BLOOD DONATION AND DONOR INFECTIOUS DISEASE TESTING

Review

Prevalence of Chikungunya, Dengue and Zika viruses in blood donors: a systematic literature review and meta-analysis

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Background - Blood transfusion centres should understand the epidemiology of emerging diseases that are transmissible through the transfusion of blood components. The risk of transmission of arboviruses through this route has become apparent in recent years. The aim of our study is to summarise the reported prevalence (viraemic rate, seroprevalence and/or antigen detection) of Chikungunya (CHIKV), Dengue (DENV) and Zika (ZIKV) viruses in blood donors according to screening test used and world region.

Materials and methods - We conducted a systematic literature review and meta-analysis having searched for information in the main bibliographic databases (MEDLINE, Embase, and Scopus). The prevalence for each of the viruses was calculated according to the screening test used and geographic location.

Results - We included 18 records on CHIKV, 71 on DENV, and 27 on ZIKV. The highest prevalences of RNA for CHIKV were 1.9% in Puerto Rico (2014), 1.0% in Thailand (2009), and 1.0% in French Polynesia (2014-15). The highest prevalences of RNA for DENV were 5.5% in Saudi Arabia (2015-16), 2.3% in Madeira, Portugal (2012-13), and 0.6% in Brazil (2012). The highest prevalences of RNA for ZIKV were 2.8% in French Polynesia (2013-14), 2.7% in Brazil (2015-16), and 1.8% in Martinique (2016). Overall seroprevalence, as assessed by IgG antibodies, was 21.6% for CHIKV, 24.0% for DENV, and 5.1% for ZIKV.

Discussion - Our study shows a high proportion of donors who are viraemic and asymptomatic, especially during outbreaks, with prevalences surpassing 5% for DENV, 1% for CHIKV, and 2% for ZIKV. These data confirm a clear threat to blood transfusion safety. The elevated seroprevalence for these three arboviruses is also indicative of their wide circulation in populations, correlating with an increased risk of infected but asymptomatic donors. Health centres and institutions must address this threat, especially in tropical regions where the biggest outbreaks occur.

Keywords: *Chikungunya virus, Dengue virus, Zika virus, blood transfusion, blood safety.*

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INTRODUCTION

Emerging and re-emerging viruses have materialised as the latest challenge to blood transfusion safety. In this sense, the World Health Organisation (WHO) has called for blood

transfusion centres to be informed of the epidemiology of different emerging transfusion-transmitted infections and to evaluate the possible impact on donor selection criteria and the supply of blood products[1].

Among these emerging viruses, arboviruses are especially relevant because of their known or theoretical potential for transmission through blood transfusions[2]. Within this group, Chikungunya virus (CHIKV), Dengue virus (DENV), and Zika virus (ZIKV) stand out for their high global incidence and the wide dissemination of their vector.

CHIKV is an alphavirus in the *Togaviridae* family, transmitted by *Aedes* mosquitoes (e.g. *A. albopictus*, *A. aegypti*). Following an incubation period of 1 to 12 days, the acute phase of infection by this virus is characterised by fever; severe, incapacitating arthralgia; and other non-specific symptoms. Some patients also develop chronic illness[3]. Since the virus was first isolated, periodic outbreaks have been reported in Africa, Asia, and islands in the Indian Ocean, while the first cases in the Americas were reported in 2013. Since then, different outbreaks have been reported across regions of South and Central America[4]. In Europe, several outbreaks have occurred since 2007[5], including one in 2015 involving 693,489 suspected and 37,480 confirmed cases[6]. Although no cases of transfusion-related infections have been notified, organisations such as the American Association of Blood Banks have sounded the alarm on the theoretical potential given the high percentage of asymptomatic people infected (3% to 28%) and the high rates of viraemia that they have[7]. One case of iatrogenic CHIKV transmission was reported following an accidental needle puncture in France[8].

For its part, DENV is a flavivirus in the *Flaviviridae* family. Four distinct serotypes have been documented: DEN-1, DEN-2, DEN-3, and DEN-4. Like CHIKV, DENV is transmitted by *Aedes* mosquitoes, usually *A. aegypti*. It is the main arbovirus worldwide in terms of mortality and morbidity; its incubation period is normally 4 to 7 days, although it can range from 3 to 10 days. The clinical classification of dengue divides cases into those with or without warning signs and severe dengue (including dengue shock syndrome)[9]. The first large epidemics date back to the 1870s[10]. Today, the disease is endemic in more than 100 countries from the WHO regions of Africa, the Americas, the Eastern Mediterranean, Southeast Asia, and the Western Pacific; in 2015 alone, more than 3.2 million cases were notified across the Americas, Southeast Asia, and the Western Pacific[11]. In Europe, 11 cases of local transmission were also reported in 2019[12]. Since 2002, numerous cases of transfusion-transmitted infections have been described in Hong Kong, Singapore, Brazil, Pakistan, and Puerto Rico (USA)[13-17].

ZIKV is another flavivirus from the *Flaviridae* family. *Aedes* spp. mosquitoes such as *A. africanus*, *A. aegypti*, and *A. albopictus* are the vectors of transmission, and the incubation period can be anywhere from 2 to 12 days. Although 80% of infected people remain asymptomatic, an acute presentation with non-specific symptoms, such as fever, arthralgia, and exanthema, can occur. Infection has also been related to the appearance of microcephalia in neonates (congenital Zika syndrome) and to a Guillain-Barré-type neurological presentation[18]. For decades, little attention was paid to this virus, as it only provoked isolated cases in Southeast Asia and Africa. However, in 2007, a large epidemic outbreak was registered on Yap Island (Micronesia), and in 2015 and 2016, another large outbreak occurred in the Americas. In 2019, the first two cases of local transmission were reported in Europe (France)[19]. Moreover, transmission via transfusion of platelets has been reported in Brazil[20,21].

Upon performing a review of the available scientific literature on the prevalence of CHIKV, DENV, and ZIKV in blood donors, we identified only two systematic reviews: one by Liu *et al.*, with very restrictive inclusion criteria and ten included studies on ZIKV, and one by Eick *et al.*, with three included studies on the prevalence of ZIKV and 11 on the prevalence of DENV[22,23]. We did not identify any similar papers on CHIKV. There is, therefore, a lack of literature giving a broad overview of the prevalence of these three arboviruses in blood donors.

The emergence of these viruses represents a real threat to obtaining blood components and has a direct impact on donor selection criteria and the stock of components. Following WHO recommendations, the aim of this study was to summarise the reported and published prevalence of CHIKV, DENV and ZIKV in blood donors according to the screening test used (viraemic rate, seroprevalence or antigen detection) and world region (geographical region and country).

We define the research question in a PICOS (population,

intervention, comparison, outcome, study) format. The population was blood donors, including conventional whole blood donors and those donating via apheresis, who were screened for the target viruses using any test and in any defined geographic region. The intervention was screening using different techniques to detect antibodies, antigens, or nucleic acids. Comparisons were not applicable to this question and the outcomes were reported and published prevalences of each virus according to the screening test used and the geographic region in which the screening was performed. Any primary studies were included.

