

Transfusion-Transmitted Malaria: A Systematic Review and Meta-analysis

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Background. Malaria transmission through blood transfusion is an accidental but preventable cause of malaria infection and is increasingly becoming a matter of concern for blood transfusion services. This systematic review was conducted to provide a summary of evidence about the prevalence of *Plasmodium* infection in asymptomatic blood donors and the effectiveness of screening methods used based on the available literature.

Methods. PRISMA guidelines were followed. Scopus, PubMed, Science Direct, and EMBASE were searched from 1982 to October 10, 2017. All peer-reviewed original research articles describing the prevalence of malaria parasitemia in blood donors with different diagnostic methods were included. The random-effects model was applied to assess the effects of heterogeneity among the selected studies. Incoherence and heterogeneity between studies were quantified by I^2 index and Cochran's Q test. Publication and population bias was assessed with funnel plots and Egger's regression asymmetry test. All statistical analyses were performed using Stata (version 2.7.2).

Results. Seventy-one studies from 21 countries, 5 continents, were included in the present systematic review. The median prevalence of malaria parasitemia among 984 975 asymptomatic healthy blood donors was 10.54%, 5.36%, and 0.38% by microscopy, molecular methods (polymerase chain reaction), and rapid diagnostic tests, respectively. The most commonly detected *Plasmodium* species was *P. falciparum*.

Conclusions. This systematic review demonstrates that compared with other transfusion-linked infections, that is, HIV, HCV, and HBV, transfusion-transmitted malaria is one of the most significant transfusion-associated infections especially in Sub-Saharan Africa. Future work must aim to understand the clinical significance of transfusion-transmitted malaria in malaria-endemic settings.

Keywords. blood donor; *Plasmodium*; systematic review; transfusion-associated infections; transfusion medicine.

Approximately 3.3 billion of the world's population resides in malaria-endemic regions, and of those, 1.2 billion are at high risk of malaria infection [1, 2]. Malaria often affects the most vulnerable, notably young children and pregnant women in the developing world, leading to significant morbidity and mortality [3]. Although malaria is usually transmitted by *Plasmodium* parasite's vector female *Anopheles* mosquitos [2, 4], it is also readily transmitted through blood transfusion [5–8], organ transplantation, and needle stick injury [9].

Transfusion-transmitted malaria (TTM) is one of the first recorded incidents of transfusion-associated infection [10]. It is an incidental transmission of *Plasmodium* parasite from an asymptomatic donor with parasitemia to a blood recipient and is a significant concern, especially in nonendemic areas. *Plasmodium* parasites were shown to survive in whole blood and plasma when stored at 4°C for approximately up to 18 days, and detectable parasites can present even up to 28 days when frozen, although with diminished infectivity [11, 12]. Some population-based studies and systematic reviews have examined the prevalence of malaria infection in blood donors in developed, nonendemic countries [2, 5–7], but a knowledge gap still exists in regard to the extent and dynamics of malaria infection in blood donors, especially in malaria-endemic areas [13, 14].

Malaria is caused by a unicellular apicomplexan called *Plasmodium*, and 5 species are known to cause disease in humans: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi* [4, 15–17]. In TTM, the most common *Plasmodium*

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species observed were *P. falciparum*, followed by *P. malariae*, *P. vivax*, and *P. ovale* [6, 8]. According to a systematic review, the incubation period for TTM was found to be longer compared with natural mosquito-transmitted malaria infection [8]. The primary concern in regard to TTM compared with natural infection is that the patients infected through transfusion may present late with severe complications due to the immediate release of parasites [18]. This could lead to fatal outcomes in children, the elderly, and patients who are pregnant or immunosuppressed.

This systematic review and meta-analysis was performed (1) to provide a summary of the evidence to understand the prevalence of *Plasmodium* infection in the asymptomatic blood donor population based on the available literature, (2) to compare the effectiveness of screening methods used to detect malaria parasitemia in blood donors, and (3) to identify risk factors associated with active malaria infection in the asymptomatic blood donor population.

METHODS

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19].

Search Strategy

We retrieved all articles on malaria infection among the blood donor population through systematic searches of major databases such as PubMed, EMBASE, Scopus, and Web of Science from 1982 to October 10, 2017, using Medical Subject Headings (MeSH) terms, including “malaria,” “*Plasmodium*,” “prevalence,” “epidemiology,” “blood donors,” “transfusion,” “transplant recipients,” and “blood pack” alone or combined together using “OR” and/or “AND.”

