave Human capital loss due to death 			

Abbreviations: cCMV, congenital cytomegalovirus.

* Costs in foreign currencies were converted and updated to 2018 US dollars using the Purchasing power parities (PPP). These values appear in parentheses. (Source for PPP: <https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm>).

Table 2A - Characteristics of Economic Studies of Vaccine-based Interventions to Prevent Congenital Cytomegalovirus (cCMV) Infection

Study	Country	Perspectives	Data Sources	Target Population	Study Type	Strategies Under Comparison	Type of Cost Ratio or Net Value Reported	Type of Sensitivity Analyses (SA)	Incidence/Prevalence of Risk Factors and Congenital CMV	Incidence/Prevalence of Clinical Sequelae
Dempsey AF, et al. Vaccine. 2012 ⁴³	USA	Societal (not explicit)	Literature review	Adolescent females prior to first pregnancy	CEA (CUA) Static decision tree model (probabilistic)	Routine vs. No Vaccination	ICER (\$/QALY) or cost-savings if negative total costs	One-way (probabilistic) (including high or low vaccine impact scenarios); Threshold analysis	<p><i>Adolescent females:</i></p> <ul style="list-style-type: none"> • Susceptible to CMV (vaccinated): 0.05 (0.01–0.20) • Susceptible to CMV (unvaccinated) 0.395 (0.01–0.99) • Primary infection during pregnancy: 0.024(0.01–0.1) • Reactivation: 0.00125 (0.010–0.0001) <p><i>Infants:</i></p> <ul style="list-style-type: none"> • Incidence of cCMV infection 0.011 (implicit) • Symptomatic proportion of cCMV infections: 0.045 (0.01–0.1) 	<p><i>Symptomatic:</i></p> <ul style="list-style-type: none"> Death: 0.041 (0.01–0.4) Vision Loss: 0.142 Hearing Loss: 0.065 Intellectual disability: 0.142 (0.005–0.3) No long-term sequelae: 0.51 (0.15–0.64) <p><i>Asymptomatic:</i></p> <ul style="list-style-type: none"> Death: 0.014 (0.01–0.1) Vision Loss: 0 (0.0001) Hearing Loss: 0.095 Intellectual disability: 0.023 (0.005–0.100) No long-term sequelae: 0.85 (0.78–0.88)
N'Diaye DS, et al. Vaccine. 2018 ⁷²	France	Societal, Healthcare, France Statutory Health System, Government	Literature review, expert opinion	Adolescent females aged 14 years	CEA Markov-based decision-analytic model (probabilistic)	Routine vaccination or screening + routine vaccination of CMV-negatives vs. no vaccination (counseling on hygiene guidelines)	ICER (\$/QALY)	One-way and two-way (probabilistic Monte Carlo analysis); Threshold analysis; Age-dependent force of infection (catalytic model based on CMV seroprevalence)	<p><i>Adolescent females:</i></p> <ul style="list-style-type: none"> • Seroprevalence at age 14: 0.20 (0.15 – 0.25) • Force of infection 1.60 (1.20 – 2.40) per 100 susceptible persons per year • Probability of vertical transmission if seroconversion in mother 0.1 (0.13–0.59) <p><i>Symptomatic:</i></p> <ul style="list-style-type: none"> Death: 0.05 (0.0–0.3) Vision Loss: 0.21 Hearing Loss: 0.41 (0.07–0.60) Intellectual disability: 0.18 (0.14–0.18) No long-term sequelae: 0.37 (0.37–0.75) <p><i>Asymptomatic:</i></p> <ul style="list-style-type: none"> Death: 0 (0–0) Vision Loss: 0.01 (0–0) 	