MATERIALS AND METHODS

Design

A systematic literature review and meta-analysis were designed and conducted in accordance with the *Cochrane Handbook of Systematic Reviews of Interventions* and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see *Online Supplementary Content*, **Table SI**). Although no published protocol is available, we collected and analysed data according to pre-specified outcomes and methods, performing meta-analyses, pooling the data obtained in the different studies, and establishing a single prevalence estimate for each virus. This information may be of interest from an epidemiological point of view and when considering measures with a possible impact on transfusion safety.

Sources of data

We conducted literature searches in MEDLINE, Embase, and Scopus using the University Miguel Hernández server.

Search strategy

We performed free text searches in the three bibliographic databases using the terms: "transfusion" AND "Dengue", "transfusion" AND "Chikungunya", "transfusion" AND "Zika", "blood donation" AND "Dengue", "blood donation" AND "Chikungunya", "blood donation" AND "Zika".

In MEDLINE, we also used Medical Subject Headings (MeSH): "blood transfusion" AND "Zika virus", "blood donors" AND "Zika virus", "blood transfusion" AND "Dengue", "blood donors" AND "Dengue", "blood transfusion" AND "Chikungunya virus", "blood donors" AND "Chikungunya virus".

Finally, in the Embase searches we used the Emtree thesaurus with the terms: "blood transfusion" AND"Zika virus", "blood donor" AND "Zika virus", "blood transfusion" AND "Chikungunya", "blood donor" AND "Chikungunya", "blood transfusion" AND "Dengue", "blood donor" AND "Dengue".

The records were entered into the Mendeley Desktop reference manager (Elsevier). The search was performed from the year of database inception to March 28, 2020. A weekly alert system was set up to update the search with any relevant results until August 7, 2020.

Study selection

First, we used the bibliographic reference manager to create folders containing records for each virus, eliminating duplicates. We then conducted an initial screening of titles and abstracts and retrieved the full text of all pre-selected records.

Eligible studies were publications in any language describing the prevalence of the virus in blood donor screening (both donors of conventional whole blood and those donating via different methods of apheresis). We included all studies (original articles, brief reports, letters to the editor, and conference papers) reporting the number of positive results as a proportion of total samples analysed, as long as the paper stated the type of test used for screening (serological tests, antigen tests or nucleic acid amplification tests [NAT]) and the geographic location of the study population. We excluded studies that involved people other than blood donors, such as patients, children, pregnant women, the general non-donor population, and other non-donor or unspecified populations.

A single review author selected all included articles, obviating the need for an analysis of interobserver concordance. We did perform an intraobserver concordance analysis, including in the review all records that were deemed to meet inclusion and exclusion criteria during two critical assessments of the full texts.

When a single record reported results for two different study populations, these were separated in the analysis if the participants' characteristics differed for important variables, for example geographic region (e.g. studies evaluating one population in Africa and another in Europe), or if the prevalence was substantially different by population (i.e. we separated populations sub-nationally if the differences in prevalence were relevant). If a single

population underwent screening using more than one type of test, separate analyses were performed for each. In the case of records with overlapping study populations, we selected the most relevant publication (i.e. with the largest number of screened donors).

Data extraction and analysis

A single review author extracted data on prevalence and populations from the studies included, directly entering the data into Comprehensive Meta-Analysis (CMA) software. A second review author double-checked that all data were entered correctly. We recalculated the prevalence for the three viruses, pooling all positive cases and donors screened for each to calculate an overall proportion of positive results in the blood donor screening for CHIKV, DENV, and ZIKV, according to the type of screening test used. We then stratified the results by geographic location or country as long as there were at least three included studies, the minimum number we considered capable of representing a geographic area. Moreover, when the number of publications and the nature of the screening test allowed it, we calculated the prevalence ratio according to whether or not the study had taken place in an endemic region or during an epidemic outbreak. If so, we calculated the prevalence.

Results are expressed as prevalences with 95% confidence intervals and are presented with forest plots. We evaluated the heterogeneity of the studies for each screening test using the I^2 statistic. To calculate the confidence intervals, create the forest plots, and analyse the heterogeneity, we used CMA software, version 2 (Borenstein, Hedges, Higgins, & Rothstein, 2005).

Quality assessment

To evaluate the methodological quality of included records, we used the STROBE (STrengthening the Reporting of Observational studies in Epidemiology) checklists for cross-sectional studies and conference abstracts. No tools were applied to letters to the editor.

RESULTS

Figure 1 presents the PRISMA flow chart, describing the study selection process. Following full-text assessment, 18 studies on CHIKV[24-41], 71 on DENV[24,26,27,31,33,36,38,40,42-104], and 27 on ZIKV[26,28,32,36,38,40,67,105-124] were included. *Online Supplementary Content*, **Tables SII-SIV**, describes the main characteristics of the studies included.

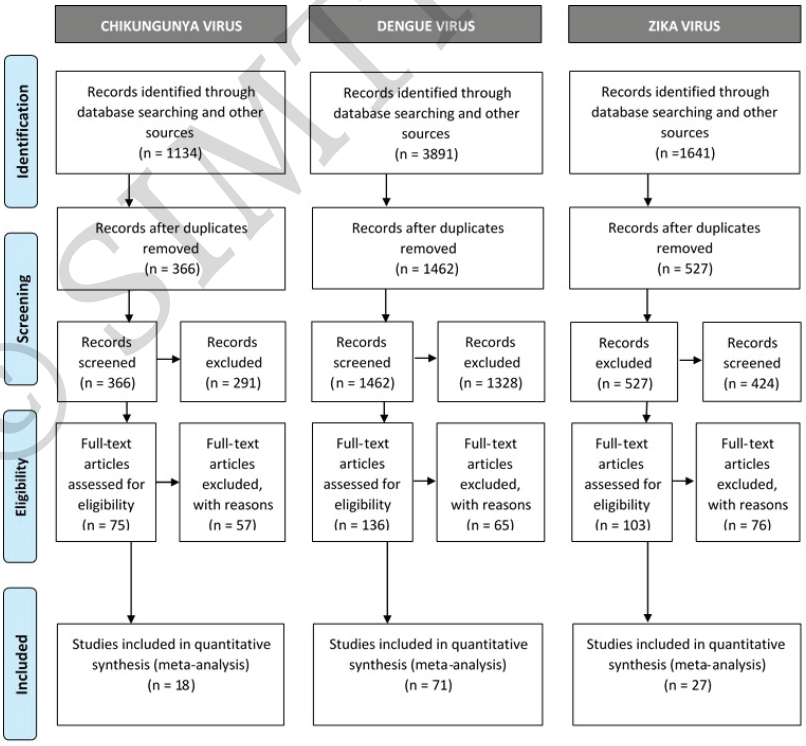

Figure 1 - PRISMA flow chart on selection of studies included for each virus covered by the literature review

Analysis of results

For each virus analysed, the prevalence varied according to the screening technique used, the geographic regions, and their characteristics.