Study Selection

Studies were eligible if they met the inclusion criteria: (1) peer-reviewed original research articles; (2) cross-sectional studies that estimated the prevalence of malaria infection in blood donors with different diagnostic methods including microscopy, rapid diagnostic testing (RDT), and molecular techniques (polymerase chain reaction [PCR]); (3) published papers in English; (4) published papers in other languages with an English abstract; (5) published online from 1982 to October 10, 2017. We also manually screened the references of the included original studies, and reviews were conducted for obtaining additional studies.

Data Extraction

Two authors (M.F. and S.M.) screened references and retrieved articles according to the eligibility criteria. Disagreements were resolved through discussion and consensus. Any study that did not match the eligibility criteria was excluded. Two reviewers

independently assessed the quality and performed the final article selection. From each study, the following variables were extracted: the name of the first author, year of publication, country, sample size, number of positive samples, diagnostic methods used (microscopy, RDT, or molecular methods), risk factors such as residence, gender, number of blood donations (the first or repeat donation), type of donors (voluntary, replacement/family, or commercial), and blood group.

Meta-analysis

For every study included, the point estimate and 95% confidence interval (CI) were calculated. The random-effects model (DerSimonian or Laird) was applied to assess the effects of heterogeneity among the selected studies. Forest plots provided a detailed representation of all studies based on the effect sizes and 95% CIs. Incoherence and heterogeneity between studies were quantified using the I^2 index and Cochran's Q test, respectively. Heterogeneity among subgroups and the relationship between prevalence, year of publication, and sample size were estimated using metaregression. Publication and population bias were assessed with funnel plots and the Egger's regression asymmetry test. All statistical analyses were performed using Stata (version 2.7.2).

RESULTS

The systematic search identified 1123 potentially relevant articles. Two hundred forty-one articles were retrieved for more detailed evaluation and assessed for eligibility. After reviewing the eligibility criteria, a total of 71 studies conducted in 21 countries and 5 continents were included in this meta-analysis. The numbers of selected papers at each step of screening and eligibility are reported in the flow diagram (Figure 1).

Baseline characteristics of all studies included in this analysis are shown in the Supplementary Data. Three types of diagnostic methods were used to detect the prevalence of malaria in the included studies: microscopy ($n = 51$), RDT ($n = 25$), and molecular techniques ($n = 14$) (Supplementary Tables 1–3). A total of 984 975 blood samples were examined for malaria infection in all studies: 374 919 samples by microscopy, 604 693 by RDT including immunochromatographic test, and 5363 by molecular techniques (PCR, real-time PCR, PCR-restriction fragment length polymorphism (RFLP) and nested PCR). The pooled proportion of malaria prevalence among the blood donor population was 10.54% (95% CI, 8.44%–12.84%) by microscopy, 5.36% (95% CI, 2.25%–9.70%) by PCR, and 0.38% (95% CI, 0.25%–0.54%) by RDT (Figures 2–4).

We then compared studies according to the publication year, categorizing studies into those published before 2010 ($n = 31$) and after 2010 ($n = 20$) to provide a recent estimate of the prevalence by microscopy in this population. The pooled prevalence of malaria infection in asymptomatic blood donors was 7.14% (95% CI, 3.61%–11.74%) among studies conducted before 2010

