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Cytomegalovirus seroprevalence among blood donors: a systematic review and meta-analysis

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Abstract

Background: Screening for cytomegalovirus (CMV)-specific antibodies is not routine in some settings. Thus, transfusion of blood products poses risks for susceptible individuals.

Objectives: To investigate the global pooled CMV seroprevalence among volunteer blood donors.

Methods: This systematic review and meta-analysis was performed according to PRISMA guidelines. The databases searched included Embase, Google Scholar, Medline, PubMed, Web of Science, and Cochrane Library. Data were extracted independently and analyzed using STATA version 11.

Results: The global seroprevalence of CMV IgG, CMV IgM, and both CMV IgM and IgG was 83.16% (95% confidence interval [CI]: 78.55–87.77%, $I^2 = 99.5\%$), 13.77% (95% CI: 11.59–15.95%, $I^2 = 98.8\%$), and 23.78% (95% CI: 10.50–37.06%, $I^2 = 98.7$), respectively.

Conclusion: The global seroprevalence of CMV was high among blood donors. Therefore, regular CMV screening should be conducted to identify CMV-seronegative blood donors.

Keywords

Blood donor, cytomegalovirus, seroprevalence, systematic review, immunoglobulin M, immunoglobulin G

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Background

Blood transfusion is a lifesaving component of many therapeutic interventions.[1] However, transmission of infectious diseases is a major challenge in transfusion services worldwide.[2] Cytomegalovirus (CMV), also known as human herpesvirus 5, is a large virus that infects humans.[3] CMV is a highly cell-associated virus and normally causes asymptomatic infections in immunocompetent individuals. Transmission of the virus can occur vertically or horizontally through contact with virus-containing body fluids including blood.[4] An important route of infection for high-risk groups is transfusion of blood products from latently infected donors (transfusion-transmitted [TT]-CMV).[5] Transfusion of contaminated blood products can result in primary infection in CMV-seronegative recipients or reinfection by a new CMV strain in CMV-seropositive recipients.[6] TT-CMV was first described by Kääriäinen and co-workers in 1966.[7] TT-CMV infections have traditionally been explained by transfer of latently infected white blood cells (WBCs).[8] The incidence of TT-CMV infection was reported to be as high as 13% to 37% in immunocompromised patients. Thus, the prevention of TT-CMV has become an important priority, especially in high-risk groups.[9]

CMV is a complex pathogen with distinct pathobiology.[3] CMV is one of the most common opportunistic pathogens in immunocompromised patients. These patients have high risks of complications following primary CMV infection, reinfection, and reactivation of latent virus. The presence of anti-CMV immunoglobulin G (IgG) indicates a previous infection by CMV, while presence of anti-CMV IgM reflects new infection, acute infection, or re-activation of CMV.[10] Donor IgM positivity is associated with higher risk of TT-CMV because of higher CMV DNA loads in both whole blood and plasma samples.[11]

CMV infection causes significant morbidity and mortality in immunocompromised patients who receive contaminated blood products.[3,12] Because CMV can cause severe illness and death in these patients, spread of the virus through blood products should be actively prevented.[13] Studies have demonstrated a high prevalence of CMV infection among various groups, including blood donors.[14] The risk of CMV transmission through blood products can be limited by improved selection of donors. However, the high prevalence of CMV seropositivity in the donor populations of many countries represents a significant problem: increasing demand for CMV-free blood products may be difficult to meet if CMV-seropositive donors are excluded.[13] In addition, use of CMV-seronegative blood cannot completely eliminate the risk of TT-CMV because of the possibility of window period donations.[15]

Leukoreduction (LR) of blood products is a common method used to decrease the risk of TT-CMV. Because latent CMV infection is restricted to small numbers of WBCs, removal of these cells significantly decreases the risk of TT-CMV.[16,17] Although LR is very effective in removing leukocyte-associated CMV, it cannot remove free CMV in plasma. As a result, newly infected blood donors could transmit CMV despite effective LR.[18] Persistence of CMV DNA following WBC removal explains rare TT-CMV in recipients of LR blood components.[19] In the era of universal LR of blood products, screening for CMV-negative blood products is thought to be unnecessary for hematopoietic stem cell transplantation because no cases of TT-CMV have been detected in some studies.[20–22] LR blood products from donors with active CMV infection have very low infectivity.[23]

CMV-seronegative products can result in TT-CMV during the window period between infection and positive results of antibody screening tests 6 to 8 weeks later. LR blood products can result in TT-CMV because of incomplete removal of WBCs in a small proportion of units. Therefore, both LR and CMV-seronegative units have low residual risks of TT-CMV. Interestingly, the few centers without dual inventories have a relatively high prevalence of CMV seropositive blood donors within their regional populations. Some countries use both CMV-seronegative and LR products for neonatal, intrauterine, and pregnancy-associated transfusion. Other countries use CMV-seronegative and LR products for all high-risk groups, while others use LR products alone.[5,24,25]

CMV seroprevalence varies significantly (from 40–100%) in different parts of the world.[26] The aim of this systematic review and meta-analysis was to estimate the pooled prevalence of CMV among blood donors worldwide.

