REVIEW

Estimation of the worldwide seroprevalence of cytomegalovirus: A systematic review and meta-analysis

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Summary

Cytomegalovirus (CMV) infection does not usually produce symptoms when it causes primary infection, reinfection, or reactivation because these three types of infection are all controlled by the normal immune system. However, CMV becomes an important pathogen in individuals whose immune system is immature or compromised, such as the unborn child. Several vaccines against CMV are currently in clinical trials that aim to induce immunity in seronegative individuals and/or to boost the immunity of those with prior natural infection (seropositives). To facilitate estimation of the burden of disease and the need for vaccines that induce de novo immune responses or that boost pre-existing immunity to CMV, we conducted a systematic survey of the published literature to describe the global seroprevalence of CMV IgG antibodies. We estimated a global CMV seroprevalence of 83% (95%UI: 78-88) in the general population, 86% (95%UI: 83-89) in women of childbearing age, and 86% (95%UI: 82-89) in donors of blood or organs. For each of these three groups, the highest seroprevalence was seen in the World Health Organisation (WHO) Eastern Mediterranean region 90% (95%UI: 85-94) and the lowest in WHO European region 66% (95%UI: 56-74). These estimates of the worldwide CMV distribution will help develop national and regional burden of disease models and inform future vaccine development efforts.

KEYWORDS

cytomegalovirus, prevalence, worldwide

1 | INTRODUCTION

Cytomegalovirus (CMV) is a common infection that has a complex natural history.[1] Individuals without CMV infection may acquire primary infection, and those with prior infection (seropositive) may reactivate latent CMV or may become reinfected with a new strain of CMV.[1] In most patients, all three types of infection remain subclinical, presumably because the immune system keeps virus replication under control. However, in patients who are immunocompromised, CMV replication may be uncontrolled and lead to high viral loads in the urine, which are associated with viraemia, dissemination to multiple organs, and end-organ diseases such as pneumonitis, retinitis, hepatitis, or gastroenteritis.[2] CMV is the most common intrauterine infection and a high priority for vaccine development.[3,4] Disease can occur when pregnant women have active CMV infection with viraemia leading to involvement of the

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List of abbreviations: CMV, cytomegalovirus; IgG, immunoglobulin G; MeSH, medical subject headings; NHANES, national health and nutrition examination survey

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placenta and then the fetus.[5] Intrauterine infection can occur following primary infection, reactivation, or reinfection in a pregnant woman.[6,7]

In addition to these direct effects that can be seen in individuals and documented histopathologically in biopsies of organs, CMV is associated with indirect effects which are apparent at a population-level rather than an individual-level. This phenomenon was first described after solid organ transplant where an excess of graft rejection, atherosclerosis, and secondary bacterial or fungal infections was seen among those with past history of detectable viraemia.[8] These indirect effects partly explain the survival disadvantage that is seen in solid organ transplant or stem cell transplant patient populations who are CMV seropositive.[9] A recent randomized controlled trial showed that stem cell transplant patients given prophylaxis with letermovir had improved survival compared to recipients of placebo, so supporting CMV as an underlying contributor to all-cause mortality.[10] Indirect effects may also be seen in people living with HIV, manifesting as more rapid progression to AIDS and/or death.[11,12] Most recently, the indirect effect of excess mortality has been defined in members of the general population without classical risk factors for CMV disease.[13,14]

Given the complex natural history of CMV infection, the emerging need to plan the evaluation of candidate vaccines[15] against CMV (which may be given to prevent primary infection and/or to the boost immunity in those with natural infection) would be facilitated by knowledge of the seroepidemiology of CMV around the world. We therefore conducted a systematic literature search to identify the parts of the world that have a relatively high burden of infection with this common virus.

2 | MATERIALS AND METHODS

2.1 | Search strategy

A systematic review was conducted and reported in line with the criteria set out by the PRISMA guidelines.[16] We reviewed articles published prior to 5 October 2016 in the databases Embase, Medline, Web of Science, POPLINE, CINAHL Plus, LILACS, Africa Index Medicus, WHOLIS, and OPENGREY. The use of OPENGREY allowed for a search of grey data (unpublished data or data published in non-commercial form).

In consultation with an expert medical librarian, we developed a search strategy and adapted it to each database. A combination of medical subject headings (MeSH) and free text searches was used to search for terms relating to CMV and seroprevalence (full search strategy available in Appendix A).

