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Estimates of congenital cytomegalovirus-attributable infant mortality in high-income countries: A review

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Abstract

As many as 5%–10% of infants with symptomatic congenital cytomegalovirus (cCMV) disease, or 0.4%–0.8% of all liveborn infants with cCMV infection, die in early infancy in high-income countries. However, estimates are uncertain due to several potential biases that can result from data limitations and study designs. First, infants with cCMV infections who die prior to diagnosis, which usually occurs at 1–4 weeks after birth, may be excluded from both the count of deaths and the denominator of cCMV births, resulting in left truncation and immortal time biases. These 'biases' are features of the data and do not reflect bias on the part of researchers, but understanding the potential existence of threats to validity can help with interpretation of findings. Left truncation of infant deaths occurring prior to diagnosis of cCMV can result in understatement of the burden of infant deaths due to cCMV. Conversely, overestimation of infant deaths associated with symptomatic cCMV may occur in clinical case series owing to greater representation of relatively severely affected infants owing to ascertainment and referral biases. In this review, we summarise the characteristics of 26 studies that reported estimates of cCMV-associated infant

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AUTHOR CONTRIBUTIONS

Scott D. Grosse conceptualised the manuscript, performed the narrative review, extracted data elements, drafted and finalised the manuscript. Patrick Fleming extracted data elements, assisted with review of the literature, contributed to drafting and finalising the manuscript. Megan H. Pesch extracted data elements, assisted with review of the literature, contributed to drafting and finalising the manuscript. William D. Rawlinson conceptualised the manuscript, and contributed to drafting and finalising the manuscript. All authors approved the final version of the manuscript submitted herein.

CONFLICT OF INTEREST STATEMENT

Scott D. Grosse: No conflict. Patrick Fleming: No conflict. Megan H. Pesch: Dr. Pesch serves on the board of directors the National CMV Foundation (unpaid) and is a paid consultant for MedScape. Neither of these organisations played any role in the conceptualisation, data collection and analysis, or preparation of this manuscript. William D. Rawlinson: No conflict.

deaths, including potential biases or limitations to which those estimates may have been subject. We discuss study designs whose implementation might generate improved estimates of infant deaths attributable to cCMV. More complete estimates of the overall public health impact of cCMV could inform current and future screening, prevention, and vaccine research.

Keywords

burden of disease; congenital cytomegalovirus; epidemiology; infant deaths; mortality

1 | BACKGROUND

Congenital cytomegalovirus (cCMV) infection occurs in 0.4%–0.6% of infants born in high-income countries and over 1% in low-and middle-income countries.[1] Infection can result in developmental disabilities.[2–4] Congenital CMV is the leading infectious cause of sensorineural hearing loss in children in high-income, and possibly low-middle income, countries.[4,5] Approximately 10%–15% of infants with cCMV are classified as symptomatic based on the presence of specific clinical signs or markers at birth.[6,7]

Symptomatic cCMV disease has also been implicated in height-ened risk of death in utero, the neonatal period (birth through 4 weeks of age), infancy (the first year of life) and childhood.[2,3,8–11] For instance, approximately 15% of stillbirths examined in Australian and Greek studies had evidence of CMV infection and associated placental abnormalities,[3,8,12] Regarding post-neonatal deaths, an Australian study reported that children with hospital diagnoses of cCMV had 18.4 times the odds of dying by age 5 years relative to matched controls.[13] Moreover, children with symptomatic cCMV who experience cerebral palsy and epilepsy are at increased risk of death in childhood and beyond as a result of those sequelae.[14–16]

Although cCMV is increasingly recognized as an important public health problem, the magnitude of cCMV-associated mortality risk remains uncertain. In order to understand the burden of cCMV and estimate the public health impact of interventions such as immunizations, it would be helpful to have accurate estimates of cCMV-attributable morbidity and mortality.[17,18] Herein, we report a narrative review of published estimates of infant deaths associated with cCMV in high-income countries in North America, Europe, and Asia. We excluded studies from low-income countries, where risk of death among infants with cCMV may be greater than in high-income countries due to disparate access to healthcare, co-occurring HIV infections, and other factors.[19] We reviewed information from both prospective birth cohort studies and period-specific surveillance studies in which infants were tested for cCMV and where results were reported either for infants with all severities of cCMV or infants with symptomatic cCMV disease alone. Following a discussion of the limitations of existing estimates, we provide suggestions for methods to generate more complete and relatively unbiased estimates of cCMV-associated infant mortality rates.

2 | METHODOLOGICAL CHALLENGES

The precise magnitude of infant mortality attributable to cCMV is undefined for several reasons. First, it is difficult to determine which deaths among infants with cCMV directly or indirectly resulted from the infection as opposed to the impact of confounding by shared risk factors. Second, individual studies are insufficiently powered to assess infant death as an outcome because of small numbers of cases and the low frequency of infant death. Third, estimates of disability and death attributable to symptomatic cCMV are subject to data limitations, commonly referred to in epidemiology or statistics as 'biases' even though they do not indicate subjective bias on the part of researchers, that can result in under-or over-estimation of risks (Table 1).

Overestimation of the risk of infant mortality in symptomatic cCMV disease can occur due to ascertainment and referral biases, which are both forms of selection bias (Figure 1).

Conversely, underestimation of infant mortality attributable to cCMV can occur due to left truncation and immortal time bias (Figure 2). Left truncation bias refers to the exclusion of individuals who experience an outcome prior to meeting study inclusion criteria.[22] Such bias when applied to relative mortality estimates is referred to in the epidemiologic literature as immortal time bias.[23] 'Immortal time' refers to the period of time between cohort entry (i.e., birth) and case ascertainment (confirmed diagnosis of cCMV). During that period, infants with cCMV are 'immortal' because those who die are counted in the non-cCMV group. This is of particular importance for infant mortality since deaths in the first week after birth account for up to half of all infant deaths.[20] For example, a US study found that although African-American children diagnosed with sickle cell anaemia had lower infant mortality than those without a diagnosis of sickle cell disease, infants with sickle cell anaemia had significantly *higher* death rates after neonatal deaths were excluded from both cohorts.[24]

3 | METHODS

The article and study selection for this narrative review were performed using databases such as PubMed, Google Scholar, BioMed Central and MEDLINE. The following phrases were used as search terms: congenital cytomegalovirus, mortality, infant mortality. The authors' personal archives of published studies on the subject matter were also used and cross referenced with search results. We selected studies that included a measure of mortality among infants with cCMV, between birth and 12 months of age. Inclusion criteria were as follows: scholarly article or report, English language publication, and study population from high-income countries.

4 | REVIEW OF ESTIMATES

We identified 26 epidemiologic studies on cCMV that reported estimates of infant mortality which are summarised in Tables 2 and 3. The included studies were published from 1980 to 2022. Most (n = 16) are cohort studies, and the remaining 10 are classified as surveillance studies.