Methods

Study setting and design

This systematic review and meta-analysis was conducted in a global setting. The study was designed according to the PRISMA-P 2015 Guidelines.[27]

Search strategy

We searched Embase, PubMed, Google Scholar, Medline, Web of Science, and Cochrane Library for articles published before 18 January 2021. The search terms were "Prevalence" OR "seroprevalence" OR "frequency" AND "CMV" OR "cytomegalovirus" OR "anti-cytomegalovirus antibody" AND "blood donors" OR "volunteer blood donors".

Study selection and eligibility criteria

Studies were eligible if they met the following criteria: (1) peer-reviewed original articles in English; (2) cross-sectional and cohort studies reporting prevalence of CMV among blood donors; (3) publication between 1 January 2000 and 18 January 2021. Case reports, case-control studies, and editorial articles were excluded. Published articles reporting CMV seroconversion and incidence rates among blood donors were also excluded.

Data extraction

Two authors (TA and SG) screened references and retrieved articles according to the eligibility criteria. The selected papers were scrutinized and discrepancies between reviewers were resolved by discussion and consensus. Additionally, the reference lists of original and review articles were checked in detail to identify additional relevant studies that were not obtained via database searching. For all included studies, the following information was extracted: name of the first author, year of publication, country, study year, sample size, diagnostic methods used, mean age, and type of blood donor.

Study quality assessment

The Newcastle–Ottawa Scale (modified for prevalence studies) was used for methodological quality assessment.[28]

Meta-analysis

For every included study, point prevalence and 95% CI were calculated. A random-effects model was applied to assess the effects of heterogeneity among selected studies. I^2 values of 25%, 50%, and 75% were considered to reflect low, moderate, and high heterogeneity, respectively.[29] Forest plots were used to summarize the effect sizes and 95% CIs for all studies.

A subgroup analysis was conducted to identify potential sources of heterogeneity among included studies. Funnel plots and Egger's test were used to investigate potential publication bias.[30,31] All statistical analyses were performed using STATA version 11.0 (StataCorp, College Station, TX, USA).

Results

A total of 1420 articles were retrieved by literature searching. Among these articles, 310 were excluded after duplicate removal, 1036 were irrelevant to the aim of this study, and 18 did not meet the eligibility criteria. Forty-three studies were included in the meta-analysis (Figure 1).

Study characteristics

Twenty studies were conducted in Africa, 21 in Asia, and two in South America. The countries with the largest number of studies were Nigeria (10 studies) and Iraq (5 studies). Thirty-seven studies used enzyme linked immunosorbent assay (ELISA) to assess anti-CMV antibody titers (IgM and IgG), two studies used enzyme immunoassay, one study used a microparticle enzyme immunoassay, one study used latex particle agglutination, one study used chemiluminescence, and the one used a chromatographic immunoassay. The number of blood donors ranged from 75 in Sudan[32] to 2400 in Japan.[18] The mean age of donors ranged from 19 years to 45 years. Thirty-three studies examined volunteer blood donors, four studies examined healthy male donors, two studies examined blood bags, one study examined family replacement donors, one study examined volunteer blood donors and family replacement donors, one study examined medical staff and volunteer donors, and one study examined regular donors (Table 1).

CMV seroprevalence among blood donors

Thirty-eight articles estimated the prevalence of anti-CMV IgG among blood donors. Among these studies, the highest