Publications were screened and catalogued on Endnote X6. A strategy involving "auto-search" and "hand-search" was used to identify duplicates, before two authors (M.Z. and G.W.) systematically screened the search results independently and applied the inclusion and exclusion criteria.

In brief, studies that included data on CMV seroprevalence (based on detection of CMV specific immunoglobulin G [IgG]), assessed in the general population, women of childbearing age, and blood and organ donors were included in this systematic review. Studies were excluded if they were systematic reviews, surveillance reports, case studies, letters, correspondence, or did not include data on CMV IgG. Studies were also excluded if they reported seroprevalence data on high-risk

groups or children only or had a sample size <80, this was to avoid low quality studies and selection bias. A full list of the inclusion and exclusion criteria is available in Appendix B. We translated non-English papers by asking colleagues proficient in the language in question or by using "google translate."

For studies from the United States, we considered the national health and nutrition examination survey (NHANES) as a representative sample of the general population.[17] Nevertheless, the same full text screening was applied for all studies from the United States, but only original data from NHANES were included.

2.2 | Data extraction

Following full text review, we extracted the following variables from each study: study characteristics (number of participants, study dates, and location), participant characteristics (age, sex, population group), sample size and number of positive individuals, or, when the latter was not specified, CMV seroprevalence. Three population groups were considered: the general population (healthy individuals), women of reproductive age (pregnant women and women of reproductive age), and blood and organ donors. Several studies presented stratified results, which were merged if data allowed. However, three types of stratification did not allow merging: different population groups (general population, women of reproductive age, and/or blood and organ donors); groups with non-representative sample sizes; and different sampling timeframes.

2.3 | Statistical analysis

We estimated the seroprevalence of CMV infection (IgG seroprevalence) by country, World Health Organisation (WHO) region, and globally, by pooling the data from eligible datasets.

Specifically, we performed a random effects meta-regression using population group as fixed effect, and country nested within WHO region as random effect. The inclusion of population as fixed effect allowed modelling the systematic differences between the considered population groups and presenting adjusted estimates per country for the different population groups. A weighted average of the country estimates based on population size was used to estimate the regional and global seroprevalence. Population size estimates for the year 2015 were obtained from the UN World Populations Prospects 2017 Revision.[18] Statistical uncertainty in the meta-analytic results was propagated to the regional and global estimates through 10 000 Monte Carlo simulations. All parameters were summarized by their mean and a 95% uncertainty interval (UI) defined as the 2.5th and 97.5th percentile. The meta-regressions were performed using the brms package[19] version 1.10.0 for R version 3.4.0.[20]

3 | RESULTS

Out of 428 unique citations assessed for full text analysis, 262 studies met the inclusion criteria (Appendix C) (Figure 1). Twenty-three publications from the United States met the inclusion criteria. However, only the NHANES study was used in the analysis since it was considered a representative sample of the general population.[17] A total of 250 datasets
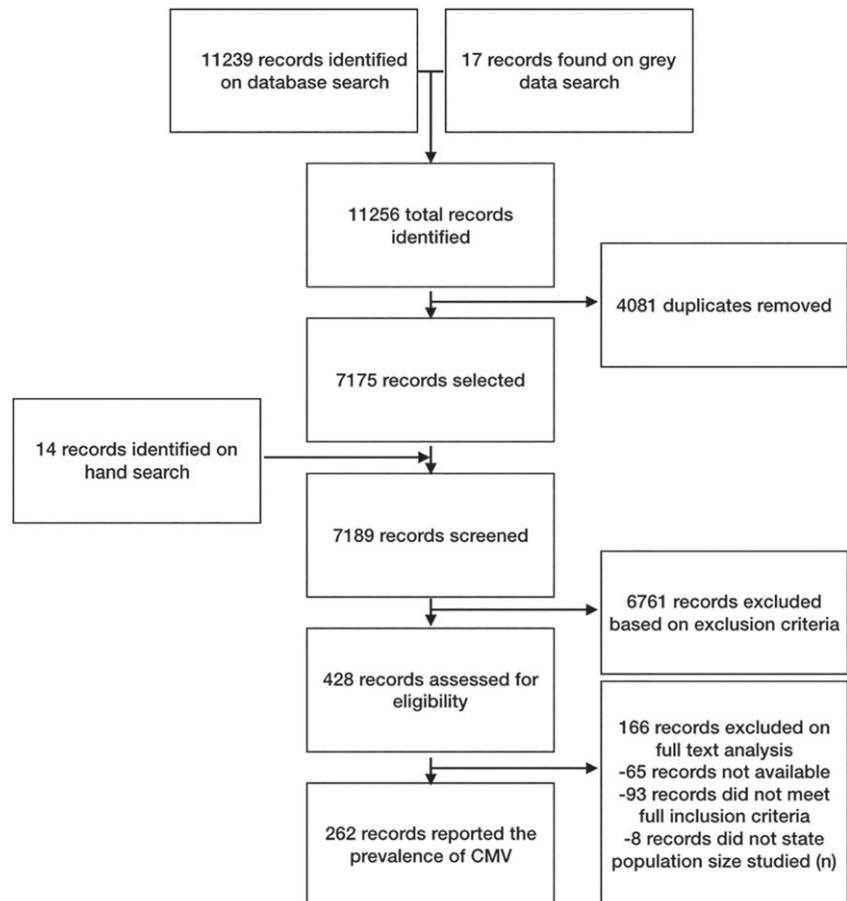
FIGURE 1 Prisma flowchart of study selection