Prevalence of Chikungunya virus

According to the assessment of IgG antibodies, the overall seroprevalence of CHIKV was 21.6% (95% CI: 20.6% to 22.5%). Several studies reported a seroprevalence of 0%, while one in Rwanda in 2015 found a seroprevalence of 63.0% (95% CI: 59.8% to 66.2%)[28]. By regions, the highest value was in Africa (seroprevalence 37.8%, 95% CI: 36.2% to 39.4%). The prevalence ratio between studies performed in an endemic area or during an outbreak and those in non-endemic regions was 24.4 (**Table I**).

The only study we identified on the seroprevalence of IgM antibodies against CHIKV in blood donors reported a seroprevalence of 5.5% (95% CI: 3.1% to 9.7%) (**Table I**).

Finally, NAT showed an overall prevalence of 0.5% (95% CI: 0.4% to 0.5%). The highest rates were in the screening in Puerto Rico in 2014 (prevalence 1.9%, 95% CI: 1.4% to 2.4%)[35]. In populations living in endemic areas or going through epidemic outbreaks, the prevalence was 0.6% (95% CI: 0.6% to 0.7%), compared to 0% in non-endemic regions (**Table I**).

Table I - *Global prevalence of Chikungunya virus in blood donors, by population*

Study ID	Population	Screening test	Positive/ Total	Prevalence	95% CI		Forest plot	Relative weight %
IgG antibodies							0.00 0.50 1.00	
Sayama 2013	Laos 2012	ELISA (Not specified)	1/199	0.005	<0.001	0.035		0.1
Humphrey 2019	Egypt 2013-16	ELISA (Euroimmun)	11/199	0.055	0.031	0.097		1.2
Humphrey 2019	India 2013-16	ELISA (Euroimmun)	22/200	0.110	0.074	0.161		2.3
Humphrey 2019	Iran 2013-16	ELISA (Euroimmun)	0/113	0.000	<0.001	0.066		0.1
Humphrey 2019	Jordan 2013-16	ELISA (Euroimmun)	1/199	0.005	<0.001	0.035		0.1
Humphrey 2019	Lebanon 2013-16	ELISA (Euroimmun)	1/116	0.009	0.001	0.059		0.1
Humphrey 2019	Pakistan 2013-16	ELISA (Euroimmun)	3/200	0.015	0.005	0.046		0.4
Humphrey 2019	Palestine 2013-16	ELISA (Euroimmun)	6/200	0.030	0.014	0.065		0.7
Humphrey 2019	Philippines 2013-16	ELISA (Euroimmun)	21/199	0.177	0.118	0.256		2.0
Humphrey 2019	Qatar 2013-16	ELISA (Euroimmun)	7/200	0.035	0.017	0.072		0.8
Humphrey 2019	Sudan 2013-16	ELISA (Euroimmun)	5/97	0.052	0.020	0.120		0.6
Humphrey 2019	Syria 2013-16	ELISA (Euroimmun)	1/200	0.005	<0.001	0.035		0.1
Humphrey 2019	Yemen 2013-16	ELISA (Euroimmun)	4/149	0.027	0.010	0.069		0.5
Seruyange 2019	Rwanda 2015	ELISA (In house)	551/874	0.630	0.598	0.662		24.1
Seruyange 2019	Sweden 2015	ELISA (In house)	17215	0.079	0.050	0.124		1.9
Moyen 2014	Congo 2011	ELISA (Not specified)	178/517	0.344	0.305	0.386		13.8
Clements 2019	Uganda 2006-07	ELISA (In house)	552/1744	0.317	0.295	0.339		44.6
Slavov 2018	Brazil 2015	ELISA (Abcam)	1/442	0.002	<0.001	0.016		0.1
Slavov 2018	Brazil 2016	ELISA (Abcam)	0/445	0.000	<0.001	0.017		0.1
Saba Villarroel 2018	Bolivia B. and S.C.* 2016-17	ELISA (Euroimmun)	87/168	0.518	0.443	0.592		5.0
Saba Villarroel 2018	Bolivia, others 2016-17	ELISA (Euroimmun)	15/281	0.053	0.032	0.087		1.7
Total			1484/6887	0.216	0.206	0.225		
Southeast Asia			44/518	0.085	0.064	0.112		
West Asia			23/1377	0.017	0.011	0.025		
Africa			1297/3431	0.378	0.362	0.394		
America			103/1346	0.077	0.064	0.092		
Endemic or epidemic area			1426/3454	0.413	0.397	0.429		
Non-endemic or epidemic area			58/3433	0.017	0.013	0.022		
Heterogeneity I^2 97.70								
IgM antibodies							0.00 0.05 0.10	
Sayama 2013	Laos 2012	ELISA (Not specified)	11/199	0.055	0.031	0.097		
NAT							0.00 0.05 0.10	
Sayama 2013	Laos 2012	Not specified	0/199	0.000	0.000	0.039		0.2
Appassakij 2014	Thailand 2009	In house	20/2000	0.010	0.007	0.015		5.8
Beau 2020	French Polynesia 2014-15	Altona D.	34/3433	0.010	0.007	0.014		9.9
Brouard 2008	Reunion Island 2005-07	Not specified	2/500	0.004	0.001	0.016		0.6
Benites 2019	Brazil 2015-16	Bio-Manguinhos	0/3737	0.000	0.000	0.002		0.2
Stramer 2019	USA 2011-12	Cobas test	0/10528	0.000	0.000	<0.001		0.2
Chiu 2015	Puerto Rico 2014	In house	3/557	0.005	0.002	0.017		0.9
Simmons 2016	Puerto Rico 2014	In house	161/26688	0.006	0.005	0.007		46.8
Simmons 2016	Puerto Rico 2014	In house	56/3007	0.017	0.014	0.024		16.1
Saá 2019	Puerto Rico 2015-16	Not specified	0/1186	0.000	0.000	0.007		0.2
Slavov 2018	Brazil 2015-16	Not specified	0/897	0.000	0.000	0.009		0.2
Sharma 2018	Brazil 2016	In house	0/676	0.000	0.000	0.012		0.2
Gallian 2017	Guadaloupe 2014-15	Altona D.	22/6189	0.004	0.002	0.005		6.4
Gallian 2017	Martinique 2014-15	Altona D.	43/10197	0.004	0.003	0.006		12.5
Sargento 2017	Portugal 2017	In house	0/110	0.000	0.000	0.068		0.2
Total			341/69904	0.005	0.004	0.005		
Americas			285/63662	0.005	0.004	0.005		
Puerto Rico			220/31438	0.007	0.006	0.008		
Brazil			0/5310	0.000	0.000	0.000		
Endemic or epidemic areas			341/54433	0.006	0.006	0.007		
Non-endemic or non-epidemic areas			0/15471	0.000	0.000	<0.001		
Heterogeneity I^2 88.03								

*Beni and Santa Cruz regions

CI: confidence interval; NAT: nucleic acid test; ELISA: enzyme-linked immunosorbent assay

Prevalence of Dengue virus

Tests for IgG antibodies showed an overall seroprevalence of DENV of 24.0% (95% CI: 23.5% to 24.4%). Several studies reported a seroprevalence of more than 90% of screened individuals, for example in the Philippines, Puerto Rico, Brazil, Guadeloupe and Martinique, and the Dominican Republic[27,81,90,98,100]. By geographic region, the Americas stand out for the high seroprevalence of 61.3% (95% CI: 60.0% to 62.6%), followed by Africa at 22.0% (95% CI: 21.0% to 23.1%) and Southeast Asia at 20.4% (95% CI: 19.7% to 21.1%). Saudi Arabia and Brazil were the individual countries with the highest seroprevalence (36.0% and 32.5%, respectively). The prevalence ratio between endemic and non-endemic regions was 13.9 (**Table II**).