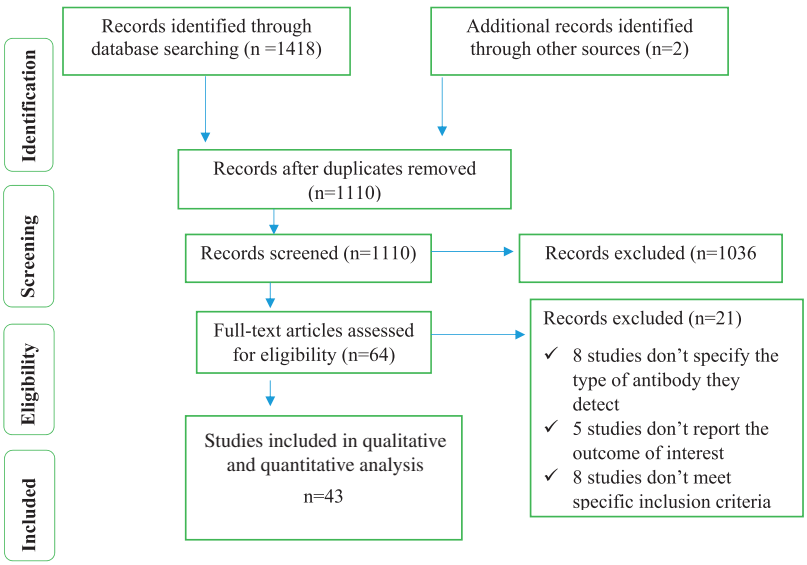

Figure 1. Flow chart of study selection for the systematic review and meta-analysis of the prevalence of anti-CMV antibodies among blood donors.

Table 1. Characteristics of included studies.

Author and year of Publication	Country	Study year	Study design	Sample size	Population	Method	Mean age (years)	IgG (%)	IgM (%)	IgM and IgG (%)	Study quality
Adjei et al. 2006[2]	Ghana	2004	NR	264	Volunteer donors	ELISA	32.1	93.2			Good
Jobier et al. 2018[4]	Sudan	2017	NR	90	Volunteer donors	ELISA	NA	85.5	42.22		Satisfactory
Akinbami et al. 2009[33]	Nigeria	2006	Cross-sectional	122	Volunteer donors	ELISA	31.3±8.7	96	19.5		Good
Bawa et al. 2019[1]	Nigeria	2013–2014	Cross-sectional	345	Volunteer donors	ELISA	NR	96.2	2.6	2.6	Very good
Bleiblo et al. 2019[34]	Libya	NR	NR	200	Volunteer donors	ELISA	NR	80.5	39		Good
Bolarinwa et al. 2014[35]	Nigeria	2013	Cross-sectional	184	Volunteer donors	ELISA	26.8 ± 6.5	97.4	52.6	52.6	Satisfactory
Oladipo et al. 2014[36]	Nigeria	2012	NR	93	Family replacement	ELISA	45±2.3	25.8	28		Satisfactory
Gawad et al. 2016[37]	Egypt	2010	Cross-sectional	88	Volunteer donors	ELISA	30.8 ± 8.6	96.6			Good
Gwarzo et al. 2017[38]	Nigeria	2012	Cross-sectional	250	Volunteer donors	ELISA	32.25±8.8		4.4		Very good
Ibrahim et al. 2014[32]	Sudan	2011	Cross-sectional	75	Donors and medical staff	ELISA	NR	97.3			Good
Ibrahim et al. 2015[39]	Sudan	2015	Cross-sectional	90	Volunteer donors	ELISA	26.7(18-50)	92.1	13.3	93.3	Good
Njeru et al. 2009[40]	Kenya	NR	Cross-sectional	400	Volunteer donors	ELISA	24.2	97	3.6		Very good
Ojide et al. 2011[41]	Nigeria	2010	NR	192	Volunteer donors	ELISA	32.39±7.9	95.8	3.1		Satisfactory
Samuel et al. 2017[42]	Nigeria	2014	Cross-sectional	93	Volunteer donors	ELISA	NR	93.5	45.2	40.9	Satisfactory
Pennap et al. 2016[43]	Nigeria	NR	NR	208	Volunteer donors	ELISA		74			Very good
Kafi et al. 2009[44]	Sudan	2003	NR	150	Volunteer donors	ELISA	NR	77			Satisfactory
Tebuka et al. 2019[45]	Tanzania	2017	Cross-sectional	228	Volunteer donors	ELISA	19		10.1		Very good
Teka et al. 2018[46]	Ethiopia	2016	Cross-sectional	605	Volunteer donors	ELISA	30.3± 8.37	94.4	4.0		Very good
Udomah et al. 2016[47]	Nigeria	NR	NR	290	Volunteer donors	Chromatography	39 ± 21	4.82	57.9	3.1	Satisfactory
Yusuf et al. 2018[48]	Nigeria	2017	Cross-sectional	185	Volunteer donors	ELISA	NR	92			satisfactory
Ahmed et al. 2016[49]	Iraq	2014	NR	370	Volunteer donors	ELISA	34.17± 7.1	95.1	3.8		Very good
Ahmed et al. 2006[50]	Malaysia	NR	NR	172	Regular blood donors	MEIA	29.3	97.6			Satisfactory
Al-sabri et al. 2017[51]	Yemen	NR	Cross-sectional	235	Volunteer donors	ELISA	29.1	96.6	5.5		Satisfactory
Amarapal et al. 2001[52]	Thailand	1998	NR	441	Volunteer donors	ELISA	NR	52.38	9.52	8.84	Satisfactory
Chaudhari et al. 2009[6]	India	NR	Cross-sectional	431	Volunteer donors	EIA	28.2±7.22	87.9			Very good
Dabbagh 2010[53]	Iraq	2007–2008	NR	90	Healthy male	ELISA	33.3±8.73		10		Satisfactory
Das et al. 2014[54]	India	2011–2012	Cross-sectional	2100	Volunteer and family replacement	ELISA	31.25	98.6	0.05		Good
Delfan-Beiranvand et al. 2012[55]	Iran	NR	Cross-sectional	270	Healthy male	ELISA	NR	55	0.4		Good
Furui et al. 2013[18]	Japan	NR	NR	2400	Volunteer donors	EIA	NR	76.6			Good
Henry et al. 2016[11]	India	NR	Cross-sectional	453	Volunteer donors	Chemiluminescence	30.55±9.2	94.9	0.44		Good