Study	Country	Perspectives	Data Sources	Target Population	Study Type	Strategies Under Comparison	Type of Cost Ratio or Net Value Reported	Type of Sensitivity Analyses (SA)	Incidence/Prevalence of Risk Factors and Congenital CMV	Incidence/Prevalence of Clinical Sequelae
Porath, A. et al. Rev Infect Dis. 1990 ⁷¹	USA	Healthcare payers (not explicit)	Literature review	Women aged 15-25 years (healthy, non-pregnant)	Partial CEA (no health outcomes) Decision-analytic model (probabilistic)	Screening + Selective vaccination OR Routine Vs. No Vaccination	Net savings	One-way Threshold: Population seroprevalence Probability of severe adverse events Vaccine induced seroconversion rate Cost of screening discount rates of 2% and 8%	<ul style="list-style-type: none"> Infants: <ul style="list-style-type: none"> Symptomatic cCMV infection if congenital infection: 0.13 (0.05-0.27) Women aged 15-25 years: <ul style="list-style-type: none"> Seroprevalence: 0.70(0.35-1). Reactivation: 0.015 (0.0014-0.03) Primary infection: 0.025 (0.005-0.04) In utero transmission: 0.35 (0.2-0.5) 	Hearing Loss: 0.11 (0.05-0.36) Intellectual disability: 0.08 (0.0-0.1) No long-term sequelae: 0.86 (0.75-0.90) Primary symptomatic congenital infection: Death: 0.25 (0.2-0.3) Early sequelae: 0.85 (range NA) Late sequelae: 0.15 (0.05-0.25) Perinatally acquired CMV pneumonia: Death: 0.1 (range NA)
									<ul style="list-style-type: none"> Infants: <ul style="list-style-type: none"> Symptomatic cCMV infection if primary infection in mother: 0.1 (0.05-0.1) Perinatal pneumonia in infant, primary CMV in mom: 0.01 (0.005-0.015) Perinatal pneumonia, reactivation in mom: 0.002 (0.001-0.003) 	

Abbreviations: CBA, cost-benefit analyses; cCMV, congenital cytomegalovirus; CEA, cost-effectiveness analyses; CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; LY, life-year; NA, not available; QALY, quality-adjusted life-year; SA, sensitivity analyses

Table 2B -

Outcomes, Cost and Sensitivity Analyses in Economic Studies of Vaccine-based Interventions to Prevent Congenital Cytomegalovirus (cCMV) Infection*

Study	Health outcome (s) reported	Medical costs assumptions (in 2018 US dollars in parentheses)	Intervention costs (in 2018 US dollars in parentheses)	Value of Ratio or Cost Difference as Reported (in 2018 US dollars in parentheses)	Sensitivity Analyses (SA) Results
Dempsey AF, et al. Vaccine. 2012 ⁴⁵	Reduction in 8 deaths, 52 infants with hearing loss, 5 infants with vision loss, 18 with intellectual disability per 100,000 births Net gain of 1823 lifetime QALYs saved for infants born to mothers in cohort Vaccination may result in 99 mild and 1 severe adverse event per 100,000 adolescents vaccinated, and 1/3 of these women may never become pregnant	Symptomatic at birth \$9062 (\$10,213). Asymptomatic at birth \$0. Death \$36,899 (\$41,585). Vision loss \$593,998 (\$669,436). Hearing loss \$417,062 (\$470,029). Intellectual disability \$1,099,529 (\$1,239,169). Cost estimates assumed premature mortality among individuals with intellectual disability through assumed no reduction in life expectancy	Vaccination Series \$180 (\$229), range \$71-\$1000 (\$80-\$1,127)	Vaccinating adolescent females with CMV vaccine with 95% vaccine effectiveness likely cost-saving.	Vaccination preferred strategy in all "high" impact scenarios (vaccine efficacy of 80% and low burden of CMV infection among pregnant women) and "low" vaccine impact scenarios (vaccine efficacy of 99% and high burden of CMV infection among pregnant women) Vaccination not preferred if vaccine efficacy <61%
N'Diaye DS, et al. Vaccine. 2018 ⁷²	Reductions in sero-conversion, numbers of infected newborns, and selected sequelae with Routine vaccination, or Routine vaccination + Screening as compared to No vaccination. Additional reductions when comparing Routine vaccination to Routine vaccination + screening, except neonatal deaths which were unchanged. LYs and QALYs ranged from 46,864,802 to 46,896,977 and 46,858,936 to 46,893,840 from "No vaccination" to Routine Vaccination strategies, respectively.	CMV serotesting €72 (US\$93), General Practitioner €23 (US\$30), Cost of care for symptomatic specific cCMV-caused-pathology ranged from €143,882 to €488,675 (US \$185,654 to US \$630,548) Cost estimates assumed 8% children with asymptomatic cCMV have intellectual disability and 1% develop vision impairment.	Vaccine dose €123 (US\$144), range €111-€540 (US \$143-US\$687)	Routine strategy €5,000 (US \$45,161) per QALYs gained, though most expensive €211 (US\$272) Million compared to Screening + Vaccination= €75 (US \$97) Million. ICERs Routine vs. No-vaccination= €6000 (or US\$7,741) per QALY and Routine vs. Screening + Vaccination= €16,000 (or US \$20,645) per QALY	Screening+vaccination preferred if seroprevalence >62% (vs 20% in case case) Routine vaccination less costly than screening +vaccination if vaccine cost < €44 Input parameters with greatest impact on effectiveness were seroprevalence rate at age of vaccination, vaccine efficacy, vaccine coverage
Porath A, et al. Rev Infect Dis. 1990 ⁷¹	Immunization would prevent at least 56% of symptomatic cases (eight fatal and 20 nonfatal SCI cases and 27 cases of late sequelae) for every 100,000 immunized women. Routine immunization prevents more cases than selective immunization though difference in two strategies is small Populations with low CMV seroprevalence or high primary infection rates would benefit most from immunization.	Symptomatic cCMV infection \$127,000 (\$230,882) Newborn death \$21,000 (\$38,177) Perinatal pneumonia \$7,200 (\$13,090) Late childhood sequelae \$53,000 (\$96,353) Special education for cCMV-related deaf, blind \$8,000 (\$14,544) per year Results assume that 50% of symp-tomatic cCMV children attend special schools for the blind or deaf and "30% of those severely retarded children" will need special education and institutionalization for 40 years	Cost of Screening \$16 (\$30) Immunization routine \$8 (\$15), selective \$18 (\$33) Severe adverse event \$3,900 (\$70,900)	As seroprevalence increases from 55% to 70%, costs decrease from \$7.2 (\$13.1) million to \$3.7 (\$6.7) million per 100,000 women at low vaccine cost Routine immunization is the dominant strategy (cost saving) regardless of vaccine cost	Routine immunization no longer advantageous if seroprevalence rate >87% No-intervention strategy preferred if primary maternal infection rate <0.8%, vaccine-induced seroconversion rate <20%, and a probability of vaccine-induced perinatal CMV infection >55 %, adverse reactions >1%, or cost of adverse effects >\$60,000 Selective immunization preferred if probability of severe vaccine adverse effects >0.2%