Table II - *Global prevalence of IgG antibodies against Dengue virus in blood donors, by population*

Study ID	Population	Screening test	Positive/ Total	Prevalence	95% CI		Forest plot 0.00 0.50 1.00	Relative weight %
Zeng 2018	China 2015	ELISA (Panbio)	34/819	0.042	0.030	0.058		0.9
Liao 2017	China 2014	ELISA (Panbio)	51/1500	0.034	0.026	0.045		1.3
Kwan 2017	China 2014	ELISA (Panbio)	86/3827	0.023	0.018	0.028		2.3
Gao 2017	China 2013-14	ELISA (Panbio)	7/1685	0.004	0.002	0.009		0.2
Ranjan 2016	India 2012	ELISA (Novatec)	116/200	0.580	0.511	0.647		1.3
Chhabra 2013	India	IC (J. Mitra & Co)	3/380	0.008	0.003	0.024		0.1
Jain 2019	India 2016	IC (R.L.)	55/369	0.149	0.116	0.189		1.3
Hossain 2003	Bangladesh 1966-1997	ELISA (Not specified)	1/184	0.005	0.001	0.038		<0.0
Sayama 2013	Laos 2012	ELISA (Not specified)	139/199	0.699	0.631	0.758		1.1
Harif 2014	Malaysia 2009-10	ELISA (Panbio)	151/360	0.419	0.370	0.471		2.4
Mohamad 2016	Malaysia 2015	ELISA (Not specified)	1/126	0.008	0.001	0.054		<0.0
Low 2015	Singapore 2009-10	ELISA (Panbio)	1885/3627	0.520	0.503	0.536		24.7
Humphrey 2019	Egypt 2013-16	ELISA (Novatec)	40/199	0.201	0.151	0.262		0.9
Humphrey 2019	India 2013-16	ELISA (Novatec)	125/200	0.625	0.556	0.689		1.3
Humphrey 2019	Iran 2013-16	ELISA (Novatec)	6/113	0.053	0.024	0.113		0.2
Humphrey 2019	Jordan 2013-16	ELISA (Novatec)	9/199	0.045	0.024	0.085		0.2
Humphrey 2019	Lebanon 2013-16	ELISA (Novatec)	6/116	0.052	0.023	0.110		0.2
Humphrey 2019	Pakistan 2013-16	ELISA (Novatec)	40/200	0.200	0.150	0.261		0.9
Humphrey 2019	Palestine 2013-16	ELISA (Novatec)	17/200	0.085	0.054	0.133		0.4
Humphrey 2019	Philippines 2013-16	ELISA (Novatec)	114/119	0.958	0.903	0.982		0.1
Humphrey 2019	Qatar 2013-16	ELISA (Novatec)	7/200	0.035	0.017	0.072		0.2
Humphrey 2019	Sudan 2013-16	ELISA (Novatec)	47/97	0.485	0.387	0.583		0.7
Humphrey 2019	Syria 2013-16	ELISA (Novatec)	26/200	0.130	0.090	0.184		0.6
Humphrey 2019	Yemen 2013-16	ELISA (Novatec)	36/149	0.242	0.180	0.317		0.8
Faddy 2013	Australia 2008-09	ELISA (Panbio)	323/3553	0.091	0.082	0.101		8.0
Faddy 2012	Australia 2008-09	ELISA (Panbio)	182/1799	0.101	0.088	0.116		4.5
Faddy 2015	Australia 2008-09	ELISA (Panbio)	31/457	0.068	0.048	0.095		0.8
Darcy 2001	Solomon Islands 1994-1995	ELISA (Panbio)	202/515	0.392	0.351	0.435		3.4
Aubry 2015	French Polynesia 2011-13	ELISA (Not specified)	476/593	0.803	0.769	0.833		2.6
Ergünay 2010	Turkey	ELISA (Euroimmun)	21/2435	0.009	0.006	0.013		0.6
Tezcan 2014	Turkey 2010-11	IC (S.D.)	153/920	0.166	0.144	0.192		3.5
Ashshi 2015	Saudi Arabia 2014	ELISA (Panbio)	7/100	0.070	0.034	0.140		0.2
Ashshi 2017	Saudi Arabia 2015-16	ELISA (Panbio)	355/910	0.390	0.359	0.422		5.9
Jamjoom 2016	Saudi Arabia	ELISA (Panbio)	68/184	0.370	0.303	0.442		1.2
Aghaie 2014	Iran 2012	ELISA (Panbio)	41/540	0.076	0.056	0.102		1.0
Larrieu 2014	Reunion Island 2008	ELISA (Not specified)	72/1825	0.040	0.031	0.049		1.9
Vairo 2014	Tanzania 2011	ELISA (Panbio)	253/500	0.506	0.462	0.550		3.4
Collemberg 2006	Burkina Faso 2003-04	ELISA (Panbio)	62/191	0.325	0.262	0.394		1.1
Sawadogo 2019	Burkina Faso 2016	ELISA (Panbio)	721/1007	0.716	0.687	0.743		5.6
Noden 2014	Namibia 2011-12	ELISA (Panbio)	25/312	0.080	0.055	0.116		0.6
Clements 2019	Uganda 2006-07	ELISA (In house)	72/1744	0.041	0.033	0.052		1.9
Mohammed 2012	Puerto Rico 2006	ELISA (Not specified)	275/300	0.917	0.880	0.943		0.6
Slavov 2019	Brazil 2015-16	ELISA (Euroimmun)	20/475	0.042	0.027	0.064		0.5
Busch 2016	Brazil 2012	ELISA (F.D.)	453/498	0.910	0.881	0.932		1.1
Ribas-Silva 2012	Brazil	IC (I-R. D.)	3/213	0.014	0.005	0.043		0.1
De Almeida 2018	Brazil 2017	IC (K.B.)	6/298	0.020	0.009	0.044		0.2
Saba Villarroel 2018	Bolivia B. and S.C.* 2016-17	ELISA (Euroimmun)	155/168	0.923	0.871	0.955		0.3
Saba Villarroel 2018	Bolivia others 2016-17	ELISA (Euroimmun)	68/281	0.242	0.196	0.296		1.4
Rodríguez 2009	Mexico 2006-07	ELISA (Panbio)	472/800	0.590	0.556	0.624		5.3
L'Azou 2015	Guadeloupe & Martinique 2011	ELISA (Panbio)	732/783	0.935	0.915	0.950		1.3
Arcuri 2012	Argentina 2010-11	ELISA (Bispot)	15/95	0.158	0.098	0.246		0.3
Arcuri 2012	Argentina 2010-11	ELISA (Bispot)	6/286	0.021	0.010	0.046		0.2
Yamashiro 2004	Dominican Republic 2002	ELISA (D.A./F.T.)	987/1008	0.979	0.968	0.986		0.6
Golubic 2012	Croatia 1997-2007	ELISA (Not specified)	0/600	0.000	0.000	0.013		<0.0
Total			9258/38658	0.240	0.235	0.244		
Southeast Asia			2768/13595	0,204	0.197	0.211		
China			178/7831	0.023	0.019	0.026		
India			299/1149	0.260	0.235	0.286		
Oceania			1214/6917	0.176	0.167	0.185		
Australia			536/5809	0.092	0.085	0.100		
West Asia			792/6466	0.123	0.115	0.131		
Saudi Arabia			430/1194	0.360	0.333	0.387		
Africa			1292/5875	0.220	0.210	0.231		
Americas			3192/5205	0.613	0.600	0.626		
Brazil			482/1484	0.325	0.301	0.349		
Endemic or epidemic area			8952/26203	0.342	0.336	0.347		
Non-endemic or non-epidemic area			306/12455	0.025	0.022	0.027		
Heterogeneity I² 99.39								