(continued)

Table 1. Continued.

Author and year of Publication	Country	Study year	Study design	Sample size	Population	Method	Mean age (years)	IgG (%)	IgM (%)	IgM and IgG (%)	Study quality
Kalid 2012[56]	Iraq	2011	Cross-sectional	100	Blood bag	ELISA	27.5±6.3	64	3		Satisfactory
Kothari et al. 2021[57]	India	NR	NR	200	Volunteer donors	ELISA	29.8 ±8.3	95			Satisfactory
Mahmood et al. 2014[58]	Pakistan	2007–2008	NR	175	Healthy male	ELISA	28.2	96.5	3.4		Good
Marzoog 2009[59]	Iraq	2008–2009	NA	214	Blood bag	ELISA	NR		7.5		Satisfactory
Moniri et al. 2004[60]	Iran	2001–2002	Descriptive	600	Volunteer donor	ELISA	NR		2.3		Good
Nanakaly et al. 2019[61]	Iraq	NR	Prospective	472	Volunteer donors	ELISA	32.58± 6.9	31.36	1.48		Good
Rizvi et al. 2015[62]	Pakistan	2013	Cross-sectional	91	Volunteer donors	ELISA	25.87±6.8	97.8			Satisfactory
Safabakhsh et al. 2014[63]	Iran	2009	Cross-sectional	1008	Volunteer donors	ELISA	NR	99.2	1.6		Good
Shaheen et al. 2020[64]	Bangladesh	2017	Cross-sectional	150	Volunteer donors	LPA	NR	91.3	4		Satisfactory
Yasir et al. 2008[65]	Iraq	2008	NR	120	Male donors	ELISA	NR	46.6			Satisfactory
Ziaei et al. 2013[66]	Iran	2010	Cross-sectional	200	Volunteer donors	ELISA	NR	98.5	85		Satisfactory
Mathos et al. 2009[67]	Brazil	NR	NR	636	Volunteer donors	ELISA	31.3	87.9	0		Very good
Souza et al. 2010[68]	Brazil	2003	Cross-sectional	1045	Volunteer donors	ELISA	NR	96.4			Very good

NR, not reported; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; MEIA, microparticle enzyme immunoassay; LPA, latex particle agglutination.

prevalence of anti-CMV IgG antibodies was 99.2% among 1008 blood donors from Iran in 2009.[63] The lowest prevalence of anti-CMV IgG antibodies was 4.82% among 290 blood donors in Nigeria.[47] The estimated global pooled prevalence of anti-CMV IgG among blood donors was 83.16% (95% CI: 78.55%–87.77%, $I^2 = 99.5\%$) (Figure 2).

Twenty-eight articles estimated the prevalence of anti-CMV IgM among blood donors. The global pooled prevalence of anti-CMV IgM among blood donors using a random effects model was 13.77% (95% CI: 11.59%–15.95%, $I^2 = 98.8\%$). The highest prevalence of anti-CMV IgM was 85% among healthy blood donors in Iran (Figure 3) (Figure 4).[66]

Four studies estimated the prevalence of both anti-CMV IgG and IgM among blood donors. The global pooled prevalence of both CMV IgM and IgG among blood donors using a random effects model was 23.78% (95% CI: 10.50%–37.06%, $I^2 = 98.7\%$) (Figure 5).

Subgroup analysis by region and method of detection

The pooled prevalence of anti-CMV IgG in Africa, Asia, and South America was 82.64% (95% CI 67.47%–97.81%), 82.75% (95% CI 78.20%–87.30%), and 99.23% (95% CI 83.90%–100.56%), respectively. The pooled prevalence of anti-CMV IgM in Africa, Asia, and South America was 22.52% (95% CI 15.89%–29.16%), 8.06% (95% CI 5.70%–10.43%), and 59.00% (95% CI 52.54%–65.48%), respectively. The pooled prevalence of anti-CMV IgG and IgM CMV measured by ELISA was higher compared with other methods of detection (Table 2).