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; CEA, cost-effectiveness analyses; CUA, cost-utility analysis; CBA, cost-benefit analyses; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; SCI, symptomatic congenital infection; SA, sensitivity analyses.

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* When needed, cost values were updated to 2018 US dollars using the Gross Domestic Product: Implicit Price Deflator (GDPDEF). Also, when needed, cost values in foreign currencies were converted and updated to 2018 US dollars using the Purchasing power parities (PPP). Updated values appear in parentheses (Source for PPP: <https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm> and for GDPDEF <https://fred.stlouisfed.org/series/GDPDEF>).

Table 3A - Characteristics of Economic Studies of Screening-based Interventions for Congenital Cytomegalovirus (cCMV) Infection

Study	Country	Perspectives	Data Sources	Target Population	Study Type	Strategies Under Comparison	Type of Cost Ratio or Net Value Reported	Type of Sensitivity Analyses (SA)	Incidence/Prevalence of Risk Factors and Congenital CMV	Incidence/Prevalence of Clinical Sequelae Attributable to Congenital CMV
Prenatal Screening										
Albright CM, et al. <i>Am J Perinatol.</i> 2019 ⁷⁶	USA	Healthcare	Literature review	Pregnant women (US birth cohort)	CEA, (CUA), probabilistic	Universal prenatal serum screening vs. risk-based screening, both followed by behavioral intervention	Incremental cost-effectiveness ratio – cost per QALY	Two- and three-way sensitivity analyses and threshold analysis focused on incidence of primary CMV infection and intervention effectiveness	CMV seroprevalence (0.55) Primary maternal CMV during pregnancy (0.01)	<ul style="list-style-type: none"> Neonatal death (0.04) Preterm delivery (0.12) Severe disability in symptomatic cCMV (0.88) Severe disability in asymptomatic cCMV (0.12)
Newborn screening										
Cahill AG, et al. <i>Am J Obstet Gynecol.</i> 2009 ⁷⁵	USA	Societal	Literature review	Pregnant women at or beyond 20 weeks' gestation	CEA (CUA), probabilistic	Universal, risk factor, or ultrasound-based, serum screening for primary CMV infection, followed by IVIG treatment vs. no screening or treatment	Incremental cost-effectiveness ratio – cost per QALY	One-way, Two-way, Three-way sensitivity analyses (probabilistic) focused on test sensitivity and specificity	<ul style="list-style-type: none"> Primary CMV infection (0.024, range 0.01–0.04) 	<ul style="list-style-type: none"> cCMV neonatal death after primary infection (0.10) Severe disability in symptomatic cCMV (0.30) Mild disability in asymptomatic cCMV (0.12)
Bergevin A, et al. <i>Int J Pediatr Otorhinolaryngol.</i> 2015 ⁷⁷	USA	Public healthcare payer (excludes costs to other payers)	Program data, published costs	Newborns and children in Utah, 2014–2015	Said to be CBA, but only reports medical cost savings, i.e., a budget	State-wide targeted cCMV screening (infants who did not pass NBHS) vs. no screening	Net costs	Focal deterministic and threshold	<ul style="list-style-type: none"> 5% (12/244) infants aged 3 weeks who failed hearing tests and were screened tested 	Among 5 infants with hearing loss, 1–2 cochlear implants in absence of treatment