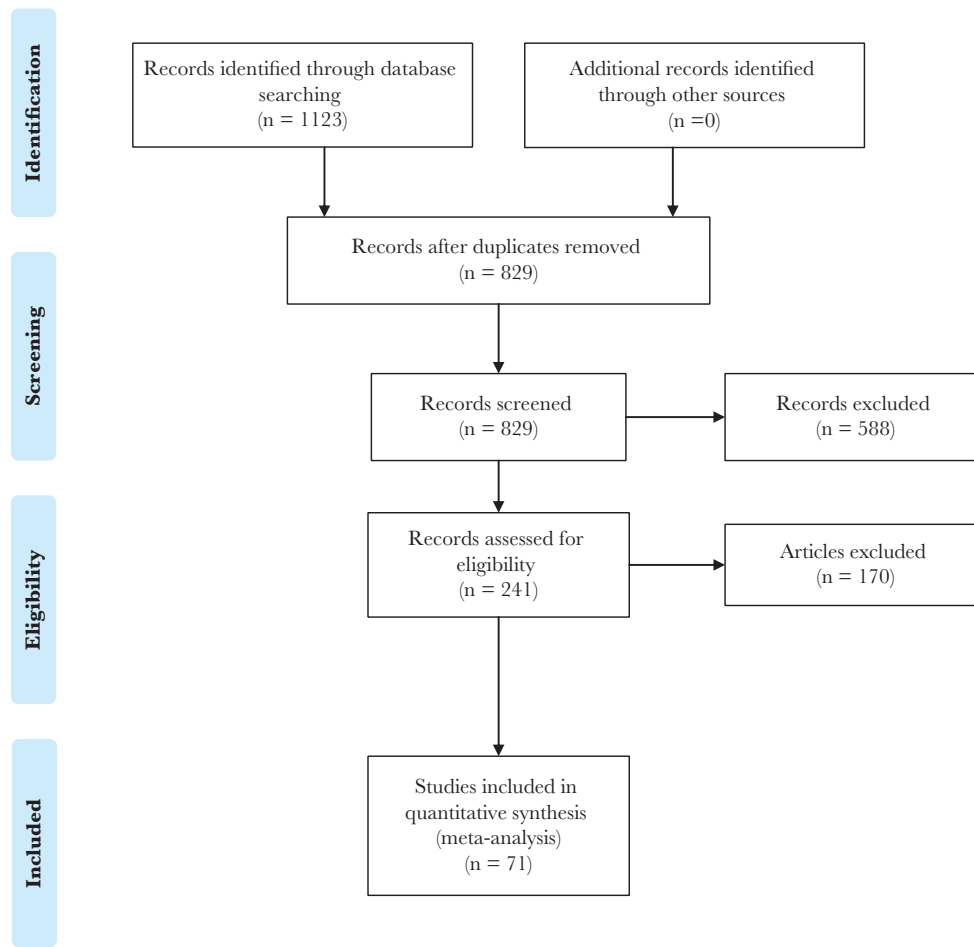


Figure 1. Flowchart describing the study design process.

vs 13.61% (95% CI, 9.33%–18.55%) among those conducted after 2010. Although we observed a difference in prevalence, this was not statistically significant ($P = .1872$).

Continents Subgroup Analysis

A subgroup analysis of the malaria prevalence among the blood donor population in different continents was conducted (Table 1). The highest prevalence of malaria infection among blood donors was observed in Africa; 21% (95% CI, 14%–29%) of blood donors had a positive malaria test detected by microscopy. By RDT, the highest prevalence was observed in Africa (7.4%; 95% CI, 3%–12%), and no parasitemia was detected in other continents. Molecular methods (PCR) have indicated a higher prevalence of malaria infection in the blood donor population in Africa (36%; 95% CI, 11%–72%). However, using a molecular technique did not impact the observed prevalence in other continents: Asia 4% (95% CI, 1%–13%), Americas 2% (95% CI, 1%–7%), and Europe 1% (95% CI, 0%–3%).

As shown in Figure 5, Nigeria had the highest estimated prevalence of malaria infection among blood donors (31.7%), followed by Ghana (19.4) and Sudan (17%). Turkey and China

had the lowest estimated prevalence of malaria infection among blood donors. Publication bias detection using Egger's regression indicated bias in the case of microscopy ($P < .0001$), RDTs ($P = .04$), and PCR ($P = .01$) studies.

Risk Factors

According to the multivariate analysis, a positive association was observed between malaria infection and female sex, commercial donor type, and blood group A ($P < .005$). Those individuals residing in rural areas and with no history of previous transfusion had a higher prevalence of infection; however, this were not statistically significant. Detailed characteristics of the associated risk factors are displayed in Supplementary Table 4.