Publication bias

Potential publication bias among the included studies were assessed statistically

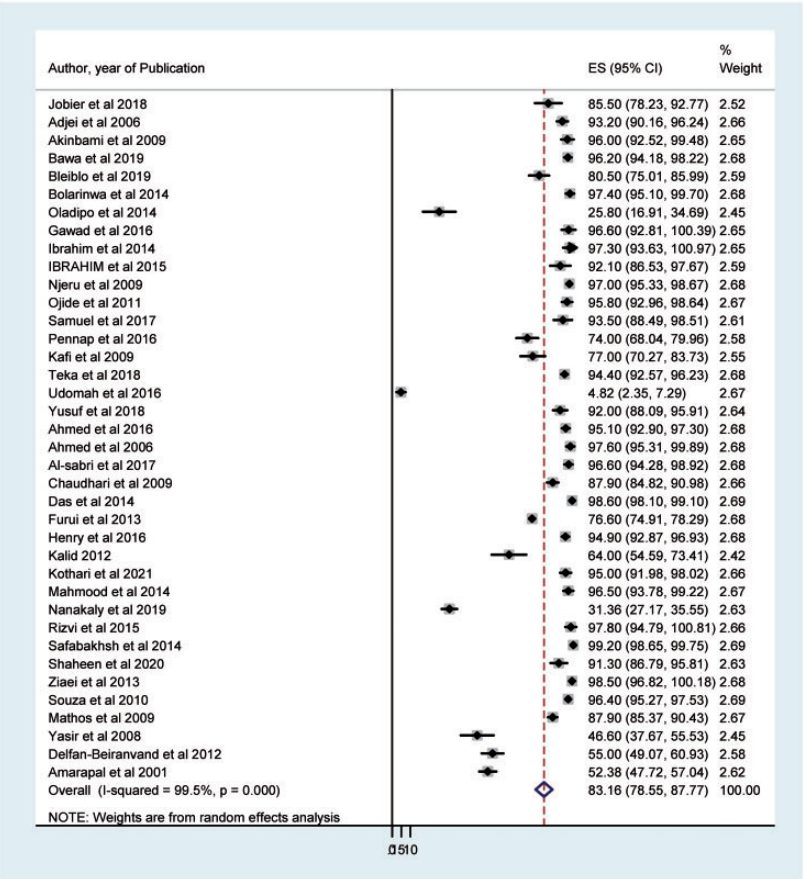

Figure 2. Forest plot of the prevalence of anti-CMV IgG among blood donors.

and graphically using Egger's test and funnel plots, respectively. Funnel plots of the prevalence of both anti-CMV IgG (Figure 6) and IgM (Figure 7) were non-symmetrical, suggesting the presence of publication bias. Egger's test also indicated publication bias in both anti-CMV IgG ($P < 0.001$) and IgM ($P < 0.001$).

Discussion

The presence of anti-CMV antibodies (IgM and IgG) among blood donors is a sign of potentially infectious virus in transfused blood products.[49] According to this systematic review and meta-analysis, the global prevalence of anti-CMV IgG and IgM among blood donors was 83.16% (95% CI: 78.55%–87.77%, $I^2 = 99.5\%$) and 13.77% (11.59%–15.95%, $I^2 = 98.8\%$), respectively. The global prevalence of both anti-CMV IgM and IgG among blood donors was 23.78% (95% CI: 10.50%–37.06%, $I^2 = 98.7\%$). The high prevalence of anti-CMV IgG identified in this meta-analysis reflects the fact that CMV infection is endemic in different parts of the world.[51] However, the pooled prevalence estimated in the current study was lower than another worldwide estimate