4.1 | Cohort studies

A 1980 study from Birmingham, Alabama reported that nine of 34 (26%) infants who had been diagnosed with symptomatic cCMV at a tertiary referral centre by age three months died by 10 months of age, all except one of whom died prior to three months of age.[39] All infants who died had severe neurologic disease that contributed to death. That cohort was subject to ascertainment and referral biases, as noted in a contemporary study.[42] As such, those infants had disproportionately severe disease sequelae and an inherently higher risk of infant mortality. A subsequent study from the same institution by Boppana and colleagues reported that 13 of 106 (12%) symptomatic infants followed prospectively at a university hospital in Alabama during 1966–1989, most of whom were referred from other centres, died in the first six weeks of life.[2] Boppana et al. reported that seven of nine (78%) infants who underwent postmortem examination had disseminated CMV infection with multiorgan involvement.[2]

Prospective studies using representative screened cohorts of infants, which are not subject to ascertainment and referral bias, may yield lower estimates of cCMV associated mortality. For example, a study tracked 443 infants born at the University of Alabama Hospital during 1980–1996 who were identified with cCMV through urine or saliva screening during the first two weeks of life. Among the 388 infants enroled in a follow-up clinic, 53 of whom were symptomatic at birth, two (0.5%) were reported to have died with no information reported on age, cause of death, or presence of symptoms.[29] Those findings were subject to underestimation as a result of left truncation bias by the exclusion of infants who died prior to enrolment.

The lead author of the Alabama screening study provided us with clarifying information (Dr. Karen Fowler, personal communication, 24 July 2023). Of the two deaths reported in the 1999 publication, one was a sudden death that occurred between six and 12 months of age to an infant with symptomatic cCMV (microcephaly and hyper-bilirubinemia). The other was a death of unknown cause in the second year of life to a child with asymptomatic cCMV. Among 36 infants who were not enroled, all three symptomatic infants died, two as neonates (prior to four weeks) and one at five weeks, compared with none of 33 asymptomatic infants. Thus, a total of four (7%) deaths occurred during infancy among 56 infants with symptomatic infections in the birth cohort versus none among infants with asymptomatic infections.

Three large prospective cohort studies conducted in Sweden, the United Kingdom, and the United States assessed outcomes in infants with cCMV who were identified in representative cohorts of infants screened for CMV after birth. Investigators in all three studies reported no neonatal deaths and only one post-neonatal infant death among a total of nearly 200 infants with diagnosed symptomatic cCMV disease.[21,35,45] However, all three studies were subject to left truncation bias, since infants who died prior to being diagnosed with cCMV were by definition not included in the cCMV study groups.

An early screening study tested umbilical-cord blood for CMV IgM antibodies in 8644 U.S. newborns during 1967–1970 of whom 53 were CMV-positive. Two of the 53 (3.7%) were perinatal deaths, including one stillbirth and one early neonatal death at 48 h of

age.[30] That study design was free from left truncation bias, unlike other newborn screening studies included in this review. The only other published studies that were not subject to left truncation bias consisted of analyses of prenatally diagnosed infants.

A screening study published in 1982 diagnosed 64 infants who were cCMV-positive from cultures of urine specimens collected at two days of age from 15,212 Canadian newborns.[42] Because of the early collection of urine specimens, that study was less subject to left truncation bias than subsequent studies that required confirmatory diagnostic tests after an initial screen. Saigal and colleagues reported no neonatal deaths among the 64 infants with cCMV. Two deaths were recorded at 4 months of age, both in asymptomatic infants due to respiratory diseases.[42]

In 2010, Pignatelli et al. reported on 74 congenitally infected infants monitored at a university hospital in Bologna, Italy during 1998–2008. These infants either had prenatal evidence of in utero infection or presented with clinical symptoms at birth. Infection with cCMV was confirmed by isolation of virus from urine within 2 weeks after birth.[40] The investigators reported that 2/29 (7%) symptomatic infants died as neonates but did not specify the causes of death.[40] Similarly, Alarcon et al. reported that among 26 Spanish infants with symptomatic cCMV but without major birth defects, diagnosed at a university hospital during 1993–2009, 3/26 (12%) died, with 2/26 (8%) dying as neonates and 1/26 (4%) dying at 7 months.[25] Both studies were potentially subject to left truncation bias as well as ascertainment and referral biases due to the increased likelihood of infants with severe disease being tested and diagnosed.

In a large prospective study in Japan, 22,262 neonates were screened during 2008–2010 within four days of birth and diagnoses were confirmed with liquid urine specimens.[34] One (5%) infant death was recorded among 20 infants with symptomatic cCMV which occurred despite intensive treatment with valganciclovir.[34] Subsequently, Koyano et al. reported a death among 17 children with symptomatic infections followed for at least 2 years after birth.[33] Another prospective screening study in Japan tested urine specimens collected from 6348 infants in the first week of life born at Kobe University Hospital and Kobe Children's Hospital during 2009–2014. Nishida et al. identified 32 (0.5%) infants with cCMV, half of whom were classified as symptomatic, one (6%) of whom died prior to initiation of antiviral therapy.[38] In both studies, infected infants dying in the first days of life may not have had specimens collected and tested for CMV, representing potential left truncation bias.

Two overlapping clinical studies of foetal therapy for cCMV with sequelae visible on prenatal imaging were also conducted in Japan.[32,44] In the first study, conducted during 2005–2010 at multiple centres, 12 women with diagnosed foetal anomalies and positive foetal tests for CMV underwent immunoglobulin therapy and their liveborn infants were followed up clinically.[32] In that study, two (16.7%) infant deaths were reported, at days 1 and 36. A study conducted at a university hospital in Kobe during 2009–2019 identified 19 infants with prenatally diagnosed cCMV of whom 15 received foetal therapy.[44] Tanimura et al. reported two (10.5%) deaths in prenatally diagnosed cases, both on the first day of life; one was also included in the previous publication. Tanimura et al. also reported clinical outcomes for 15 infants with symptomatic cCMV diagnosed as newborns who underwent

antiviral therapy, of whom one (6.7%) died at day 29; some of the infants in the study were also included in the screening study by Nishida et al. All three neonatal deaths in the Kobe cohort were attributed to complications of prematurity, either hypoplastic lung or diffuse peritonitis.[44] The Kobecohort of 34 newborns appears to have been selective of severely affected infants, 80% of whom were born preterm.

Canadian researchers at a university hospital in Quebec identified 54 foetuses with cCMV based on suspected maternal CMV exposure and another 30 infants who were diagnosed with cCMV through testing following birth for reasons other than suspected maternal exposure.[37] Of 54 prenatally diagnosed cases, Minsart et al. classified 25 foetuses or infants as moderately to severely symptomatic. Six of the 54 affected pregnancies were terminated, one ended in spontaneous foetal demise after 21 weeks of gestation, and 3/24 (12.5%) prenatally diagnosed cases resulted in neonatal deaths, all attributed to cCMV. No deaths were reported among the 30 postnatally diagnosed cases, of whom 22 were moderately to severely symptomatic. The postnatally diagnosed cases were subject to left truncation bias owing to timing of collection of specimens, unlike the prenatally diagnosed cases, some of whom were diagnosed with cCMV based on tests of amniotic fluid or foetal tissue.