*Beni and Santa Cruz regions
CI: confidence interval; IC: immunochromatography;

Table III - *Global prevalence of IgM antibodies against Dengue virus in blood donors, by population*

Study ID	Population	Screening test	Positive/ Total	Prevalence	95% CI		Forest plot	Relative weight %
							0.00 0.10 0.20	
Zeng 2018	China 2015	ELISA (Panbio)	3/819	0.004	0.001	0.011		0.5
Chen 2015	China 2014	ELISA (Not specified)	71/3000	0.024	0.019	0.030		10.7
Gao 2017	China 2013-14	ELISA (Panbio)	1/685	0.004	0.007	0.008		0.9
Tsai 2018	Taiwan 2014	IC/ELISA (Not specified)	17/8000	0.002	0.001	0.003		2.6
Ranjan 2016	India 2012	ELISA (Novatec)	27/200	0.135	0.094	0.190		3.6
Chhabra 2013	India	IC (J. Mitra & Co)	2/380	0.005	0.001	0.021		0.3
Kulkarni 2018	India 2016-17	ELISA (Panbio)	31/520	0.060	0.042	0.084		4.5
Harif 2014	Malaysia 2009-10	ELISA (Panbio)	25/360	0.069	0.047	0.101		3.6
Mohamad 2016	Malaysia 2015	ELISA (Not specified)	0/126	0.000	0.000	0.060		0.1
Low 2015	Singapore 2009-10	ELISA (Panbio)	113/3995	0.028	0.024	0.034		16.9
Faddy 2013	Australia 2008-09	ELISA (Panbio)	24/10906	0.002	0.002	0.003		3.7
Faddy 2012	Australia 2008-09	ELISA (Panbio)	8/10024	<0.001	<0.001	0.002		1.2
Tezcan 2014	Turkey 2010-11	IC (Standar D.)	8/920	0.009	0.004	0.017		1.2
Ashshi 2015	Saudi Arabia 2014	ELISA (Panbio)	6/100	0.060	0.027	0.127		0.9
Ashshi 2017	Saudi Arabia 2015-16	ELISA (Panbio)	50/910	0.055	0.042	0.072		7.3
Slavov 2019	Brazil 2015-16	ELISA (Panbio)	32/475	0.067	0.048	0.094		4.6
Busch 2016	Brazil 2012	ELISA (Focus D.)	44/498	0.088	0.066	0.117		6.2
Ribas-Silva 2012	Brazil	IC (I-R. D.)	0/213	0.000	0.000	0.036		0.1
De Almeida 2018	Brazil 2017	IC (Katal B.)	5/298	0.017	0.007	0.040		0.8
De Carvalho 2010	Brazil 2008	ELISA (Panbio)	137/3000	0.046	0.039	0.054		20.1
Arellanos-Soto 2015	Mexico 2010-12	ELISA (Panbio)	53/2061	0.026	0.020	0.034		7.9
Rodríguez 2009	Mexico 2006-07	ELISA (Panbio)	16/800	0.020	0.012	0.032		2.4
Arcuri 2012	Argentina 2010-11	ELISA (Bispot)	0/286	0.000	0.000	0.027		0.1
Arcuri 2012	Argentina 2010-11	ELISA (Bispot)	0/95	0.000	0.000	0.078		0.1
Total			**678/49671**	**0.014**	**0.013**	**0.015**		
Southeast Asia			295/19085	0.016	0.014	0.017		
China			75/4504	0.017	0.013	0.020		
India			60/1100	0.055	0.041	0.068		
West Asia			64/1930	0.033	0.026	0.042		
Americas			287/7726	0.037	0.033	0.042		
Brazil			218/4484	0.049	0.042	0.055		
Heterogeneity I^2 96.67								

CI: confidence interval; IC: immunochromatography; ELISA: enzyme-linked immunosorbent assay

Tests for IgM antibodies against DENV show a seroprevalence of 1.4% (95% CI: 1.3% to 1.5%), with individual studies reporting values ranging from 0% to 13.5% (95% CI: 1.3% to 1.5%); this top value was reported in greater Delhi (India) in 2012[50]. By geographic region, the highest percentage of positive results was in the Americas, with a seroprevalence of 3.7% (95% CI: 3.3% to 4.2%). By country, the highest seroprevalence was reported in China, at 5.5% (95% CI: 4.1% to 6.8%). Most studies took place in regions where DENV is endemic and/or had epidemic outbreaks at the time (**Table III**).

The NAT showed an overall DENV viraemic rate of 0.2% (95% CI: 0.2% to 0.2%), with the highest results coming from Saudi Arabia in 2015 to 2016 (prevalence 5.5%, 95% CI: 4.2% to 7.2%)[71]. In the Americas, the prevalence was 0.2% (95% CI: 0.2% to 0.2%). The only three studies undertaken in non-endemic regions found a prevalence of 0.0% (**Table IV**). The highest prevalence was in Brazil, at 0.3% (95% CI: 0.3% to 0.3%).

Finally, several studies tested donors for the dengue NS1 antigen, which showed an overall prevalence of 0.2% (95% CI: 0.1% to 0.2%), with results in individual studies ranging from 0% to 5.3% (95% CI: 4.0% to 6.9%). These latter results came from Saudi Arabia in 2015 to 2016, in the screening reported by Ashshi *et al.*[72]. By region, the Americas again led the ranking for the highest prevalence, with a pooled proportion of 0.1% (95% CI: 0.1% to 0.1%). All the studies took place in endemic regions or in areas with an epidemic outbreak (**Table IV**).

Prevalence of Zika virus

The overall seroprevalence of IgG antibodies against ZIKV was 5.1% (95% CI: 4.6% to 5.7%). The highest rate was in the donor screening programme in the Bolivian regions of Beni and Santa Cruz in 2016 to 2017, at 27.5% (95% CI: 22.8% to 32.8%)[40]. By region, the highest seroprevalence was again in the Americas, at 7.4% (95% CI: 6.3% to 8.7%). The prevalence ratio between endemic and non-endemic regions was 9.0 (**Table V**).