DISCUSSION

This systematic review and meta-analysis provide comprehensive data on the prevalence of malaria in the asymptomatic blood donor population. The median worldwide prevalence of malaria parasitemia in healthy blood donors was 10.54% (95%

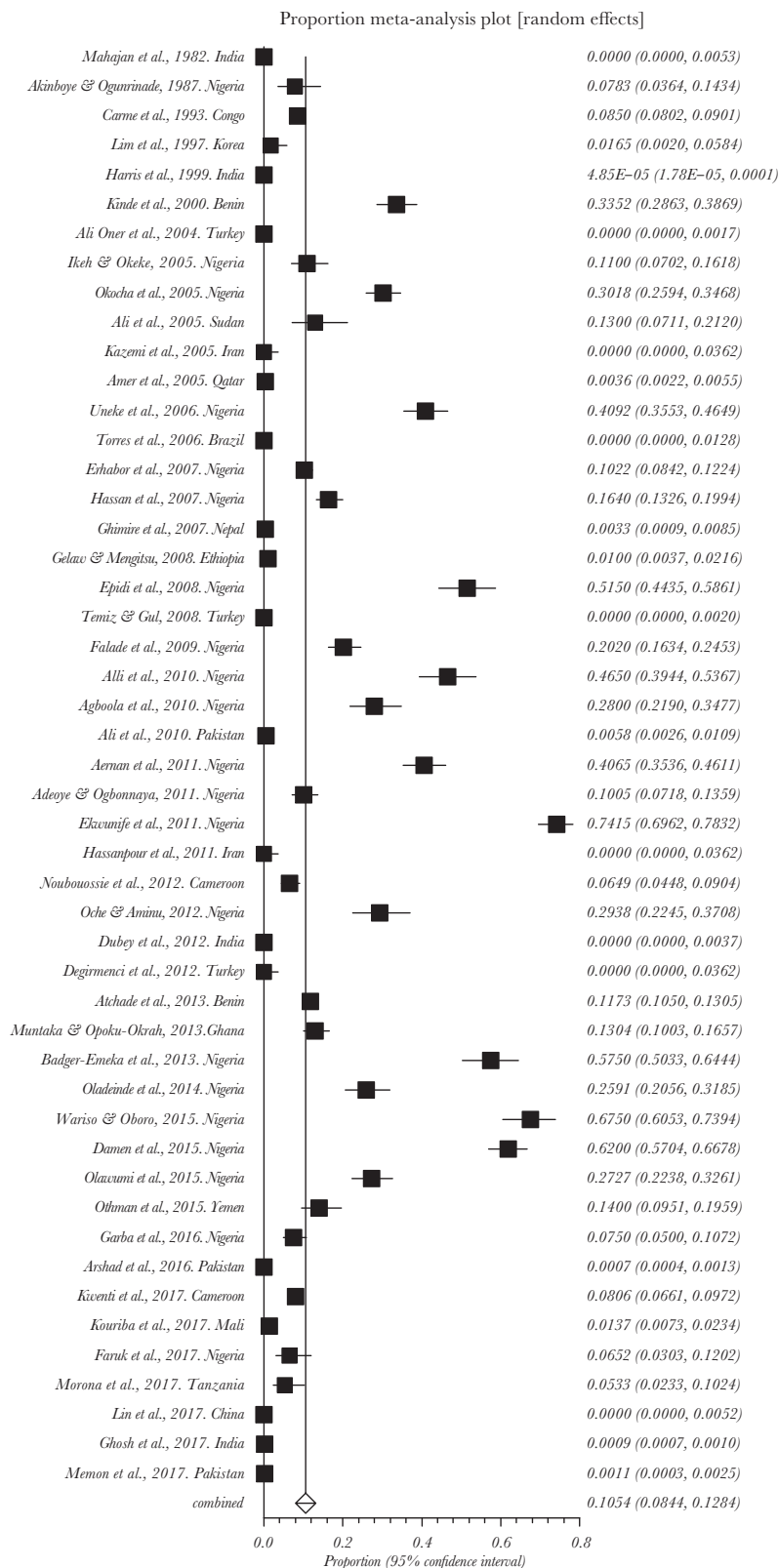


Figure 2. Forest plot diagram of the studies reporting malaria prevalence among blood donors by microscopy.

CI, 8.44%–12.84%) by microscopy, 5.36% (95% CI, 2.25%–9.70%) by molecular techniques, and 0.38% (95% CI, 0.25%–0.54%) by RDTs.