Another cohort study likewise reported no neonatal deaths among infants confirmed with cCMV, likely due to left truncation bias, even though postneonatal infant deaths were reported. Among 21,760 hospital births in Italy, nine infants were diagnosed with symptomatic cCMV following clinical referral, of whom one infant born preterm with human immunodeficiency virus died at 6 months of age.[26]

4.2 | Estimates from surveillance studies

Several surveillance studies have reported neonatal deaths among infants identified with cCMV.[27,28,31,36,41,43,46–48] For example, a British Paediatric Surveillance Unit study published in 2011 noted 86 cases of confirmed cCMV reported by pediatricians in the United Kingdom and Ireland.[46] A total of 10 (12%) infant deaths were reported, all of whom had cCMV involvement of the central nervous system. Four (5%) deaths occurred in the first week of life, four deaths occurred at 2–8 weeks of life, and the other two deaths occurred later in infancy. This and other surveillance studies using reports of clinical diagnosis were subject to ascertainment bias.[49]

A surveillance study in Michigan identified 175 potential cCMV cases during 2004–2011 through the state birth defects registry, infant death and live birth records, or hospital discharges.[41] After review of medical records when available, investigators confirmed 88 infants with cCMV, five (5.7%) of whom died in infancy, representing 0.07% of all infant deaths in the state during that period. However, since the birth prevalence of confirmed cases, 0.9 per 10,000 live births, was 2% of the minimal birth prevalence of all cCMV cases, implying that only 20% of symptomatic cCMV cases were identified and included in this cohort.[41] These estimates were subject to ascertainment bias.

Two analyses of US administrative healthcare databases reported in-hospital deaths associated with cCMV.[31,36] In an analysis of 20 million US birth hospitalizations in the during 2000–2012, analysts reported deaths prior to discharge in 70 (5.1%) of 1349

hospitalised infants who had a diagnosis of symptomatic cCMV.[31] No information was available on cause of death. In a study of electronic health records from 2010 to 2021, 13 (3.8%) of 342 infants with cCMV who received antiviral therapy died between 7 and 59 days after birth as did six (1.7%) of 347 infants not prescribed antivirals.[36] Those prescribed antivirals were presumably more likely to have moderately or severely symptomatic cCMV although administrative diagnoses of cCMV are not necessarily accurate and are insensitive owing to infrequent testing and underreporting of cCMV diagnoses.[50,51] Early neonatal deaths were not reported, likely as a result of left truncation bias. These analyses were also limited by administrative underreporting of cCMV diagnoses.

Three studies used US clinical databases to analyse the relative frequency of in-hospital deaths among high-risk neonates with and without cCMV administrative diagnoses.[28,47,48] First, deaths amongvery low birth weight (VLBW) infants in a regional neonatal intensive care unit (NICU) in Alabama during 1993–2008 were recorded among 3/18 (17%) cCMV-positive infants and 34/180 (19%) CMV-negative infants.[48] Second, a sentinel surveillance analysis of NICU records in California during 2005–2016 identified 319 infants positive for CMV—including postnatal infections—during the NICU admission, 27 (8.5%) of whom died >12 h after NICU admission.[47] Among VLBW (<1500 g) infants, death rates were equally high for those with or without diagnosed CMV infections. In non-VLBW infants, the NICU death rate was twice as high with CMV diagnoses. Similarly, in a national sample of 128,141 VLBW and/or very preterm (<30 weeks of gestation) infants with birth hospitalizations during 2018–2020, neonatal deaths were reported in 12.6%–12.7% of those with cCMV infections and those with no diagnosed viral infection.[28] All three studies may have been subject to immortal time bias since infants who died before specimen collection were not included.

Vital records are another source of information for cCMV surveillance, although infant death certificates often fail to record infectious causes of death identified on autopsy.[52] In 2011, Bristow and colleagues analysed US multiple cause of death records for deaths at all ages during 1990–2006 with cCMV diagnosis codes listed as an underlying or contributing cause of death.[27] Most (557, 72%) cCMV-coded deaths were among infants, 0.11% of all infant deaths. The majority of those deaths (n = 319) were in the neonatal period (<28 days). Finally, an analysis by Smithers-Sheedy and colleagues of Australian mortality records for 1999–2011 to children <15 years of age identified 83 child death records that included a diagnosis code for cCMV. Most (n = 68) of those deaths occurred prior to age 1 year, which constituted 0.22% of all infant deaths in Australia during that period.[43] It should be noted that cCMV, like other infectious agents, can lead to sudden unexplained infant deaths, although infectious agents are not generally identified.[32,53,54]

4.3 | Syntheses of estimates

It is often reported that approximately 5% of infants with symptomatic cCMV die, most of which are presumed to be a result of the infection.[4,6,55–57] Because there is no evidence that infants with asymptomatic cCMV are at risk of death due to the infection, the overall risk of death among all infants with cCMV infection is a 10th as great, that is, up to 0.5%. Two cCMV modelling studies assumed increased risk of death in asymptomatic cCMV

infection,[58,59] an assumption that was based on a single report of post-neonatal infant deaths among infants with ‘asymptomatic’ cCMV in a 1982 Canadian study that used an extremely restrictive definition of symptomatic cCMV.[42]

Other experts have proposed ranges of estimates that take into account statistical uncertainty. For example, Cannon et al. and the American Academy of Paediatrics Committee on Infectious Disease stated that infant deaths occur in 3%–10% of symptomatic infants or 0.3%–1.0% of all infants with cCMV.[60,61] That implies that the number of infant deaths from cCMV is 3–10 times greater than the frequency in death records reported by Bristow.[60] A 2018 cost-effectiveness analysis of a potential cCMV vaccine modelled a 5% infant death rate in symptomatic cCMV cases with an uncertainty range from 0% to 10%.[62] Individual studies may report higher or lower point estimates of infant deaths associated with cCMV due to wide uncertainty intervals. For example, Koyano et al. reported death of 1/66 (1.5%) infants diagnosed with cCMV through newborn screening,[34] with the 95% binomial exact confidence interval for that estimate ranges from 0.004% to 8.2%.

A major challenge in assessing the attributable burden of infant mortality is the difficulty of determining whether death that occurs in an infant with symptomatic cCMV is due to the disease itself or to co-occurring factors, notably prematurity. Researchers have found that the risk of mortality appears to be elevated among infants with extreme prematurity independently of cCMV infection status.[28,47,48]

5 | FUTURE STUDY DESIGNS

Improved estimates of the risk of infant death associated with cCMV might be generated if researchers were to examine deaths among infants with positive initial screens using specimens collected on the first day or two after birth rather than requiring a confirmed diagnosis of cCMV. Ideally, complete information would be reported for all deaths in screened cohorts, including deaths prior to the collection of initial specimens. Such information would include the time of death relative to the time of specimen collection, along with gestational age, birth weight, and the presence of clinical signs indicative of symptomatic illness. Collection of frozen tissue samples could allow for the post-mortem identification of infectious agents, such as CMV.[54]

A potential approach to generate population-based estimates of both birth prevalence of cCMV and associated infant deaths would be to test large numbers of stored specimens collected at birth. One specimen type is the placenta. Researchers in Brazil tested 17 placentas for Zika virus associated with exanthematic febrile manifestations and found that 14 were positive for Zika virus.[63] Japanese investigators recently stained placental sections for 59 infants with unexplained foetal growth retardation, of whom four (6.8%) were positive for CMV antigen.[64] Multiple studies of placental tissue associated with foetal demise have reported the presence of CMV.[3,8,12] However, CMV DNA has also been reported to be common in placental tissue in uncomplicated pregnancies, especially those ending in preterm delivery.[65]

Another potential specimen type is umbilical-cord blood, which was used in at least one cCMV screening study.[30] Multiple retrospective research studies conducted in Japan have successfully retrieved and tested dessicated umbilical cord specimens stored by families to identify children suspected of having cCMV disease.[66–68] It is unknown whether it might be acceptable to test stored umbilical cord specimens from deceased offspring for the presence of CMV.