NAT showed an overall prevalence of ZIKV of 0.7×10^{-2}% (95% CI: 0.7×10^{-2}% to 0.8×10^{-2}%), varying from 0% to 2.8% (95% CI: 2.1% to 3.8%). The highest viraemic rate was recorded in a study in French Polynesia in 2013 to 2014[26]. The country with the highest prevalence estimate for ZIKV was Brazil (0.5%, 95% CI: 0.4% to 0.7%). The studies in endemic populations, with local transmission or an epidemic outbreak, documented a prevalence of 0.1% (95% CI: 0.1% to 0.1%) (**Table V**).

Table IV - *Global prevalence of Dengue virus in blood donors according to nucleic acid amplification and NS1 antigen, by population*

Study ID	Population	Screening test	Positive/ Totals	Prevalence	95% CI		Forest plot	Relative weight %
NAT							0.00 0.05 0.10	
Zeng 2018	China 2015	In house	0/1164	0.000	0.000	0.007		0.1
Liao 2017	China 2014	In house	2/3000	0.001	<0.001	0.003		0.4
Gao 2017	China 2013-14	In house	0/1685	0.000	0.000	0.005		0.1
Tsai 2018	Taiwan 2015	In house	1/8000	<0.001	0.000	0.001		0.2
Lin 2016	Taiwan 2015	LightMix Kit (T.B.)	16/6515	0.003	0.002	0.004		3.2
Lu 2018	Taiwan 2015	Procleix (Grifols)	21/5000	0.004	0.003	0.006		4.2
Ranjan 2016	India 2012	In house	0/200	0.000	0.000	0.039		0.1
Sayama 2013	Laos 2012	Not specified	0/199	0.000	0.000	0.039		0.1
Linnen 2008	Australia 2003	Procleix (Chiron)	0/5879	0.000	0.000	0.001		0.1
Linnen 2008	Brazil 2004-05	Procleix (Chiron)	9/2994	0.003	0.002	0.006		1.8
Linnen 2008	Honduras 2003	Procleix (Chiron)	3/4858	<0.001	<0.001	0.002		0.6
Rooks 2016	Australia 2008-09	Procleix (Hologic)	0/664	0.000	0.000	0.012		0.1
Rooks 2016	Australia 2012-13	Procleix (Hologic)	0/5518	0.000	0.000	0.001		0.1
Faddy 2015	Australia 2008-13	Not specified	0/6182	0.000	0.000	0.001		0.1
Beau 2020	French Polynesia 2013-18	RealStar (Altona)	5/34000	<0.001	<0.001	<0.001		1.0
Ashshi 2017	Saudi Arabia 2015-16	In house	50/910	0.055	0.042	0.072		9.4
Stramer 2019	USA 2015	Cobas test	0/10528	0.000	0.000	<0.001		0.1
Mohammed 2012	Puerto Rico 2005	NAT (Gen-Probe)	12/16521	<0.001	<0.001	0.001		2.4
Stramer 2013	Puerto Rico 2012-13	Not specified	114/49909	0.002	0.002	0.003		22.7
Stramer 2010	Puerto Rico 2007	NAT (Gen-Probe)	29/15350	0.002	0.001	0.003		5.8
Saá 2019	Puerto Rico 2015-16	Not specified	0/1186	0.000	0.000	0.007		0.1
Slavov 2019	Brazil 2015-16	In house	0/475	0.000	0.000	0.017		0.1
Slavov 2018	Brazil 2015-16	In house	1/631	0.002	<0.001	0.011		0.2
Sharma 2018	Brazil 2016	In house	0/676	0.000	0.000	0.012		0.1
Sabino 2013	Brazil 2012	Not specified	102/20132	0.005	0.004	0.006		20.3
Lavezzo 2010	Brazil 2006	In house	0/205	0.000	0.000	0.038		0.1
Dias 2012	Brazil 2010	In house	2/500	0.004	0.001	0.016		0.4
Busch 2016	Brazil 2012	Procleix (Hologic)	87/16241	0.005	0.004	0.007		17.3
Levi 2009	Brazil 2007-08	In house	0/23568	0.000	0.000	<0.001		0.1
De Almeida 2018	Brazil 2017	Not specified	0/298	0.000	0.000	0.026		0.1
Escoval 2013	Portugal 2012-13	Not specified	44/1948	0.023	0.017	0.030		8.6
Sargento 2017	Portugal	Not specified	0/110	0.000	0.000	0.068		0.1
Total			498/245046	0.002	0.002	0.002		
Southeast Asia			40/24599	0.002	0.002	0.001		
China			2/5849	<0.001	0.000	0.001		
Taiwan			38/19515	0.002	0.001	0.003		
Oceania			5/52243	<0.001	0.000	<0.001		
Australia			0/18243	0.000	0.000	0.000		
Americas			359/164072	0.002	0.002	0.002		
Puerto Rico			155/82966	0.002	0.002	0.002		
Brazil			201/65720	0.003	0.003	0.003		
Heterogeneity I^2 95.59								
NS1 antigen							0.00 0.05 0.10	
Tsai 2018	Taiwan 2015	IC (Not specified)	0/8000	0.000	0.000	0.001		0.4
Lin 2016	Taiwan 2015	Platelia (Bio-Rad)	2/6515	<0.001	<0.001	0.001		1.5
Chhabra 2013	India	Not specified	0/380	0.000	0.000	0.021		0.4
Mangwana 2014	India 2013	Platelia (Bio-Rad)	0/1709	0.000	0.000	0.005		0.4
Jain 2019	India 2016	Not specified	2/369	0.005	0.001	0.021		1.5
Kulkarni 2018	India 2016-17	Microlisa (J. Mitra	3/520	0.006	0.002	0.018		2.3
Mohamad 2016	Malaysia 2015	Not specified	0/126	0.000	0.000	0.060		0.4
Yusuf 2018	Malaysia 2016	Platelia (Bio-Rad)	0/374	0.000	0.000	0.021		0.4
Fellizar 2012	Philippines	Platelia (Bio-Rad)	3/158	0.019	0.006	0.057		2.3
Rooks 2016	Australia 2008-13	Platelia (Bio-Rad)	0/973	0.000	0.000	0.008		0.4
Flower 2011	Australia 2008-09	Platelia (Bio-Rad)	20/1087	0.018	0.012	0.028		15.0
Ashshi 2015	Saudi Arabia 2014	ELISA (Panbio)	1/100	0.010	0.001	0.068		0.8
Ashshi 2017	Saudi Arabia 2015-16	ELISA (Panbio)	48/910	0.053	0.040	0.069		34.7
Stramer 2011	Puerto Rico 2010	Platelia (Bio-Rad)	8/53019	<0.001	<0.001	0.000		6.1
Stramer 2011	Puerto Rico 2010	Platelia (Bio-Rad)	1/2837	<0.001	0.000	0.003		0.8
Stramer 2010	Puerto Rico 2007	Platelia (Bio-Rad)	3/4401	0.001	<0.001	0.002		2.3
Slavov 2019	Brazil 2015-16	Platelia (Bio-Rad)	0/475	0.000	0.000	0.017		0.4
Patavino 2009	Brazil 2007	Platelia (Bio-Rad)	1/4000	<0.001	0.000	0.002		0.8
De Carvalho 2010	Brazil 2008	Platelia (Bio-Rad)	39/3000	0.013	0.010	0.018		29.4
Total			131/88953	0.002	0.001	0.002		
Southeast Asia			10/18151	<0.001	<0.001	0.001		
India			5/2978	0.002	0.002	0.003		
Americas			52/67732	<0.001	0.001	0.001		
Puerto Rico			12/60257	<0.001	<0.001	<0.001		
Brazil			40/7475	0.005	0.004	0.007		
Heterogeneity I^2 95.59								