The overall prevalence of malaria in blood donors was, expectedly, higher in Africa compared with the other continents, and the highest prevalence was observed in Nigeria. Although

Proportion meta-analysis plot [random effects]

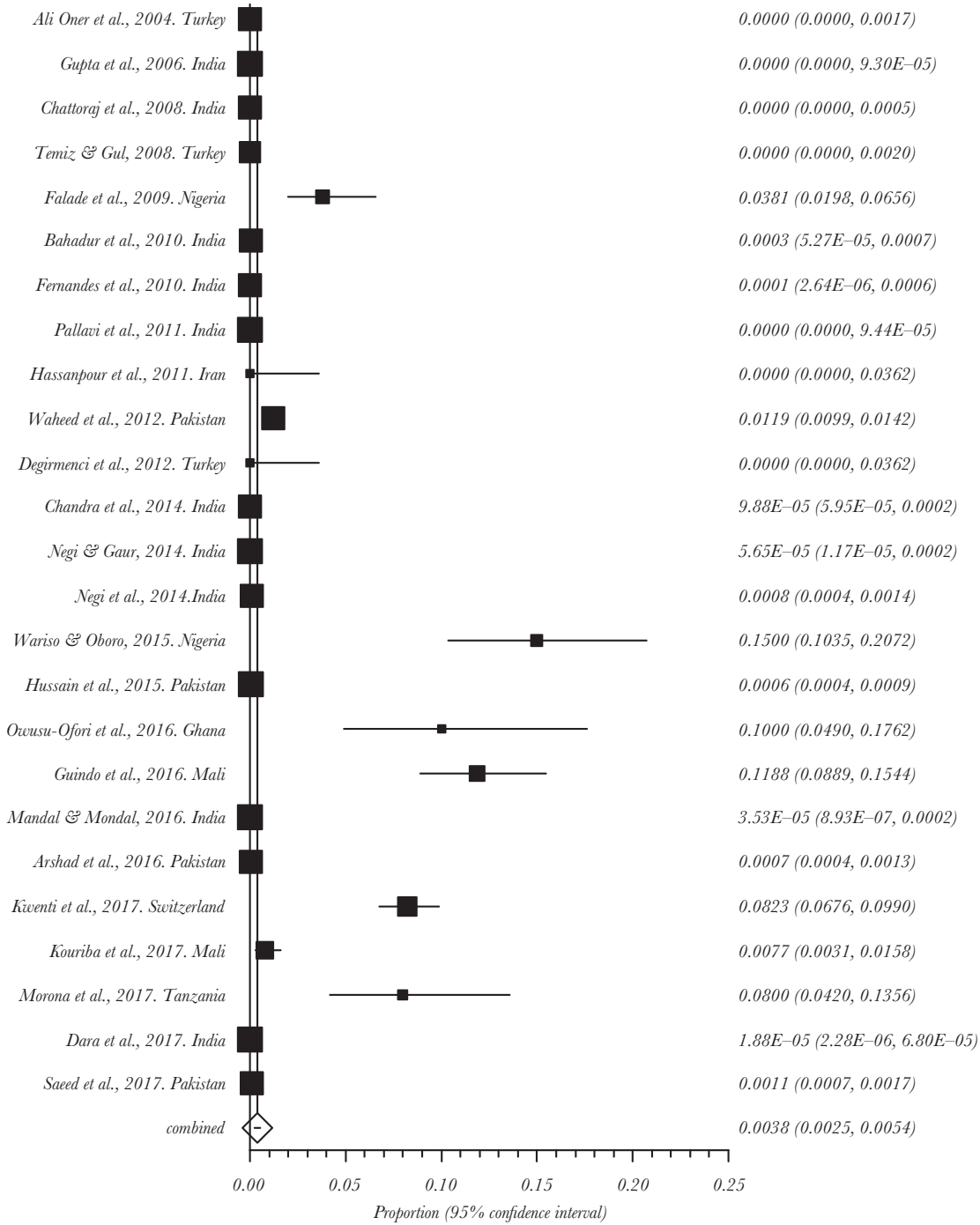


Figure 3. Forest plot diagram of studies reporting malaria prevalence among blood donors based on immunochromatographic rapid testing (rapid diagnostic test and immunochromatographic test).

it is not surprising to observe high prevalence in Nigeria given that it is one of the most malaria-affected countries [1], primarily due to the increased number of vector mosquitos, socio-economic conditions, and favorable climate [20–22], worryingly one-third of healthy donors by microscopy were found to be malaria-infected. This emphasizes that TTM is one of the most

significant transfusion-associated infections in Sub-Saharan Africa compared with other infections such as HIV, hepatitis C, and hepatitis B, where the prevalence ranges from 0.5% to 16%, 0.5% to 3%, and 5% to 25%, respectively [23]. These findings have several implications: (1) although significant scientific progress has been made in blood donation screening,