Finally, neonatal DBS specimens, which in many places are stored long term, are a fairly commonly used specimen type in research studies. Although viral DNA is present in lower levels in blood than in saliva or urine, a recently completed cCMV pilot screening study in Minnesota reported analytic sensitivity of roughly 75% with a single primer polymerase chain reaction assay using DBS.[69] Stored DBS have been used to identify cCMV cases in two published epidemio-logic studies.[70,71]

Research studies in Sweden and England each tested samples of more than 100,000 stored neonatal DBS specimens for disorders other than cCMV to assess the frequencies of adverse outcomes, including death, identified by linking to other databases with personally identifiable information.[72,73] Those studies generated important information on the preventable burden of late diagnosis of the studied disorders.

Dutch investigators tested more than 30,000 stored DBS specimens for CMV for a national sample of children aged five years whose parents provided consent and used other information to identify cCMV-attributable disabilities and healthcare utilization.[70,74,75] However, because of the need to obtain parental consent, infants who had died were excluded from the sample.

In order to achieve adequate power to estimate death rates among infants positive for cCMV at birth, large numbers of specimens might need to be tested. Donaldson and Grosse recently observed that testing 1.2 million DBS specimens for a disorder present in one in 20,000 newborns would result in 60 cases. The authors acknowledged financial, regulatory and ethical concerns and suggested that given the challenges and costs of undertaking such a study, testing for multiple rare disorders might be needed to justify funding.[76] Although cCMV infection is not itself rare, the prevalence of cCMV-attributable infant death is likely between one in 20,000 and one in 67,000 births assuming a birth prevalence of five per 1000 and an attributable infant mortality rate of 0.3%–1.0%. Because of the low frequency of neonatal death, investigators wishing to generate reliable estimates would need to link hundreds of thousands of DBS specimens to vital records to identify which infants had died. Ideally, researchers would obtain access to medical records to confirm cCMV as a likely cause of death.

6 | CONCLUSION

Although infants with symptomatic cCMV disease at birth are at increased risk of death, the magnitude of risk remains uncertain. An estimate of excess infant deaths of 0.4%–0.8% deaths among birth cohorts of liveborn infants with cCMV infection is plausible but cannot be established definitively. In addition to infant deaths, the total burden of mortality from

cCMV includes foetal deaths and excess deaths in childhood experienced by children with cCMV. The public health impact of cCMV warrants attention to the development and assessment of potentially cost-effective cCMV prevention strategies such as vaccination.

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Abbreviations:

CMV	cytomegalovirus
cCMV	congenital cytomegalovirus
NICU	neonatal intensive care unit
VLBW	very low birth weight

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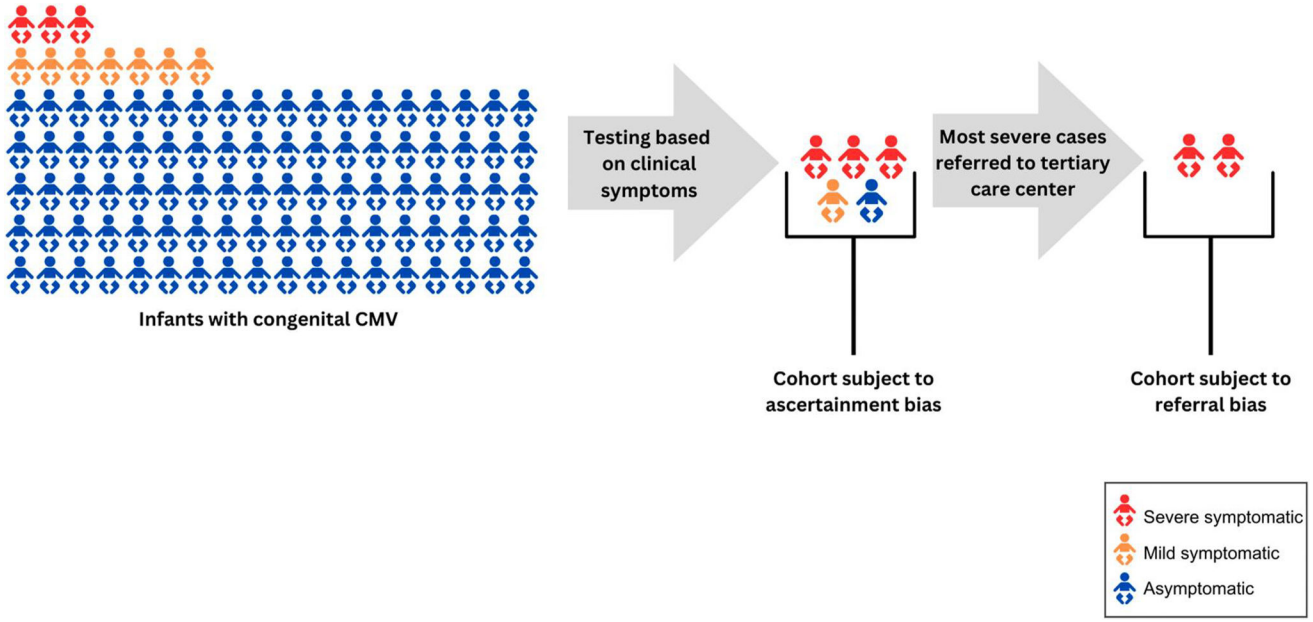
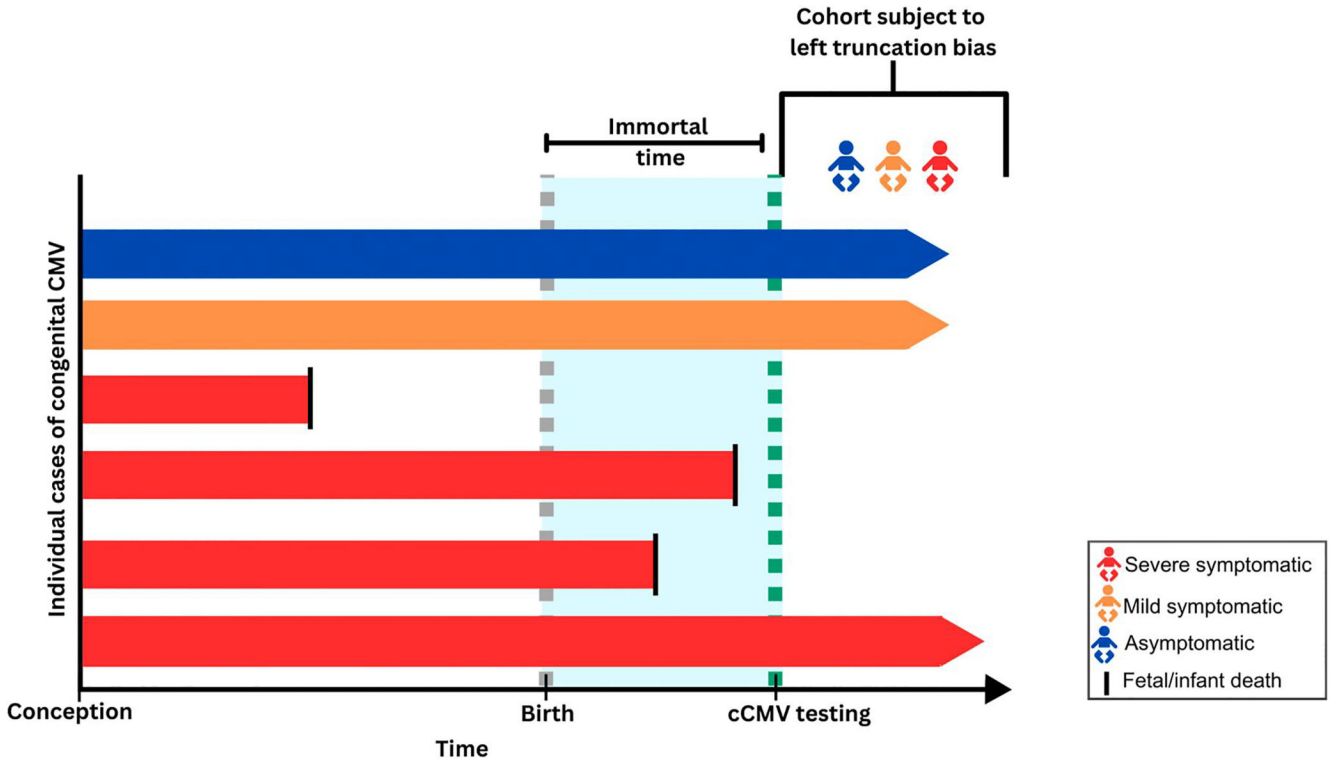