Study	Country	Perspectives	Data Sources	Target Population	Study Type	Strategies Under Comparison	Type of Cost Ratio or Net Value Reported	Type of Sensitivity Analyses (SA)	Incidence/Prevalence of Risk, Factors and Congenital CMV	Incidence/Prevalence of Clinical Sequelae Attributable to Congenital CMV
Beswick R, et al. J Paediatr Child Health. 2019 ⁸⁰	Australia		Combined literature review	Newborns aged 0-21 days referred for hearing screening from Queensland, AU	CEA probabilistic impact analysis	Targeted cCMV screening (infants who did not pass NBHS) vs. no screening	Average differential	One-way sensitivity analyses	<ul style="list-style-type: none"> 1.2% (347/28,286) referred additional hearing screen 3.42% infants tested positive for CMV among those referred for testing 	<ul style="list-style-type: none"> Severe or profound HL if true positive & diagnosed with HL 0.43 Cochlear implant 0.5 among those with severe or profound HL
Chen K, et al. JAMA Netw Open. 2020 ²⁰		Healthcare system	Program data, Secondary literature review	Newborns in China	CEA	Targeted (infants who did not pass NBHS) and universal cCMV screening vs. no screening	Incremental cost-effectiveness ratio – cost per QALY	One-way sensitivity analyses	<ul style="list-style-type: none"> 0.7% cCMV infection 14% symptomatic 86% asymptomatic 	<ul style="list-style-type: none"> 13% of asymptomatic infants have hearing loss at birth and 3.1% have late-onset hearing loss 1.2% of asymptomatic infants have hearing loss at birth and 1.8% have late-onset hearing loss
Gantt S, et al. JAMA Pediatr. 2016 ⁷⁹	USA	Provider's (Payers') perspective (Medical cost only) Societal perspective (inclusive of education and productivity costs)	Secondary literature review (base case & ranges)	Birth cohort, newborn children	CEA	Targeted (infants who did not pass NBHS) and universal cCMV screening vs. no screening	Net costs	Deterministic sensitivity and scenario analyses: Focal deterministic and threshold. Scenario: Focal deterministic	<ul style="list-style-type: none"> 0.5% cCMV infection 13.3% of infants with hearing loss at birth had cCMV infection 1.5% newborns fail hearing test (out of these 10% with 	

Study	Country	Perspectives	Data Sources	Target Population	Study Type	Strategies Under Comparison	Type of Cost Ratio or Net Value Reported	Type of Sensitivity Analyses (SA)	Incidence/Prevalence of Risk Factors and Congenital CMV	Incidence/Prevalence of Clinical Sequelae Attributable to Congenital CMV
Williams EJ, et al. Arch Dis Child Fetal Neonatal Ed. 2015 ⁷⁸	UK	Healthcare, UK-NHS, Government	Secondary-literature review (base case & ranges)	100,000 newborns		Targeted cCMV screening (infants who did not pass NBHS) vs. no screening	Differential costs	One-way discrete sensitivity analyses of cCMV rates: reducing base- case rates 50% or increasing 100%	34 per 100,000 infants undergoing NBHS	<ul style="list-style-type: none"> 1.5% have cCMV-related SNHL

permanent HL)

Abbreviations: CBA, cost-benefit analyses; cCMV, congenital cytomegalovirus; CEA, cost-effectiveness analyses; CMV, cytomegalovirus; CUA, cost-utility analysis; HL, hearing loss; ICER, incremental cost-effectiveness ratio; LY, life-year; NBHS, newborn hearing screening; NHS, National Health Service; QALY, quality-adjusted life-year; SA, sensitivity analysis; SNHL, sensorineural hearing loss