were used in the analysis. "Google translate" was used 23 times; in all cases, the translation was considered sufficient if it was fully comprehensible and allowed a decision to be made about inclusion in the study.

The seroprevalence in the selected datasets ranged from 18% among a cohort in Canada to 100% in some studies within Bahrain, Benin, Egypt, Gambia, Iran, Nepal, Thailand, and Turkey. Similarly, the sample size ranged from 80 to 1 223 217. Figures 2 and 3 show the estimated mean seroprevalence per country in women of reproductive age gained from the meta-regression. The estimated mean seroprevalence and UI by country and population group can be found in tabular and graphic form in Appendix D.

Table 1 shows the estimated seroprevalence per WHO region and globally for the different population groups. The estimated global mean seroprevalence for the general population was 83% (95%UI: 78-88). The highest mean seroprevalence of 90% (95%UI: 85-94) was estimated in the Eastern Mediterranean region, compared to the lowest of 66% (95%UI: 56-74) in the European region. When looking at the different countries, the highest seroprevalence was estimated in Turkey with a mean of 96% (95%UI: 93-98) and the lowest in Ireland with a mean of 39% (95%UI: 18-62).

The estimated mean seroprevalence for women of reproductive age was 86% (95%UI: 83-89) globally, with the highest mean seroprevalence estimated in the Eastern Mediterranean region (92% (95%UI: 88-95)) and lowest in the European region (70% (95%UI: 63-76)). In the different countries, the highest seroprevalence was estimated in Turkey with a mean of 97% (95%UI: 95-98) and the lowest in Ireland with a mean of 44% (95%UI: 23-67).

The global mean seroprevalence for blood and organ donors was estimated to be 86% (95%UI: 82-89), again with the highest mean seroprevalence estimated in the Eastern Mediterranean region (92% (95%UI: 87-95)) and in Turkey (96% (95%UI: 94-98)) and the lowest in the European region (69% (95%UI: 61-77)) and Ireland (43% (95%UI: 22-66)).

4 | DISCUSSION

Our results summarize extensive information on the prevalence of CMV in different populations around the world. The results are consistent with a socio-economic link with CMV that has been well established in multiple studies showing that, at any given age, CMV prevalence is higher in individuals of lower socio-economic group.[21] It has also been reported that the children of individuals born in a developing country with a high prevalence of CMV have a lower prevalence once they become established in their adopted country.[22] It therefore seems likely that unidentified cultural and behavioural factors also interact with socio-economic group.

The observed increased seroprevalence for women of reproductive age is likely because of their exposure to children as reported previously.[21,23] However, the reason behind an increased seroprevalence among blood donors was counter intuitive, and the causes are less clear.