FIGURE 1.

Ascertainment and referral biases may result in over-estimation of congenital CMV related morbidity and mortality.



FIGUR 2.

Immortal time and left truncation biases may result in under-estimation of congenital CMV related morbidity and mortality.

TABLE 1

Biases that can impact estimates of congenital cytomegalovirus (cCMV)-associated infant mortality in observational studies.

Types of bias	Definition	Application to studies estimating cCMV-associated infant mortality	Potential impact on mortality estimate	Study design method to minimise bias risk
Ascertainment	Systematic differences in the identification of individuals included in a study, such that some individuals are more likely than others to be included in the cohort.	Ascertainment bias can occur if infants with serious clinical symptoms are more likely to be tested for cCMV, resulting in a non-representative cohort with a disproportionately high degree of disease severity.	Overestimation	Prospective studies using representative cohort from universal screening
Referral	Individuals who experience specific sequelae are more likely to be referred into the study population.	Referral bias can occur if severely affected infants are more likely to be referred to tertiary institutions.[4,20] resulting in a cohort with a disproportionately high degree of disease severity, and thus a non-representative cohort.	Overestimation	Prospective studies using representative cohort from universal screening.
Left truncation	Bias arises when individuals are excluded from the sample because their events occur before a specific milestone.	Exclusion of foetuses or neonates who experience a study outcome (i.e., death) prior to meeting study inclusion criteria (e.g., newborn screening at 24 h of life).	Underestimation	Early collection of specimens for cCMV testing; using specimen types that are conducive to early collection.
Immortal time	Bias in the comparison of mortality between affected and unaffected infants in the presence of left truncation bias. If death occurs during the 'immortal time' period between cohort entry and case ascertainment (cCMV diagnosis), individual is categorised as a control (vs. case).[21]	An infant with cCMV is born and enters the birth cohort but dies prior to cCMV testing (case ascertainment) and therefore is likely counted in the non-cCMV group.	Underestimation	Early collection of specimens for cCMV testing; using specimen types that are conducive to early collection. Post-mortem testing of foetal or neonatal samples.

Abbreviation: cCMV, congenital cytomegalovirus.

TABLE 2

Characteristics of studies reporting congenital cytomegalovirus (cCMV)-associated mortality in infancy.

Study	Country	Study design	Target population	Recruitment period	Method of cCMV identification and data sources to identify cases	Follow-up
Ahlfors et al. 1999[21]	Sweden	Long-term prospective cohort study assessing diagnosis, incidence, prognosis, maternal factors of infection	Infants at one hospital in Malmo alive at 2 weeks after birth and screened for cCMV	1977–1986	Urine CMV isolation sampled ≤2 weeks of life, umbilical cord blood, maternal sera	Followed for general, neurological, audiological, and ophthalmological status and development through 7 years of age
Alarcon et al. 2013[25]	Spain	Retrospective (1993–2000) and prospective (2001–2009) cohort study of predictors of neurodevelopmental outcomes for patients with symptomatic cCMV	Infants with symptomatic cCMV at one hospital in Madrid	1993–2009	CMV isolation, DNA detection, antibody/antigen in urine or blood within 2 weeks of life	Age of neurologic examination follow-up ranged from 19 months to 18 years, with a mean age of 8.7 years
Barbi et al. 1998[26]	Italy	Prospective cohort study of cCMV prevalence and burden	Infants from two 15-day sample periods (Group A), as well as infants showing clinical or laboratory signs throughout the year (Group B), from 11 neonatal divisions in Lombardy	1994–1995	CMV isolation from saliva at 2–4 days after birth, supplemented with urine and blood samples PCR from Guthrie cards	Followed virologically and clinically through 6–24 months
Boppana et al. 1992[2]	USA	Prospective cohort study of the natural history of symptomatic cCMV with outcomes assessed using hospital records	Infants with symptomatic cCMV infection born at or referred to hospitals of the University of Alabama Birmingham	1966–1989	Urine viral isolation	NA
Bristow et al. 2011[27]	USA	Surveillance study to assess burden and demographics of deaths coded for cCMV	USA resident deaths with ICD-9/10 code for cCMV infection, congenital cytomegalic inclusion disease	1990–2006	Underlying or contributing cause of death, death certificates, National Centre for Health Statistics	NA
Dreher et al. 2014[6]	USA	Prospective cohort study to evaluate differences in presentation, outcomes, and demographics of children identified with symptomatic cCMV disease through different methods	Infants with symptomatic cCMV identified through newborn screening at two hospitals in Birmingham, Alabama, and infants referred based on clinical findings	1980–2002	Urine or saliva viral isolation within the first 3 weeks of life plus reported clinical findings.	Serial audiologic, visual, and neurologic examinations of surviving participants.Average length of follow up 4.6 ± 3.77 years
Edwards et al. 2022[28]	USA	Surveillance study of congenital infection prevalence among VLBW and/or preterm infants	Live-born infants inborn or transferred to a Vermont Oxford Network reporting hospital within 28 days of birth	2018–2020		NA
Fowler et al. 1999[29]	USA	Prospective cohort study to assess detection of hearing loss in infants with cCMV detected through newborn screening.	Infants identified with cCMV through newborn screening at one hospital in Birmingham, Alabama (some overlap with samples in previous studies, Fowler et al 1992)	1980–1996	Urine or saliva viral isolation within the first 2 weeks of life	Audiological assessment for up to 6 years of age