CI: confidence interval; IC: immunochromatography; NAT: nucleic acid test; ELISA: enzyme-linked immunosorbent assay

Table V - *Global prevalence of Zika virus in blood donors, by population*

Study ID	Population	Screening test	Positive/ Total	Prevalence	95% CI		Forest plot	Relative weight %
IgG antibodies							0.00 0.20 0.40	
Postorino 2019	Laos 2015	ELISA (Euroinmun)/VNT	16/359	0.045	0.028	0.072		5.1
Postorino 2019	Laos 2016	ELISA (Euroinmun)/VNT	68/687	0.099	0.079	0.124		20.3
Aubry 2015	French Polynesia 2011-13	Not specified	5/593	0.008	0.004	0.020		1.6
Gake 2017	Cameroon 2015	ELISA (Euroinmun)/VNT	53/1084	0.049	0.038	0.064		16.7
Nurtop 2020	Congo 2011	ELISA (Euroinmun)/VNT	7/386	0.018	0.009	0.038		2.3
Seruyange 2019	Rwanda 2015	ELISA (Euroinmun)/VNT	12/874	0.014	0.008	0.024		3.9
Seruyange 2019	Sweden	ELISA (Euroinmun)/VNT	0/215	0.000	0.000	0.036		0.2
Diarra 2020	Mali 2013	ELISA (Euroinmun)/VNT	47/637	0.074	0.056	0.097		14.4
Saba Villarroel 2018	Bolivia B. and S.C.* 2016-17	ELISA (Euroinmun)/VNT	84/305	0.275	0.228	0.328		20.1
Saba Villarroel 2018	Bolivia others 2016-17	ELISA (Euroinmun)/VNT	1/510	0.002	<0.000	0.014		0.3
Slavov 2019	Brazil 2010-15	ELISA (Euroinmun)/VNT	0/180	0.000	0.000	0.043		0.2
Slavov 2019	Brazil 2016	ELISA (Euroinmun)/VNT	19/320	0.059	0.038	0.091		5.9
Slavov 2019	Brazil 2017	ELISA (Euroinmun)/VNT	29/317	0.092	0.064	0.129		8.7
Diefenbach 2019	Brazil 2016-17	ELISA (Euroinmun)/VNT	1/182	0.006	<0.001	0.038		0.3
Total			342/6649	0.051	0.046	0.057		
Africa			119/2981	0.040	0.034	0.048		
Americas			134/1814	0.074	0.063	0.087		
Brazil			49/999	0.049	0.036	0.062		
Endemic or epidemic areas			317/3891	0.082	0.073	0.091		
Non-endemic or non-epidemic areas			25/2758	0.009	0.006	0.013		
Heterogeneity I² 95.28								
NAT							0.00 0.025 0.05	
Zheng 2019	China Shenzhen	Procleix (Grifols)	0/9309	0.000	0.000	<0.001		0.1
Lam 2017	Singapore 2016-17	Procleix (Not specified)	1/63144	<0.001	0.000	<0.001		0.2
Beau 2020	French Polynesia 2013-14	In house	42/1505	0.028	0.021	0.038		7.4
Slavov 2019	Brazil 2016	In house	0/475	0.000	0.000	0.017		0.1
Magnus 2018	Brazil 2016	Lanciotti's & Pyke's	3/1857	0.002	<0.001	0.005		0.6
Benites 2019	Brazil 2015-2016	Multiplex (B-M. /F.)	4/3737	0.001	<0.001	0.003		0.7
Slavov 2017	Brazil 2015-16	In house	37/1393	0.027	0.019	0.036		6.6
Sharma 2018	Brazil 2016	Multiplex (Kit Biomol)	0/616	0.000	0.000	0.013		0.1
Gallian 2016	Martinique 2016	RealStar (Altona)	76/4129	0.018	0.015	0.023		13.6
Williamson 2018	Puerto Rico 2016	Cobas test (Roche)	339/52942	0.006	0.006	0.007		61.3
Saá 2019	Puerto Rico 2015-16	Cobas test (Roche)	1/1186	<0.001	<0.001	0.006		0.2
Pate 2017	USA 2016-17	Cobas test (Roche)	12/1776190	<0.001	<0.001	<0.001		2.2
Fedyk 2019	USA 2016-17	Cobas test (Roche)	4/92618	<0.001	<0.001	<0.001		0.7
Galel 2017	USA 2016-17	Cobas test (Roche)	14/358786	<0.001	<0.001	<0.001		2.6
Williamson 2017	USA 2016-17	Procleix (Hologic/Grifols)	10/933831	<0.001	<0.001	<0.001		1.8
Saá 2018	USA 2017	Procleix (Grifols)	9/4325889	<0.001	<0.001	<0.001		1.6
Covin 2017	USA 2016-17	Procleix (Hologic)	0/30493	0.000	0.000	<0.001		0.1
Diefenbach 2019	Brazil 2016-17	In house	0/500	0.000	0.000	0.016		0.1
Borena 2017	Austria 2016	RealStar (Altona)	0/1001	0.000	0.000	0.008		0.1
Total			552/7659601	<0.001	<0.001	<0.001		
Americas			509/7584642	<0.001	<0.001	<0.001		
Brazil			44/8578	0.005	. 0.004	0.007		
USA			49/7517807	<0.001	<0.001	<0.001		
Endemic or epidemic area			516/489084	0.001	0.001	0.001		
Non-endemic or non-epidemic areas			36/7170517	<0.001	<0.001	<0.001		
Heterogeneity I² 99.23								

*Beni and Santa Cruz regions
CI: confidence interval; NAT: nucleic acid test; VNT: virus neutralization test

DISCUSSION

Since the advent of blood transfusions, patients' safety has been threatened by the transmission of infectious agents[125]. Since the turn of the century, a high number of transfusion-transmitted arbovirus cases have been notified, in some instances ending in a fatal outcome for the patient[2]. The chance that an asymptomatic but viraemic person donates blood is an important concern for transfusion safety and is a possibility for all of the three arboviruses studied. To understand the magnitude of the problem, it is essential to review the published literature reporting viraemic rates in blood donors. Our study updates, collates, and summarises all the notified and published data to date.

The viraemic rates of the three arboviruses in areas experiencing outbreaks were high according to NAT screening (from 1.9% for CHIKV to 5.5% for DENV and 2.8% for ZIKV)[35,71,26]. Such donors are asymptomatic but infected, often with high levels of viraemia, so there is a real risk of transmission of these viruses via transfusion. NAT methods are expensive and complex, and they require a series of material and human resources that are not accessible in all settings. Health services in most countries do not make routine use of NAT assays capable of detecting these viruses during the donation process. No study in Africa used this screening technique. On the other hand, when NAT assays are used in areas with no outbreaks, the prevalence is practically zero. Consequently, it is

important to select the target population appropriately for these screening tests.