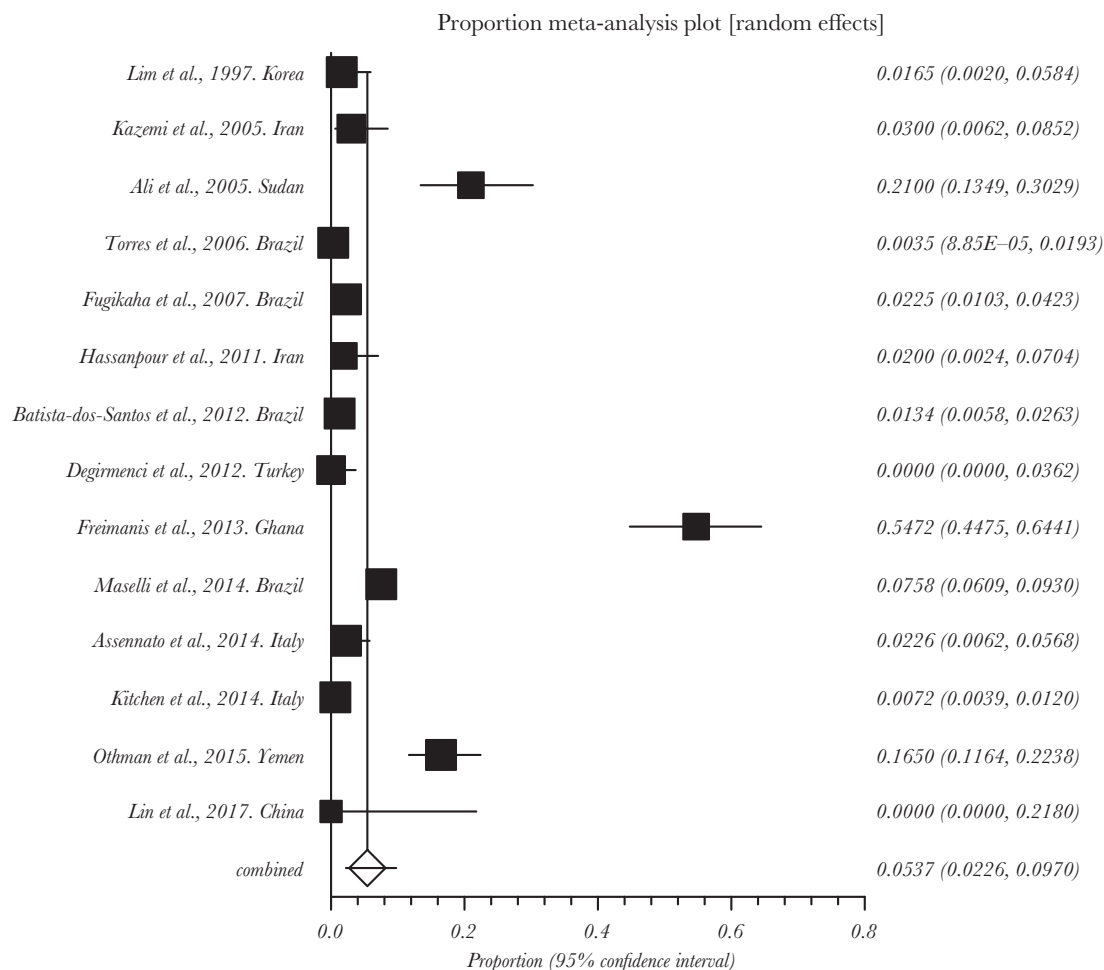


Figure 4. Forest plot diagram of the studies reporting malaria prevalence among blood donors based on molecular techniques.

TTM remains a potential risk for blood transfusion recipients; (2) infected recipients who do not manifest clinical disease may become asymptomatic carriers and thus constitute a reservoir of malaria parasites if competent vectors are transmitted; (3) the

incident may lead to serious consequences, especially among vulnerable patients (the elderly, children, those who are immunosuppressed, and pregnant women) and in nonendemic countries where most people have never been exposed to malaria.