Study	Country	Study design	Target population	Recruitment period	Method of cCMV identification and data sources to identify cases	Follow-up
Hanshaw et al. 1976[30]	USA	Prospective cohort study of longterm outcomes for infants with CMV IgM in umbilical cord serum.	Infants identified with cCMV at Strong Memorial Hospital	1967–1970	Umbilical cord serum specimens were tested for CMV IgM with an indirect immunofluorescence assay	General physical exam and development assessment at 3.5–7 years of age
Inagaki et al. 2018[31]	USA	Retrospective serial cross sectional study to assess risk factors, demographics, and burden of symptomatic cCMV-related birth hospitalizations	Birth hospitalizations of infants with ICD-9 diagnosis code 771.1 for cCMV. Symptomatic cCMV based on ≥1 diagnosis of characteristic cCMV symptoms	2000, 2003, 2006, 2009, and 2012	Kids' Inpatient Database, Healthcare Costs and Utilization Project, Agency for Healthcare Research and Quality	NA
Japanese cCMV Infection Immunoglobulin foetal Therapy Study Group[32]	Japan	Multi-centre study to assess the efficacy of immunoglobulin therapy for symptomatic cCMV	Women with infants with foetal anomalies that tested positive for cCMV, received Ig, and were liveborn	2005–2010	Viral culture and/or PCR analysis for amniotic fluid, foetal blood, and/or foetal ascites	Complete workup for cCMV at birth, with neurodevelopmental follow-up for at least 2 years
Koyano et al. 2018[33]	Japan	Long-term follow-up for a pilot study of cCMV screening (essentially same cohort as Koyano et al. 2011 but with a few more births)	Infants participating in a urine-filter cCMV screening programme at more than 25 sites across Japan	2006–2010	Methods documented in Koyano et al. 2011	Mental and physical development monitored for at least 2 years
Koyano et al. 2011[34]	Japan	Pilot study to evaluate the feasibility of cCMV screening (essentially same cohort as Koyano et al. 2018) complemented by retrospective testing of some infants	Infants participating in a urine-filter cCMV screening programme at 25 sites across Japan	2008–2010	Quantitative PCR of dried urine collected within 4 days of birth. Confirmation by virus isolation in repeat urine specimens collected at 1–3 weeks or in umbilical cord blood, dried blood spots for retrospective inclusion	Clinical data extracted from patient medical records for at least 3 months
Lanzieri et al. 2022[35]	USA	Prospective cohort study of longterm hearing outcomes in children with symptomatic cCMV	Infants with symptomatic cCMV enroled in the Congenital CMV longitudinal Study, mostly referrals from hospitals in Houston, Texas	1983–2005	Urine culture within 3 weeks of birth	Hearing assessments performed up to 18 years of age
Leung et al. 2022[36]	USA	Retrospective review of EHRs to evaluate antiviral use among infants with clinically recognized cCMV	Infants with ICD-9, ICD-10, or SNOMED-CT cCMV diagnosis codes in first 45 days of life	2010–2021	Cerner HealtheDataLab EHR database	NA
Minsart et al. 2020[37]	Canada	Retrospective cohort study of 84 mother-foetus/infant pairs with cCMV diagnosed either prenatally based on abnormal ultrasound or maternal history (n = 54) or postnatally based on cCMV symptoms without suspected maternal exposure ($n = 30$)	84 mother-child pairs with cCMV at an academic hospital in Montreal, Quebec	2003–2017	Culture and/or PCR results from amniotic fluid, urine, saliva, blood, spinal fluid, or foetal tissue ≤3 weeks of birth. Records from the Paediatric Infectious Diseases Division, prenatal and delivery charts	NA
Nishida et al. 2016[38]	Japan	Prospective newborn screening cohort and antiviral treatment study	Infants screened at hospitals in Kobe	2009–2014	PCR in urine within 1 week of life	Infants followed for 12 or more months to assess neurological outcomes of symptomatic cCMV

Study	Country	Study design	Target population	Recruitment period	Method of cCMV identification and data sources to identify cases	Follow-up
Pass et al. 1980[39]	USA	Prospective cohort study evaluating long term outcomes for symptomatic cCMV positive newborns	31 infants with symptomatic cCMV identified through viral isolation during the first month of life, with 3 other symptomatic cCMV positive infants referred at 7 weeks	1965–1979	Isolation of virus from urine within the first month of life, or at 7 weeks in 3 cases of later referral	Clinical, psychometric, audiometric, and visual assessments performed through up to 14 years
Pignatelli et al. 2010[40]	Italy	Prospective cohort study evaluating impact of host and viral factors on outcomes of newborns with cCMV	Infants diagnosed with cCMV at University of Bologna—no explanation of selection criteria for testing infants	1998–2008	Urine viral isolation within 2 weeks of life	Mean duration of clinical, instrumental, and laboratory evaluation follow up was 20.8 months after birth, with a range from 6 months through 60 months
Quarshie et al. 2016[41]	USA	Surveillance study of cCMV records reported by hospitals to Michigan birth Defects Registry (MBDR) (n = 101) and additional cases identified through infant death and live birth records or hospital discharges (n = 74)	Medical records reviewed for 68/101 MBDR cases and 43/74 other cases to confirm cCMV diagnoses in 57/68 MBDR cases and 31/43 other cases	2004–2011	MBDR hospital discharge data linked to birth and death records	NA
Saigal et al. 1982[42]	Canada	Prospective cohort study of developmental and audiologic status in infants with cCMV	Infants from 3 maternity units in Hamilton, Ontario	1973–1976	Urine culture within 2 days of life	Physical and neurological examination through 5 years of age
Smithers-Sheedy et al. 2015[43]	Australia	Surveillance study of Australian mortality records to identify deaths attributable to CMV in children	Children <15 years old who had cCMV (ICD-10 P35.1) listed as underlying or contributing cause of death	1999–2011	Data from Medical Certificates for Cause of Death records provided to the Australian Bureau of Statistics	NA
Tanimura et al. 2021[44]	Japan	Clinical study to evaluate combination of immunoglobulin foetal therapy and neonatal therapy with antiviral drugs	Infants in 1 hospital in Kobe who either underwent foetal therapy for symptomatic cCMV following prenatal diagnosis (n = 15), or were prenatally diagnosed, did not receive foetal therapy but received antiviral therapy after birth (n = 4), or newborns diagnosed with symptomatic cCMV and received antiviral therapy (n = 15). Prenatally diagnosed cases ending in termination of pregnancy not included (no data reported).	2009–2019	Prenatal diagnosis: Foetal imaging + positive CMV DNA PCR in amniocentesis Newborn diagnosis: positive urine PCR with at least 1 clinical symptom suggesting cCMV.	Physical exam and neurological assessment through 3 years of age
Townsend et al. 2013[45]	United Kingdom	Long-term prospective cohort study assessed outcomes in cCMV in West London, also repeated findings of Swedish study previously reported by Ahlfors et al (1999)	Pregnant women and infants in West London. Data pooled for a well-defined cohort enroled in pregnancy with vague data on other newborns	1979–1986	Throat swab within 1 week of life, confirmed by urine culture within 2 weeks of life.	Most (87%) were followed for general development by a paediatrician through at least 5 years of age
Townsend et al. 2011[46]	United Kingdom, Ireland	Surveillance study of cCMV identified through routine clinical investigations	Infants with confirmed or suspected cCMV	2001–2002	Pediatricians reported confirmed or suspected congenital CMV infections through the British Paediatric Surveillance Unit.	Follow up information requested in second or third year of life