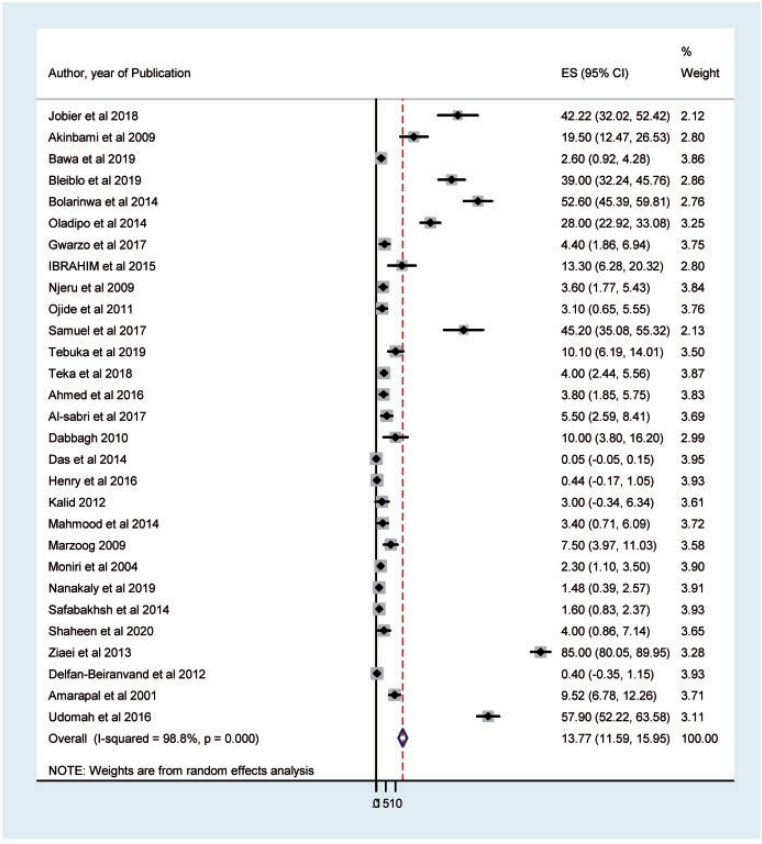

Figure 3. Forest plot of the prevalence of anti-CMV IgM among blood donors.

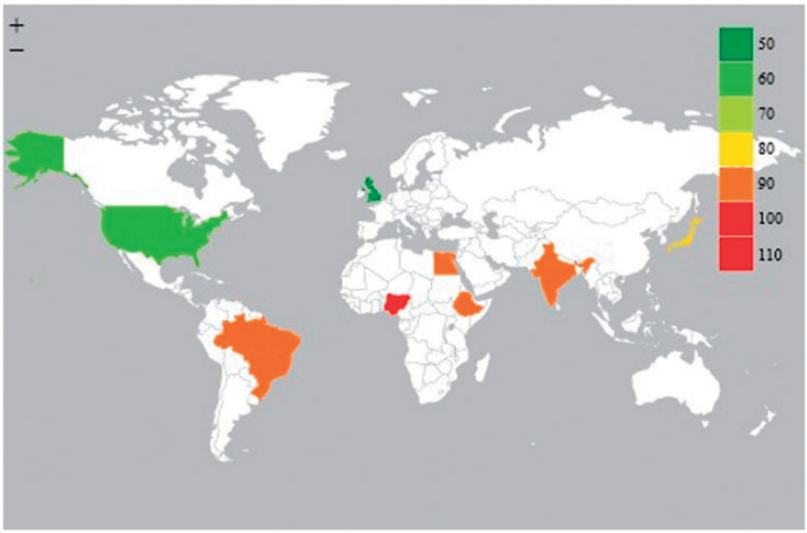

Figure 4. Estimated global CMV seroprevalence among blood donors.