These results are important for several reasons. First, they will help to estimate the burden of disease attributable to congenital
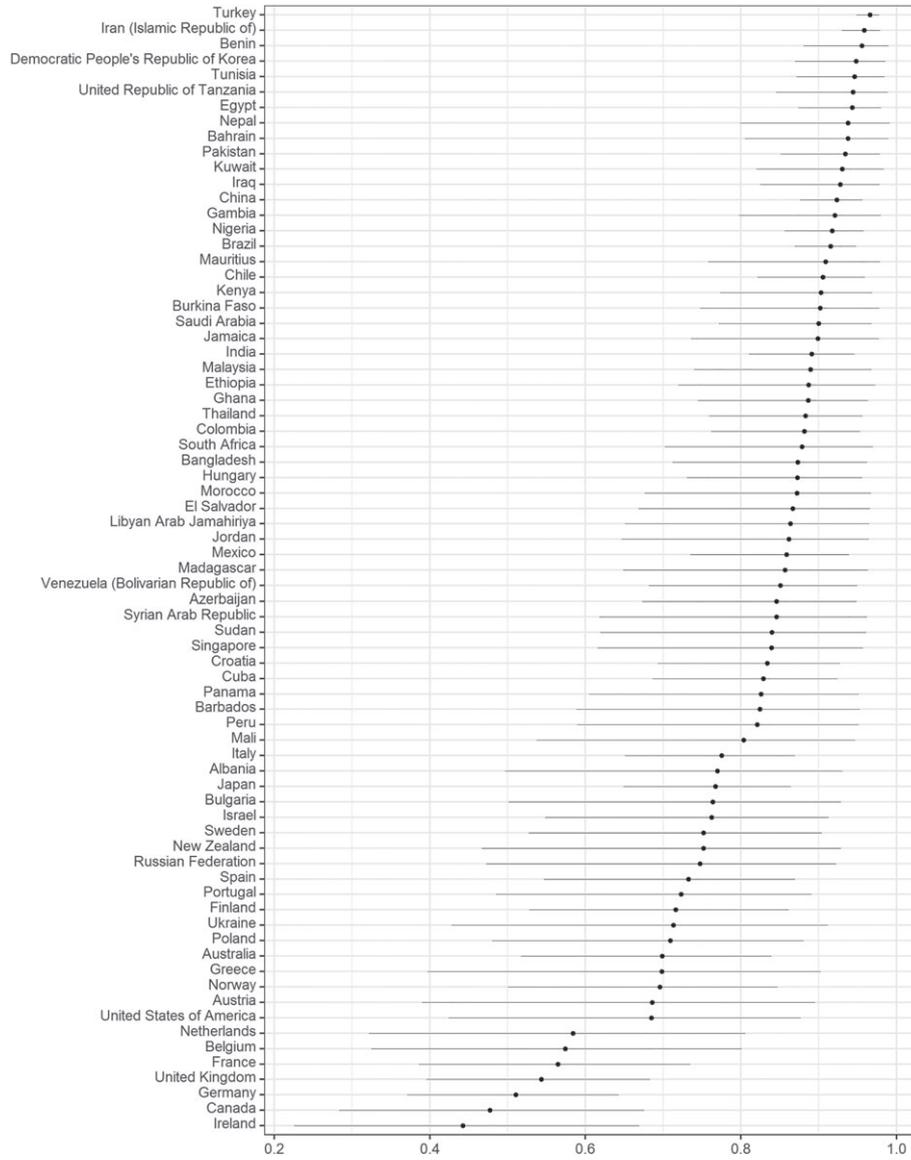
FIGURE 2 Meta-regression–based estimates of country specific mean seroprevalence and 95% uncertainty interval in women of reproductive age
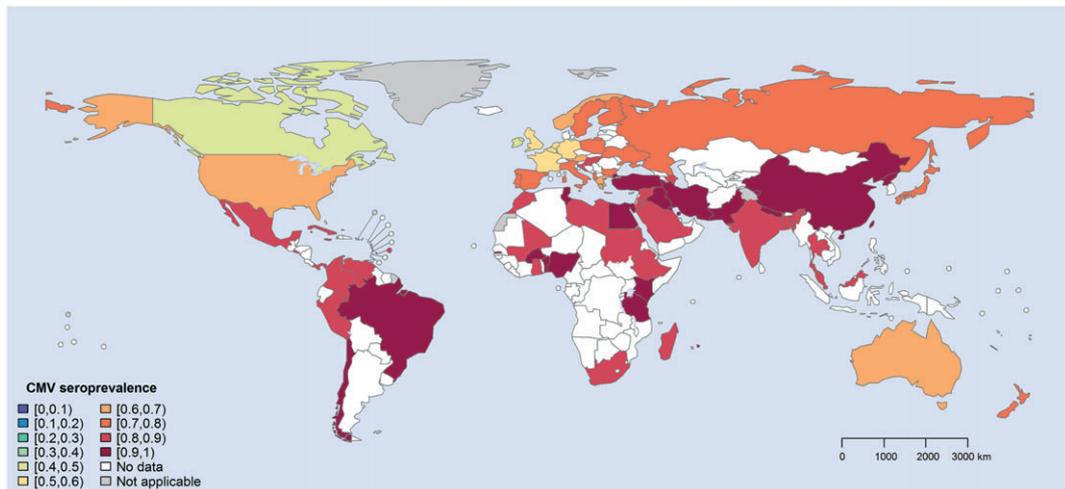
FIGURE 3 Estimated global cytomegalovirus seroprevalences in women of reproductive age