Study	Country	Study design	Target population	Recruitment period	Method of cCMV identification and data sources to identify cases	Follow-up
					Based on positive PCR, virus isolation, or detection of antigen in urine, blood, saliva, tissue taken within 3 weeks of birth, or clinical symptoms under 12 months of age with CMV isolated after 3 weeks of age.	
Tran et al. 2020[47]	USA	Sentinel surveillance study to assess trends in cCMV in California NICUs	Infants with birth weight ≤1500 g and acutely ill infants >1500 g admitted to NICUs from 137 hospitals	2005–2016	CMV-positive viral culture or PCR results reported to California perinatal Quality Care Collaborative	NA
Turner et al. 2014[48]	USA	Retrospective cohort study to evaluate incidence and outcomes of preterm VLBW infants with cCMV infection	Preterm VLBW infants admitted to regional NICU in Birmingham, Alabama who did not die before CMV testing	1993–2008	All infants screened for cCMV by urine or saliva rapid culture in first 2 weeks of life. Outcomes assessed from medical records	NA

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; ICD, International Classification of Diseases; MBDR, Michigan Birth Defects Registry; NA, not applicable; NICU, neonatal intensive care unit; PCR, polymerase chain reaction; VLBW, very low birth weight.

TABLE 3

Estimates of congenital cytomegalovirus (cCMV)-attributable infant mortality.

Study	Total population of interest	Study population	Potential study biases	Cohort birth prevalence of cCMV *n* (%)	cCMV positive and symptomatic at birth[a] *n* (%)	cCMV positive neonatal deaths (0–28 days) *n* (%)	cCMV positive post-neonatal deaths (29—365 days), *n* (%)	cCMV positive post-infancy deaths in early childhood (1–4 years)
Ahlfors et al. 1999[21]	19,589 infants born alive and 91 stillbirths	16,474 infants alive at 2 weeks who had urine specimens collected in first week. Note: 63 liveborn infants died in first week of life, not included in those with urine collection	Left truncation bias owing to exclusion of deaths <2 weeks of birth	76 (0.46)	22 (28.9)	0	0	0
Alarcon et al. 2013[25]	Not reported	26 infants with symptomatic cCMV. Note: 29 total with symptomatic cCMV, 2 excluded due to major malformation and 1 with chromosome abnormality)	Left truncation, ascertainment, and referral biases	NA	26 (100)	2 (7.7)	1 (3.8) at 7 months	0
Barbi et al. 1998[26]	21,760 infants born in participating hospitals	1453 examined infants, 1268 in group A (born during two 15-day periods at participating hospitals), 185 in group B (those with clinical or laboratory signs)	Left truncation bias	Group A: 6 (0.47) Group B: 9 (4.9)	Group A: 0 (0) Group B: 3 (33)	0	1 (0%) Infant co-infected with HIV, developed hepatitis, pneumonia and died at 6 months	0
Boppana et al. 1992[2]	Not reported	106 infants with symptomatic cCMV (32 born at hospitals of the University of Alabama Birmingham, 74 referred from other hospitals)	Left truncation, ascertainment, and referral biases	NA	106 (100)	13 (12.3) deaths ≤6 weeks of life from all causes, including 2 deaths with NEC, 1 with sepsis, 1 with portal hypertension. 7/9 deaths with autopsy had disseminated CMV infection in multiple organs. Deaths beyond 6 weeks not reported		-
Bristow et al. 2011[27]	39,755,734 total deaths among US residents	777 cCMV-associated deaths at all ages (525 with cCMV as underlying cause and 252 with cCMV as contributing cause)	Potential bias: Most cases of cCMV in general are not detected or reported	NA	NA	319 (41.1)	238 (30.6)	90 (11.6) (Ages 1–5 years)
Dreher et al. 2014[6]	Not reported	178 symptomatic infants (78 screened and 100 referred) were enroled in follow-up study. An additional 7 infants who died and 2 lost to follow-up were not enroled in the follow-up study.	Not clear whether study was subject to left truncation bias	NA	178 (100)	10 (5.3) died in infancy, age not specified		-

Study	Total population of interest	Study population	Potential study biases	Cohort birth prevalence of cCMV *n* (%)	cCMV positive and symptomatic at birth[a] *n* (%)	cCMV positive neonatal deaths (0–28 days) *n* (%)	cCMV positive post-neonatal deaths (29—365 days), *n* (%)	cCMV positive post-infancy deaths in early childhood (1–4 years)
Edwards et al. 2022[28]	Not reported	128,141 VLBW (401–1500 g) and/or preterm (22–29 weeks of gestation) infants with birth hospitalizations	Immortal time bias	424 (0.3)	Not reported explicitly, however 45 (10.6) had congenital anomaly, 182 had SGA (43.4), 117 had microcephaly (30.7)	54 (12.7)	-	-
Fowler et al. 1999[29]	Not reported	443 infants identified with cCMV through newborn screening, of whom 407 were enroled for follow-up and 388 were followed.	Left truncation bias	NA	53/388 (13.7) infants followed; 56/443 (12.6) of birth cohort	2 (3.6) of 56 symptomatic infants in birth cohort died prior to age 4 weeks	2 (3/6%) symptomatic infants in birth cohort: 1 who died at 5 weeks was not enroled and 1 enroled with microcephaly experienced sudden death prior to 12 months personal communication, K. Fowler, 24 July 2023	1 asymptomatic child died between 18 and 24 months of age, cause of death unknown
Hanshaw et al. 1976[30]	8664 infants tested for CMV-IgM cord blood antibody	53 infants were identified through CMV IgM screening, with 44 of those receiving follow-up examination.	No identifiable biases	53 (0.6)	Not reported. One infant was clinically suspected due to a transient petechial rash	2/53 (3.8) all births 1/52 (1.9) live births One was stillborn, one died at 48 h with microcephaly, facial anomalies, chromosome deletion.	No post-neonatal deaths reported among 44 children who were followed up.	0
Inagaki et al. 2018[31]	19,638,452 in-hospital births	1773 with a cCMV diagnosis code	Potential biases: Only deaths prior to discharge; Reliance on administrative diagnosis codes	1773 (0.009)	1349 (76.1)	70 (3.9) deaths prior to discharge, age not specified(5.2% of 1349 symptomatic infants)		
Japanese cCMV Infection Immunoglobulin foetal Therapy Study Group 2012[32]	Not reported	12 live born infants diagnosed with cCMV in utero, with foetal anomalies, whose mothers received immunoglobulin therapy during pregnancy	Ascertainment bias	NA	12 (100)	1 (8.3) at 1 day	1 (8.3) at 36 days	0
Koyano et al. 2018[33]	23,405 newborns born at 25 hospitals or clinics	60 cCMV patients followed for 2–6 years, (Cohort overlaps with Koyano et al. 2011[26])	Left truncation bias	NA	17 (23.9)	1 (1.4%), age at death not stated, but ≥2 years. Infant was symptomatic (5.9%), born preterm (31 weeks of gestation), and developed severe respiratory failure		1