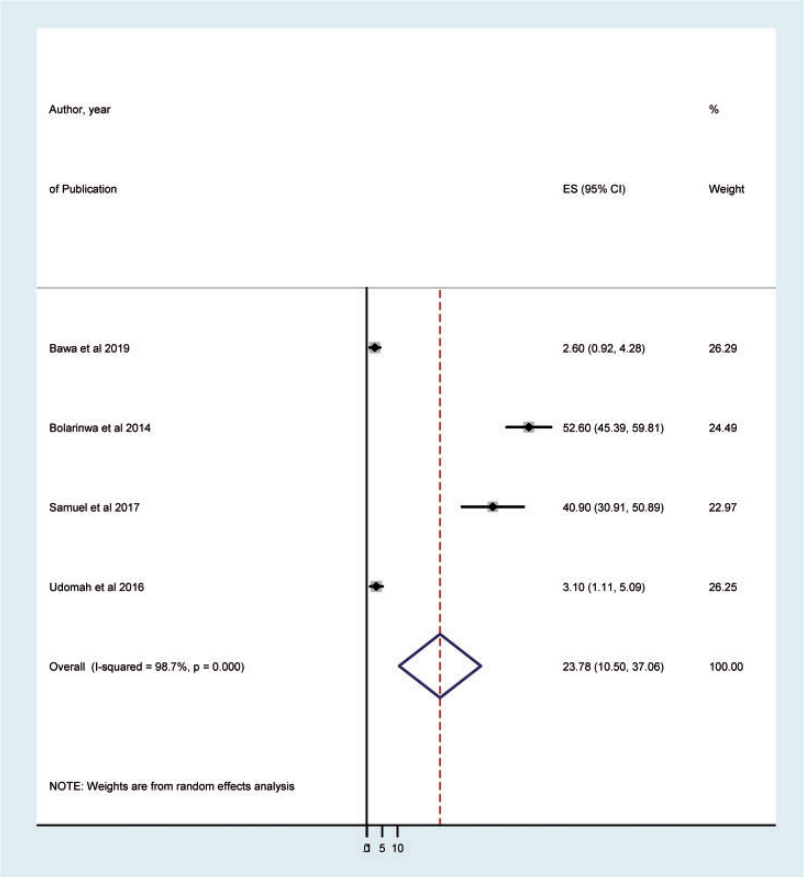

Figure 5. Forest plot of the prevalence of anti-CMV IgM and IgG among blood donors.

of among blood and organ donors (86% seroprevalence).[69] The prevalence of anti-CMV IgG among blood donors varies according to local infection rates in the general population as well as the socioeconomic characteristics of the blood donors.[70] The high seroprevalence of IgG indicates frequent past exposure to CMV. Low socioeconomic status is associated with increased exposure to CMV because of factors such as large household size, crowding, child care practices, and sexual practices.[51] We found that 14.8% of blood donors were positive for anti-CMV IgM, indicating the presence of recent acute CMV infection.[71] This type of infection could be either primary or recurrent.[52] Because of the sensitivity of detection assays, IgM may be detectable both prior to the appearance of IgG and shortly after IgG seroconversion, and remains positive for several months.[72,73]

In this study, the prevalence of anti-CMV IgG in Africa, Asia, and South America was 82.64% (95% CI: 67.47%–97.81%), 82.75% (95% CI: 78.20%–87.30%), and 99.23% (95% CI: 83.90%–100.56%), respectively. The prevalence of anti-CMV IgM was 22.52% (95% CI: 15.89%–29.16%), 8.06% (95% CI: 5.70%–10.43%), and 59.00% (95% CI: 52.54%–65.48%) in Africa, Asia, and South America, respectively. CMV

Table 2. Prevalence of anti-CMV antibodies among blood donors.

Characteristic	No. of studies	Sample size	Prevalence (95% CI)	I^2 (%)	P-value
CMV IgG					
Region					
Africa	18	3881	82.64% (67.47–97.81%)	99.8	<0.001
Asia	18	9388	82.75% (78.20–87.30%)	99.3	<0.001
America	2	1681	99.23% (83.90–100.56%)	97.2	<0.001
Global	38	14743	83.16% (78.55–87.77%)	99.5	<0.001
Method of anti-CMV antibody detection					
ELISA	32	10847	85.34% (82.44–88.24%)	98.6	<0.001
Others	6	3896	75.51% (47.87–103.15%)	99.9	<0.001
CMV IgM					
Region					
Africa	14	3389	22.52% (15.89–29.16%)	98.4	<0.001
Asia	15	6878	8.06% (5.70–10.43%)	98.9	<0.001
Global	29	10267	13.77% (11.59–15.95%)	98.8	<0.001
Method of anti-CMV antibody detection					
ELISA	26	9419	13.41% (10.97–15.85%)	98.7	<0.001
Others	2	558	1.87% (−1.55–5.30%)	79.0	0.029

CMV, cytomegalovirus; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay.

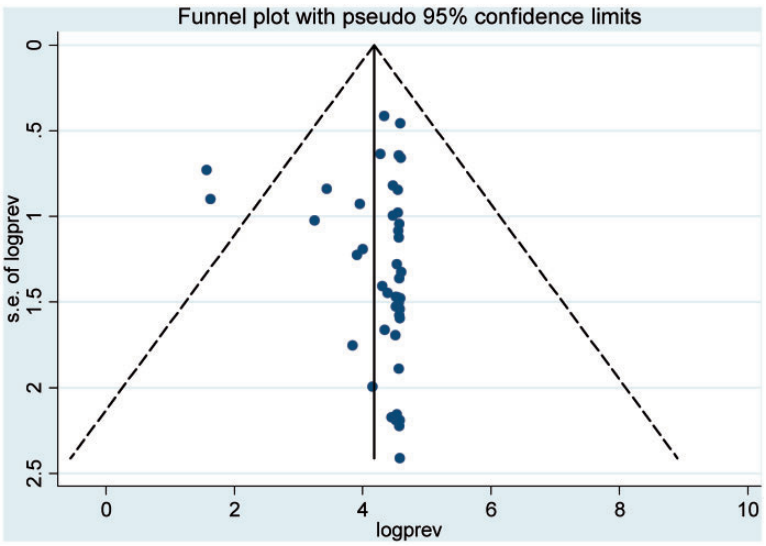

Figure 6. Funnel plot of the prevalence of anti-CMV IgG among blood donors in the included studies.