Table 1. Subgroup Analysis of Malaria Prevalence in Different Continents

Continent	No. of Studies	Type of Study	Prevalence (95% CI)	I_2 , %	Heterogeneity		Egger Test	
					Q	PValue	T	PValue
Africa	33	Microscopy	0.21 (0.14–0.29)	99	3299.3	<.0001	9.5	$P < .0001$
	2	PCR	0.36 (0.11–0.72)	96	25.8	<.01	-	-
	7	RDT	0.074 (0.03–0.12)	95.8	142.04	<.0001	5.5	.02
America	1	Microscopy	0	-	-	-	-	-
	4	PCR	0.02 (0.01–0.07)	93	65.5	<.01	13.3	.21
Asia	14	Microscopy	0.005 (0.01–0.05)	98	333.1	<.01	2.1	.04
	5	PCR	0.04 (0.01–0.13)	85	34.9	<.01	2.3	.5
	15	RDT	0.00 (0.00–0.00)	97.5	550.8	<.0001	3.34	.0063
Europe	3	Microscopy	0.00 (0.00–0.00)	34	-	.22	-	.01
	3	PCR	0.01 (0.00–0.03)	54	4.1	.11	-	-
	3	RDT	0.00 (0.00–0.00)	0	0.59	.74	-	-

Abbreviations: CI, confidence interval; PCR, polymerase chain reaction; RDT, rapid diagnostic testing.

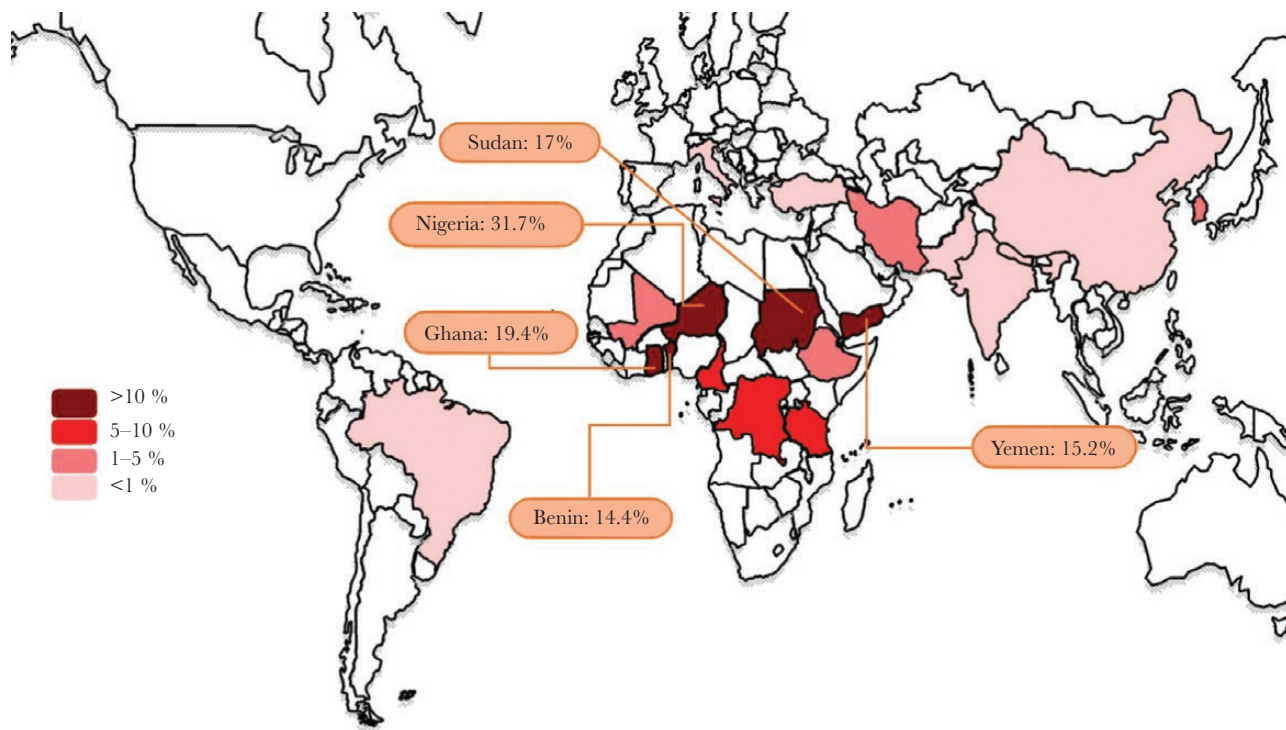


Figure 5. Overall malaria prevalence among asymptomatic blood donors in different geographical regions.