Study	Total population of interest	Study population	Potential study biases	Cohort birth prevalence of cCMV *n* (%)	cCMV positive and symptomatic at birth[a] *n* (%)	cCMV positive neonatal deaths (0–28 days) *n* (%)	cCMV positive post-neonatal deaths (29—365 days), *n* (%)	cCMV positive post-infancy deaths in early childhood (1–4 years)
Koyano et al. 2011[34]	21,272 newborns born at 25 hospitals or clinics	21,272 infants screened for cCMV, 70 CMV-positive with 66 cases confirmed	Left truncation bias	66 (0.31)	20 (30.3)	1 (1.5%), age at death not stated. Infant, treated with valganciclovir at a tertiary hospital, was symptomatic at birth (6.7%)		-
		14,642 births at municipal hospitals or clinics	Left truncation bias	35 (0.24)	6 (17.1)	-	-	
		6630 births at tertiary hospitals	Left truncation bias	31 (0.47)	14 (45.2)	-	-	
Lanzieri et al. 2022[35]	Not reported	76 children with symptomatic cCMV 6 died in childhood, including 3 at ages 12 or 13 years	Left truncation bias	NA	76 (100)	0	1 (1.3) death at 2 months listed as sudden infant death syndrome	2 (2.6) at 2 years, from postsurgical complications or respiratory failure
Leung et al. 2022[36]	Not reported	689 infants with cCMV diagnosis codes 203 admitted to NICU	Left truncation, ascertainment, and incomplete reporting biases	NA	NA	19 (2.8) deaths in infancy 13 (3.8) deaths among 342 infants prescribed antivirals. Median age at death: 25 days, IQR 7–59 6 (1.7) deaths among 347 infants not prescribed antivirals. Median age at death: 116 days, IQR 17–288		-
Minsart et al. 2020[37]	103 mothers with suspected cCMV and 30 newborn infants referred for other reasons	Foetuses prenatally diagnosed (N = 54), 6 TOP, 1 spontaneous foetal demise, and 47 live births. 30 liveborn infants diagnosed with cCMV based on failed hearing screen (n = 8), maternal HIV (n = 2), or neonatal symptoms (n = 20)	Postnatally diagnosed cases subject to left truncation bias	NA	47 (61.0)	3 (3.9% overall, 6.4% of symptomatic live births)	0	0
Nishida et al. 2016[38]	Not reported	6348 infants screened for cCMV	Immortal time, left truncation biases	32 (0.50)	16 (50.0)	1 infant died prior to antiviral therapy (3.1% overall, 6.3% of symptomatic cases)	-	-
Pass et al. 1980[39]	Not reported	34 infants with symptomatic cCMV	Ascertainment and referral biases	NA	34 (100)	8 (23.5) occurred by 3 months of age (exact ages not specified), 1 (2.9) at 10 months. 10 (29%) deaths in total, 9 (26%) prior to 12 months. All had severe neurological damage contributing *t* death, 2 also had gram negative sepsis, and 1 had cirrhosis of the liver.		1 at 26 months
Pignatelli et al. 2010[40]	Not reported	74 infants with cCMV, follow up data available for 64 children	Left truncation and selection biases	NA	29 (39.2)	2 (2.7% overall, 6.9% of symptomatic cases)	0	0

Study	Total population of interest	Study population	Potential study biases	Cohort birth prevalence of cCMV *n* (%)	cCMV positive and symptomatic at birth[a] *n* (%)	cCMV positive neonatal deaths (0–28 days) *n* (%)	cCMV positive post-neonatal deaths (29—365 days), *n* (%)	cCMV positive post-infancy deaths in early childhood (1–4 years)
						Causes of death not specified		
Quarshie et al. 2016[41]	175 infants with suspected cCMV, of whom 111 had health records reviewed	88 infants with confirmed cCMV	Left truncation, ascertainment, reporting biases	0.9 per 10,000	NA	5 (5.7%) deaths in infancy Complications or causes of death in 3 infants included necrotising enterocolitis, heart problems, perforated bowel, organ failure and massive infection		-
Saigal et al. 1982[42]	Not reported	15,212 neonates with urine culture	Left truncation and immortal time biases	64 (0.42)	4 (6.3)	0	2 (3.1) deaths from respiratory disease at 4 months disseminated CMV	1 death from congenital heart disease at 3 years in child with Down syndrome
Smithers-Sheedy et al. 2015[43]	Not reported	83 children with cCMV as an underlying or contributing cause of death	Reporting bias	NA	NA	22	35	26 deaths between 1 year and 15 years of age
Tanimura et al. 2021[44]	Not reported	34 infants with symptomatic cCMV who received antiviral therapy: 19 diagnosed prenatally and 15 diagnosed postnatally.	Selection and ascertainment bias (relatively severe cases)	NA	33 (97); 1 infant who received foetal therapy was not symptomatic at birth	3 (9) of symptomatic infants. Deaths were due to complications of prematurity: Respiratory failure due to hypoplastic lungs (n = 2) or diffuse peritonitis	0	0
Townsend et al. 2013[45]	21,213 live-born infants delivered by 21,917 women screened prenatally also ~15,000 other infants	19,354 infants tested for cCMV whose mothers had been screened and ~15,000 other infants	Left truncation bias	61 (0.32) infants whose mothers were screened, plus 39 other infants whose mothers were not enroled in pregnancy	5 (5)	0	0	0
Townsend et al. 2011[46]	Not reported	86 confirmed cCMV cases, of whom 78 had outcomes reported	Ascertainment and reporting biases	NA	64 (75.3)	8/78 (10.3) deaths <8 weeks, all symptomatic cases: 3 severe cCMV symptoms, 1 sepsis, 4 with complications of prematurity	2 deaths at 8–52 weeks, both due to pneumonia and complications of prematurity	-

Study	Total population of interest	Study population	Potential study biases	Cohort birth prevalence of cCMV *n* (%)	cCMV positive and symptomatic at birth[a] *n* (%)	cCMV positive neonatal deaths (0–28 days) *n* (%)	cCMV positive post-neonatal deaths (29—365 days), *n* (%)	cCMV positive post-infancy deaths in early childhood (1–4 years)
Tran et al. 2020[47]	~180,000 infants admitted to California NICUs	319 cCMV positive infants	Ascertainment bias acknowledged- more severely infected infants more likely to be tested	319 (0.18) 174 (0.27) VLBW; 145 (0.12) BW > 1500g	NA	27 (8.5) overall 15 (8.6) VLBW and 12 (8.3) BW > 1500g	-	-
Turner et al. 2014[48]	Not reported	4594 preterm VLBW infants	Immortal time bias	18 (0.39)	-	3 (17) for cCMV versus 34/180 (19) matched controls (prior to 24 months)		

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; NA, not applicable; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; SGA, small for gestational age; TOP, termination of pregnancy; VLBW, very low birth weight.

[a]Definitions of symptomatic cCMV vary according to study.