TABLE 1 Estimated cytomegalovirus mean seroprevalence % and corresponding 95% uncertainty interval in the different World Health Organisation regions and globally per population group

Regions	General Population	Women of Reproductive Age	Blood and Organ Donors
European region	66 (56-74)	70 (63-76)	69 (61-77)
Region of the Americas	75 (64-84)	79 (69-87)	78 (67-87)
South-east Asian region	86 (77-93)	89 (82-94)	88 (81-94)
African region	88 (80-93)	90 (85-94)	90 (84-94)
Western Pacific region	88 (81-93)	91 (86-94)	90 (85-94)
Eastern Mediterranean region	90 (85-94)	92 (88-95)	92 (87-95)
Global	83 (78-88)	86 (83-89)	86 (82-89)

infection which has a complex relationship with maternal serostatus. Although it is believed that women who acquire primary infection during pregnancy are most at risk of delivering babies severely damaged by intrauterine infection, such women are in a minority in many countries of the world.[24] Instead, most babies are born to women who are seropositive prior to conceiving because of their abundance in the community. Even in countries with relatively low seroprevalence, the majority of babies may be infected as a result of CMV reactivation or reinfection in the mother.[25] A high prevalence of infection in a community therefore contributes to all three types of maternal infection.[26] Vaccine studies have been conducted in seronegative and seropositive women.[27,28]

Second, the results may help predict the incidence of CMV infection and disease after solid organ transplant which may originate from the donor or the recipient.[1] Phase 2 randomized clinical trials have been conducted with vaccine candidates given to recipients awaiting solid organ transplant.[22,29] The situation is more complex following stem cell transplantation where vaccine may be given to recipients or donors or both to take advantage of adoptive transfer of immunity from a donor with or without prior immunity.[30,31]

Many countries in the world do not undertake organ transplantation or stem cell transplantation because high-technology medicine is not available. However, it is those same countries that often have a burden of HIV infection, which allows CMV to become an important opportunistic infection. CMV may therefore act as an important pathogen in patients with impaired immunity whether this results from iatrogenic or HIV induced immunosuppression. The incidence of congenital or perinatal CMV is also greatly increased in women with underlying HIV infection.[32,33]

We anticipate that the results presented here will improve understanding of diseases attributable to CMV in different parts of the world and will allow vaccine manufacturers to consider where to recruit individuals for clinical trials. These may either administer vaccine to seronegatives to prevent primary infection or administer vaccine to seropositives to boost immunity.[15]

This work had some limitations. There was a paucity of prevalence studies within some countries worldwide and the quality of reported studies also varied. Many of the studies were focused on adults and did not provide age or sex-specific prevalence. The lack of age stratification may be a cause of variation between studies, as CMV seroprevalence is known to increase with age.[34] Some prevalence data collected were also country specific, whereas a substantial within-country variability could be expected. In large countries with high geographic variation, seroprevalence estimates may not be representative of the national level. In some countries, there was a lack of available up-to-date seroepidemiological studies. Relying on data from older studies may risk generating seroprevalence estimates that do not represent the current epidemiological state of a country.

5 | CONCLUSION

Knowledge of worldwide CMV distribution will be helpful in informing national health care models of burden of disease and help future vaccine development.

AUTHORS' CONTRIBUTIONS

M.Z. developed the study protocol, designed, and coordinated the study. M.Z. and P.G. developed the search strategy. M.Z. and C.S. tailored the search strategy to each database, piloted the search, and performed the literature searches. M.Z. and G.W. performed the systematic review and assessed the relevance and accuracy of reports for use in generation of estimates. F.J. extracted data from selected studies. P.G. and B.D. provided technical expertise and advice. M.Z. developed and maintained the Endnote citation database. G.S.A.S. maintained the customized data extraction Excel sheet, and B.D. developed the analysis technique and generated global estimates, maps, and statistical analysis. M.Z. and G.S.A.S. wrote the manuscript with significant contributions from B.D. and P.G. All authors read and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.