Blood donor selection and deferral instructions are the initial fundamental steps in ensuring safety and preventing transfusion-transmissible infections. Understanding risk factors and the timing of the disease is key in the donor selection process. Self-reported history and risk factors associated with malaria infection in relation to residence or travel to malaria-endemic areas are used as part of a primary donor screening tool in nonendemic areas [24]. However, screening tools developed for nonendemic countries are not applicable to malaria-endemic areas. Similarly, although the majority of blood recipients in malaria-endemic areas are exposed to malaria, the degree of immunity this provides and the clinical impact of TTM in these settings are unknown. Given that the majority of blood recipients in low- and middle-income countries are children and pregnant women [23] and only a few parasites in a unit of blood are enough to cause infection in exposed individuals [18], international guidelines recommend malaria screening in blood donors [25]. The World Health Organization (WHO) guidelines on blood donor selection emphasize the importance of implementing screening tools tailored to the local context for all transfusion-transmissible infections including malaria [25]. Given the wide variation of malaria prevalence in donors, it is essential for each country to define the donor population with a high risk of infection and establish donor selection criteria. A geographical model for TTM displaying prevalence of malaria infection among blood donors could easily be incorporated into this primary screening tool. Our meta-analysis indicates that healthy donors with certain risk factors have increased odds of having malaria infection, such

as being a commercial donor, residence in an urban area, and first blood transfusion. It is important to note that in the subgroup analysis, the majority of studies reporting prevalence in urban vs rural donors included donors residing in urban settings, which might have influenced this observation. Identification of risk factors nevertheless may help to narrow down donor selection criteria, particularly in countries where there is no agreed-upon framework to screen all donations for parasitemia. Exclusion of malaria-positive or high-risk blood donors may not be feasible in some settings due to the high demand for blood transfusion. In areas with high prevalence of malaria infection, clear donor deferral instructions could nevertheless be implemented to ensure continuous blood supply.

An important caveat for determining the actual burden of *Plasmodium* infection in the blood donor population and accordingly understanding the risk of TTM is to detect low-level parasitemia. Additionally, there is very limited evidence to inform which malaria screening methods are effective for use by transfusion services in malaria-endemic settings. Although the microscopic diagnosis is the gold standard technique [26], in recent years, molecular methods such as PCR have been developed, providing increased sensitivity [27]. We observed lower prevalence detected by molecular techniques compared with microscopy. The difference observed in prevalence might be due to the differences in the studies included; only 14 studies reported prevalence among blood donors using molecular techniques, the majority of which were conducted in malaria-nonendemic countries. Although PCR is the most sensitive and possibly ideal

screening method for malaria infection in the blood donor population, due to the costs involved and expertise required, molecular methods cannot easily be implemented in every setting. RDTs are an alternative where good quality services are not readily available [28]. Serological tests can also be applied to detect malaria antibodies for screening blood donors, with the caveat that a positive test does not necessarily indicate active infection, and the majority of residents in endemic areas would have antimalarial antibodies, so serologic tests are likely unhelpful for screening blood donors in malaria-endemic settings [24, 29]. Therefore, a combination of different approaches needs to be consolidated to ensure the safety of blood transfusions by screening with a diagnostic technique that is sensitive enough to detect low-level parasitemia, taking into consideration the costs and the laboratory personnel expertise obtainable in a given setting.

This meta-analysis has several strengths. First, this is the first study examining the global epidemiology of malaria infection in the asymptomatic blood donor population. Second, we reported differences in the prevalence of malaria infection according to the screening methods used in studies. In contrast, the most important study limitation relates to the inherent nature of systematic reviews, based on differences in the studies included in this review; that is, the methodology, quality, different diagnostics tests with variable sensitivity and specificity used in various studies, and data on the malaria prevalence are not available in many parts of the world.

CONCLUSIONS

This systematic review demonstrates that TTM is one of the most significant transfusion-associated infections, especially in Sub-Saharan Africa, compared with other transfusion-linked infections. World Health Organization guidelines for screening and deferral need to be reinforced in each country and tailored to the local context. Future work must aim to understand the clinical significance of transfusion-transmitted malaria in malaria-endemic settings.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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