seroprevalence varies geographically across the world.[49] A systematic review and meta-analysis conducted in Iran by Shaiegan et al.[10] showed that the prevalence of anti-CMV IgG and IgM was 92% (95% CI: 90%–94%) and 2.6% (95% CI: 1.7%–3.6%), respectively. Another single center study conducted in Nigeria by Gwarzo et al.[38]

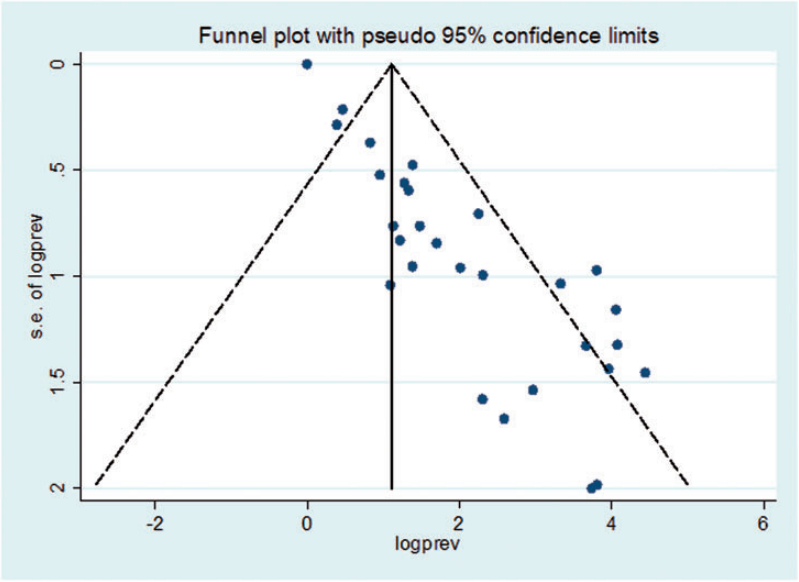

Figure 7. Funnel plot of the prevalence of anti-CMV IgM among blood donors in the included studies.

showed that the prevalence of anti-CMV IgG was 100% among blood donors.

The prevalence of anti-CMV IgG among blood donors observed using ELISA and rapid kits was 85.34% (95% CI: 82.44%–88.24%) and 75.51% (95% CI: 47.87%–103.15%), respectively. The prevalence of anti-CMV IgM among blood donors observed using ELISA and rapid kits was 13.41% (95% CI: 10.97%–15.85%) and 1.87% (95% CI: −1.55% to 5.30%), respectively. We found that the prevalence of anti-CMV IgG and IgM among blood donors was higher using ELISA compared with rapid kits. This might be because rapid screening kits are associated with more false negative results compared with ELISA.[74] Moreover, a study conducted by Chameera et al.[75] showed that rapid kits had lower sensitivity and negative predictive values compared with ELISA.

LR of cellular blood products and/or selection of CMV-seronegative donors are measures used to reduce the risk of TT-CMV. The risk of TT-CMV is closely associated with transfer of leukocytes from infected donors to the recipient.[76] However, because of the window period between CMV infection and seroconversion, apparently seronegative donors with transient viremia may be able to transfer CMV.[77] CMV-seropositive blood donors are CMV carriers and latently infected cells may be present in their blood that can be reactivated after transfusion and thus may be infectious.[76] Blood donations from newly CMV IgG-positive donors should have the highest risks of TT-CMV because they contain the highest levels of CMV DNA and early anti-CMV antibodies cannot neutralize the virus.[70] However, because of the high rate of CMV seropositivity in different parts of the world and the need for screening of large numbers of blood donations, use of exclusively CMV-seronegative blood is not practical.[78] Use of pathogen-inactivated blood products is another strategy to reduce the risk of TT-CMV and many other infections.[5]

The findings of this systematic review and meta-analysis should be considered in the context of some important limitations. Heterogeneity was observed in all analyses, including subgroup analyses. High heterogeneity may have arisen from inclusion of studies only in the English language. We also did not explore potential risk factors associated with presence of anti-CMV IgG and IgM among blood donors because this information was not available in most of the included studies.

Conclusion and recommendations

This study revealed that CMV seroprevalence was high among blood donors globally. CMV seropositivity among blood donors is a challenge for safe blood transfusion and can lead to high mortality and morbidity in high-risk transfusion recipients. Therefore, routine CMV screening should be performed to identify CMV-seronegative blood donors.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Author contributions

TA and SG were involved in the literature search, statistical analysis, study quality assessment, and manuscript drafting, review, and final approval. Both authors critically revised the paper and agree to be accountable for all aspects of the work.

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