Assessing seroprevalence of different arboviruses is important for understanding population exposures in the past. High rates of exposure could be correlated to a greater number of infected and asymptomatic donors capable of transmitting the infection, so this could constitute a source of information on the magnitude of the problem. Moreover, as Liu *et al.* pointed out in their review, quantifying the seroprevalence of these viruses is of interest from an epidemiological point of view[22]. In some populations, blood donor screening is the only type of seroprevalence study that has been performed.

The seroprevalence of IgG antibodies against the three arboviruses was high, especially for CHIKV and DENV. In the case of CHIKV, we found the highest seroprevalence of IgG antibodies in sub-Saharan Africa, where periodic outbreaks have been recorded since the 1950s. Some of the most prominent occurred in the Republic of Tanzania in 1954, in the Democratic Republic of Congo in 1999 to 2000, and in Kenya in 2017. The high seroprevalence found in the regions of Beni and Santa Cruz (Bolivia)[40], areas with very specific climatic, environmental, and economic conditions, was also noteworthy. We found high seroprevalence rates for IgG against DENV in hyperendemic regions or where studies took place following extensive epidemic outbreaks. Fourteen studies reported seroprevalence rates of more than 50%, with several reporting rates over 90%. DENV has been producing epidemic outbreaks for more than 200 years. This long epidemiological trajectory has translated into its wider geographic dissemination and generally higher seroprevalence rates. The seroprevalence of IgG against ZIKV in blood donors is clearly the lowest for the three arboviruses studied, reflecting the very recent appearance of this virus, which has only caused significant outbreaks since about 2007. As with CHIKV, the highest seroprevalence was found in the Beni region of Bolivia, as well as in Laos and the São Paulo region in Brazil, where outbreaks have been registered since 2016[40,106,114]. However, the seroprevalence in African blood donors is very low, indicating the limited transmission of the virus on this continent, in contrast to DENV and CHIKV. The areas in which seroprevalence is highest have some similarities: a tropical climate with a clear, rainy season, abundant vegetation and water resources, and a low level of economic resources. All health centres and institutions should support efforts to reduce the risk of transmitting arboviruses through blood transfusions. A wide range of interventions could have an impact, from broad environmental policies directed at addressing the climate crisis or the use of water, agricultural, and forestry resources, to community-based environmental measures targeting vector control, improved conservation of wetlands and water resources, and improvements to health systems.

Blood transfusion centres also have a role to play: first, we should improve screening in potential blood donors using specific questions about the symptomology of potential infections. It is also important that donors understand the symptoms of possible infections and are encouraged to report any they experience in the days and weeks following the donation. Secondly, it may be worth establishing a quarantine period for red blood cell concentrates, postponing their release until after the incubation period for infections has passed. Implementation of these measures requires adequate training among personnel working in donor selection or haemovigilance and co-responsibility among donors in terms of monitoring their own health. However, these measures would not enable identification of asymptomatic donors[126]. The following measure would therefore be the suspension of blood donation collections in a region, as done during the 2007 CHIKV outbreak in Italy, although this measure is difficult to apply in low-resource areas[127]. Donor screening (ideally using NAT) to detect a virus or its biomarkers is another possibility. When NAT is not available, one more affordable and accessible option of interest is point-of-care testing (immunoassay, reverse transcriptase polymerase chain reaction [RT-PCR], reverse-transcription loop-mediated amplification [RT-LAMP]), which has demonstrated an acceptable sensitivity and specificity for CHIKV, DENV, and ZIKV, respectively[128,129,130]. Finally, where available, techniques for the deactivation of pathogens could also be applied, as these methods have proven effective against several different arboviruses [131,132,133,134].

Our study has several limitations, chief among which is the considerable heterogeneity of the diagnostic

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tests used by different groups on the same virus (from commercial test kits to in-house techniques). These tests have different sensitivities and specificities. Moreover, in the case of DENV, different NAT assays could fail to detect some serotypes or genotypes in naïve populations. Most commercial techniques have an acceptable sensitivity for the four serotypes: MA assay Gen-Probe (limit of detection [LoD] 95% 14.9 copies/mL; specificity 99.91%), RealStar dengue RT-PCR assay Altona Diagnostic (sensitivity 83.2%, 95% CI: 77.6% to 89.1%), Cobas CHIKV/DENV test Roche Molecular Sistems (LoD 95% 0.37 to 1.05 copies/mL, specificity 100%)[104,135,33]. However, in-house techniques are more variable: some are capable of detecting all four serotypes with acceptable sensitivity, while others have been designed to detect only the serotype in circulation in the specific setting in which it is being used.

Another problem is cross-reactivity between different arboviruses. Although the highest prevalence of CHIKV was in Africa, most studies did not perform neutralisation tests or only performed them on a subsample of those yielding positive results. CHIKV shows cross-reactivity with other alphaviruses such as the O'nyong-o'nyong and Mayaro viruses. Clements *et al*. identified 552 donors with a positive result for CHIKV, but neutralisation tests were run in just 24; of these, 23 showed higher titres for O'nyong-o'nyong virus than for Chikungunya[31]. Thus, the results for prevalence of IgG antibodies against CHIKV should be interpreted with caution, especially in Africa, where other alphaviruses have been shown to circulate. Although DENV also shows some cross-reactivity with other flaviviruses, authors of the studies on this virus usually did perform neutralisation tests (normally to identify the DENV serotype). In the case of ZIKV, all the studies included virus neutralisation tests. We selected studies performed in the blood donor population in order to obtain data that are representative of that population. However, the results may not be applicable to the general population. Studies are not available in all geographic areas, and a substantial proportion have been in areas known to have high prevalence, which may lead to an overestimation of results. In addition, the between-study heterogeneity was quite high (I^2 >75% in all cases). As a single review author selected the studies for inclusion, we cannot rule out the risk of selection bias. Moreover, some risk of publication bias is possible, as there may have been unpublished studies finding negligent prevalence estimates. So, the external validity of the study may be limited by the real prevalence.

CONCLUSIONS

Our review has helped to elucidate the prevalence of CHIKV, DENV, and ZIKV in blood donors around the world, as determined by different screening tests. We have demonstrated that in regions where large epidemic outbreaks have occurred, the donor population has been widely exposed to the viruses, and the viraemic rate observed from donor screening may be high. This fact represents a threat to blood transfusion safety, so it is important that centres involved in these procedures understand the epidemiology driving the emergence of these transfusion-transmissible arbovirus infections.

Over the next few years, it is likely that the vector will expand into new settings, increasing the risk of outbreaks worldwide. The transmission of different arboviruses through transfusion will become a global threat. Institutions, authorities, blood transfusion centres, and blood banks should make efforts to design a clear path forward.

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AUTHORSHIP CONTRIBUTIONS

All Authors contributed to the study design and final approval of manuscript.

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