Table 3B -

Outcomes, Costs and Sensitivity Analyses in Economic Studies of Screening-based Interventions for Congenital Cytomegalovirus (cCMV) Infection*

Study	Health outcome(s) reported	Medical costs assumptions (in 2018 US dollars in parentheses)	Intervention costs (in 2018 US dollars in parentheses)	Value of Ratio or Cost Difference as Reported (in 2018 US dollars in parentheses)	Sensitivity Analyses (SA) Results
Prenatal screening					
Albright CM, et al. Am J Perinatol. 2019 ⁷⁶	Maternal quality adjusted life year (QALY) gained			\$84,773 per maternal QALY gained	
Cahill AG, et al. Am J Obstet Gynecol. 2009 ⁷⁵	Incremental effectiveness in reduction of severely affected children: Universal vs risk factor-based (by 7638) and Universal vs Sonographic-based (by 7712)	Assumed costs: <ul style="list-style-type: none"> Pregnancy termination \$700 (\$820) Severe disability \$995,940 (\$1,166,533) (sum of medical and non-medical costs) 	Unit costs <ul style="list-style-type: none"> Serum screen \$151 (\$177) Amniocentesis and PCR \$182 (\$213), HIG \$730 (\$855) 	Cost per QALY of screening all (universal) with intention to treat \$89 (\$104). Risk factor-based screening \$95 (\$111). Sonographic-based screening \$97 (\$113) and No screening or treating \$100 (\$117)	If sensitivity 80% and specificity \leq 70.1%, then risk factor-based becomes dominant
Newborn screening					
Bergevin A, et al. Int J Pediatr Otorhinolaryngol. 2015 ⁷⁷	12/244 (5%) infants tested had cCMV. Of 9 cCMV positive infants, 5 confirmed to have hearing loss and provided antiviral treatment. Assumed 1-2 children would not require cochlear implants (no source).	Antiviral treatment and monitoring costs per year: \$4,839 (\$5148) to \$9,678 (\$10,296) depending on rate of public insurance coverage among infants	Cost to screen <ul style="list-style-type: none"> \$66 (\$70.2) per infant screened, calculated as \$7,260 for screenings divided by 244 infants screened \$65,600 (\$69,800) administrative cost for 2 years Total screening cost \$126 (\$134) per infant screened Antiviral treatment \$4839 (\$5,148) per infant per year 	Net cost savings (described as benefits - costs) = \$47,000 (\$50,000) to \$87,000 (\$93,000) Benefit/cost ratio 1.99-2.18 assuming 2 cochlear implants prevented each year	
Beswick R, et al. J Paediatr Child Health. 2019 ⁸⁰		Cost to care for child with HL: AUD \$3314 (US\$2,313) per year		Mean cost reduced in screened vs. non-screened infants by 3.92%	Results did not differ from base-case scenario after varying assumed valganciclovir efficacy

Study	Health outcome(s) reported	Medical costs assumptions (in 2018 US dollars in parentheses)	Intervention costs (in 2018 US dollars in parentheses)	Value of Ratio or Cost Difference as Reported (in 2018 US dollars in parentheses)	Sensitivity Analyses (SA) Results
Chen K, et al. JAMA Netw Open. 2020 ²⁰	Quality-adjusted life-years (QALYs)	<ul style="list-style-type: none"> Cost over 18 years, with inflation, is AUD \$77,547 (US \$54,115) Annual cost of care: \$300 for mild-to-moderate hearing loss, \$450 for severe-to-profound hearing loss in absence of cochlear implants Cochlear implants in 50% of individuals with severe-to-profound SNHL cost \$30,000 plus \$1,500 per year 	<ul style="list-style-type: none"> inclusive of confirmatory testing Cost to confirm and treat 1 case of cCMV AUD 3215 (US\$2,244) Screening cost \$15 per infant for PCR assay 	<ul style="list-style-type: none"> \$79 per QALY for NBHS-targeted screening vs. no screening \$2,087 per QALY for universal NBS vs. no screening 	<ul style="list-style-type: none"> ICERs were most sensitive to the prevalence of cCMV; cost of the PCR test, and the cost of antiviral treatment. Targeted screening would be cost-saving at a cCMV prevalence of 0.9% and universal NBS would be cost-saving at a prevalence of 2% or the probability of true CMV positives.
Gantt S, et al. JAMA Pediatr. 2016 ⁷⁹	Effectiveness of screening in identifying cCMV cases and cCMV-related hearing loss AND efficacy of antiviral treatment in reducing profound hearing loss and need for cochlear implantation by 2/3, from 13% to 4.2%.	<ul style="list-style-type: none"> Total annual cost to care an infant with cCMV-associated HL: <ul style="list-style-type: none"> <6 y M-M \$1850 (\$1959), S-P \$8805 (\$9325) 6 to <13 y M-M \$1530 (\$1620), S-P \$20,771 (\$21,998) 13 to <18 y M-M \$1527 (\$1617), S-P \$20,762 (\$21,989) 18 y M-M and S-P \$948 (\$1004) 	<ul style="list-style-type: none"> Screening cost \$1050 (\$10,50-\$52.50) per infant for specimen collection, testing, and confirmatory analysis if positive Universal screening: cost of Identifying 1 cCMV case= \$2000-10000 (\$2100-\$10500), cost of identifying 1 cCMV-related hearing loss ~ \$27000 (\$28500) Targeted screening: cost of identifying 1 cCMV case \$566-\$2832 (\$6003,000); cost of identifying 1 cCMV-related hearing loss \$975 (\$1035). 	<ul style="list-style-type: none"> Assuming a screening cost of \$10.50 per infant and assuming valganciclovir protects against hearing loss and eliminates lost productivity and need for special education services, authors projected net savings of \$37.97 (\$40.22) with universal screening and \$27.31 (\$28.93) with targeted screening to treat cCMV-infected asymptomatic and with hearing loss at birth Net savings of \$21.34 (\$22.62) with universal screening and \$10.66 (\$11.29) with targeted 	<ul style="list-style-type: none"> Depending on assumptions related to antiviral treatment, universal and targeted screening net costs ranged from increased direct costs of \$10.86 (\$11.50; sensitivity analysis range, \$6.97 to \$14.73 (\$7.38 to \$15.60) to net savings of \$37.97 (\$40.21) and a sensitivity analysis range, \$14.60 to \$61.34 (\$15.43 to \$64.96) per newborn undergoing screening.

Study	Health outcome(s) reported	Medical costs assumptions (in 2018 US dollars in parentheses)	Intervention costs (in 2018 US dollars in parentheses)	Value of Ratio or Cost Difference as Reported (in 2018 US dollars in parentheses)	Sensitivity Analyses (SA) Results
Williams EJ, et al. Arch Dis Child Fetal Neonatal Ed. 2015 ⁷⁸	Infants with cCMV identified and "protected" by treatment with valganciclovir	Cost per single case of cCMV-related SNHL identified: Screening £4062 (US\$5,452), Postscreening treatment and follow up £2621 (US \$3,518)	<ul style="list-style-type: none"> Cost of screening £75.7 (US\$102) per infant screened, £760 (US \$1,020) per infant with cCMV; £4062 (US \$5,452) per case of cCMV-related SNHL Cost of treatment and follow-up £659 (US\$ 885) per infant with cCMV; £2621 (US \$3,518) per case of cCMV-related SNHL 	<ul style="list-style-type: none"> Cost of targeted screening & treatment per infant with cCMV and SNHL £6683 (US \$8,970). Cost per infant treated with val-ganciclovir (47% of those identified) £14 202 (US \$19,063). 	The authors also present estimates of possible cost-effectiveness depending on the efficacy of valganciclovir.

Abbreviations: AUD, Australian dollars; CBA, cost-benefit analyses; cCMV, congenital cytomegalovirus; CEA, cost-effectiveness analyses; CMV, cytomegalovirus; CUA, cost-utility analysis; HIG; intravenous hyperimmune globulin; HL, hearing loss; M-M, mild to moderate hearing loss; NHS, National Health Service; ICER; incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; NBHS, newborn hearing screening; PCR, polymerase chain reaction; SA, sensitivity analysis; SNHL, sensorineural hearing loss; S-P, severe to profound hearing loss; y, years old.

* When needed, cost values were updated to 2018 US dollars using the Gross Domestic Product: Implicit Price Deflator (GDPDEF). Also, when needed, cost values in foreign currencies were converted and updated to 2018 US dollars using the Purchasing power parities (PPP). Updated values appear in parentheses (Source for PPP: <https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm> and for GDPDEF <https://fred.stlouisfed.org/series/GDPDEF>).