REVIEW ARTICLE

Transfusion-Transmitted Malaria in Countries Where Malaria Is Endemic: A Review of the Literature from Sub-Saharan Africa

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(See the editorial commentary by Allain, on pages 1199–1200.)

Although international policies recommend that blood for transfusion should be screened for transfusion-transmitted infections, malaria screening is not performed in most malaria-endemic countries in sub-Saharan Africa. Our literature review identified 17 relevant studies from the period 1980–2009 and indicated that the median prevalence of malaria among 33,029 blood donors was 10.2% (range, 0.7% in Kenya to 55.0% in Nigeria). Malaria screening methods, including microscopy (used in 16 of 17 studies), are either insensitive or impractical for donor screening in resource-poor countries. Even if a suitable screening method were available, rejection of malaria-positive donors would jeopardize the blood supply. Only 1 study established the prevalence of parasitemia among transfusion recipients. This review highlights the need for more evidence about the clinical impact of transfusion-transmitted malaria to justify the policy of screening for blood for malaria in areas of endemicity and for a critical analysis of the feasibility of implementing such a policy and its effect on blood supply.

Blood for transfusion in most malaria- endemic countries in sub-Saharan Africa (SSA) is not tested for malaria [1], despite recommendations that all donated blood should be tested for malaria where "appropriate and possible" [2] and that there should be quality assured testing for transfusion-transmissible infection [3]. There are several reasons why it is difficult to screen blood for malaria in SSA. Severe blood shortages are widespread and would be exacerbated by rejecting blood that contained malaria parasites. Most malaria tests are not sensitive enough to detect low levels of parasites, and there is no evidence-based guidance to indicate which malaria screening methods are effective for use by transfusion services in malaria-endemic countries in SSA or what action should be taken if the donated blood tests positive.

An adequate supply of blood is essential for reducing mortality and morbidity in SSA, especially among young children and pregnant women [4], but critical shortages are common. For example, in SSA, 26% of maternal hemorrhage deaths during the period 1970–2007 were due to lack of available blood for transfusion [5]. Some African countries, such as Benin [6], have reported malaria prevalence rates in blood donors of >30%. If all of these donors were rejected, the amount of blood available for transfusion would be significantly reduced, undoubtedly leading to increased mortality.

When malaria is transmitted through a blood transfusion to a nonimmune recipient, it can be rapidly fatal. The majority of recipients of blood transfusions living in malaria-endemic areas in SSA are semi-immune to malaria [7], but the degree of protection that this immunity confers against transfusion-transmitted malaria

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is unknown. Young infants in areas where malaria is endemic who have not had repeated exposure to the parasite may be regarded as a nonimmune recipients. Therefore, they may be as susceptible to transfusion-transmitted malaria as a nonimmune person who lives in a non–malaria-endemic country. The clinical severity of transfusion-transmitted malaria is likely to be very different in countries where it is endemic from that in countries where it is not endemic. Because of their immunity to malaria, blood donors in SSA are able to harbor low levels of parasites without developing clinical symptoms [8]. Any malaria screening test used by the transfusion services therefore needs to be very sensitive [9]. Transfusion services in countries where malaria is not endemic use travel history and serologic tests to identify donors at risk of transmitting malaria. However, the majority of residents in malaria-endemic countries, such as Nigeria [10], have anti-malarial antibodies, so serologic tests are unhelpful for screening donors in malaria-endemic SSA.

Ninety-five percent of transfusions in SSA involve whole blood rather than components. Whole-blood and red blood cell concentrates are the most common source of transfusion-transmitted malaria. Platelets, fresh frozen plasma, and leukocytes may infrequently transmit malaria, but in contrast to the situation in more wealthy countries, these products are not in common use in SSA [11–13]. Malaria microscopy is by far the most frequently used method in SSA for screening blood for transfusion, but it has limited sensitivity. A bite from an infected mosquito may cause malaria by introducing as few as 15 parasites [14]. A single parasite identified on microscopic evaluation of a thick blood film (4 μL) is equivalent to ~10,000 parasites in a 450-mL unit of blood.

In view of the lack of evidence to guide better practice about transfusion-transmitted malaria, providers and users of blood transfusions in SSA recently identified transfusion-transmitted malaria as a priority topic area for research [4]. This review synthesizes existing knowledge about the prevalence of malaria in blood donors in malaria-endemic countries in SSA, the effectiveness of screening methods, and the risks to recipients of receiving malaria-infected blood, to inform policy development and guide future research.

METHODS

Identification and selection of studies. To identify potential studies, we conducted searches of the PubMed, Ovid, Scopus, and Web of Knowledge electronic databases for articles published during the period from January 1980 through May 2009 using combinations of the following keywords: "blood donors," "blood transfusion," "malaria," and "transfusion-transmitted infections." The full texts of any articles that appeared relevant were retrieved. We also searched for relevant studies by screening titles of references on the World Health Organization (WHO) Web site, by checking the lists of references in relevant studies and reviews, and by identifying others identified through personal communications. We only included studies in the review that met all the following criteria: they were conducted in SSA, they focused on blood donors or blood donated for transfusion, and they provided original quantitative data about the prevalence of malaria in donors or donated blood.

Ensuring quality and consistency of data extraction. Two authors (A.K.O.-O. and I.B.) assessed all studies and agreed on those that met the criteria and should therefore be included. A data extraction form was designed to collect information that consultations with clinicians and transfusion service staff in SSA had identified as important in guiding decisions about if, when, and how to reduce the risks of transfusion-transmitted malaria. Data extracted comprised information about the malaria transmission season when the study was conducted, the diagnostic method used to detect malaria parasites, the malaria species identified, the recipients of malaria-infected blood, and recommendations arising from the study. Two authors (A.K.O.-O. and I.B.) independently extracted data from the studies using the form, which had been pretested on 3 studies. Any discrepancies in data extraction by the 2 authors were reconciled through discussion. Authors of articles were contacted to provide additional information if data were missing from the published studies.

Data analysis. Summary statistics were used for quantitative data, and medians, means, and ranges were calculated to describe malaria prevalence in donors in SSA. Frequencies for study variables such as testing method, transmission season, and type of transfusion recipients were determined from information provided in the articles.

To ensure uniformity and to enable prevalence to be compared between studies, the season when each study was conducted was classified as either high or low transmission season. We identified the transmission season by comparing information provided by authors about the time when the study was conducted, with published information about malaria transmission rates for the study location [15–17] . The authors' own determinations of high or low transmission season were used if they did not state the months in which the study was conducted.

RESULTS

One hundred thirty-nine studies were identified using the search terms; 124 of these were rejected because the abstracts showed they did not fulfil the selection criteria. Eight additional studies were identified from a search of the bibliographies of the 15 selected articles. After a detailed review of the full publications, 6 additional studies were rejected because they were review articles (2 studies), they were not directly related to transfusion-transmitted malaria (2 studies), they were not performed in SSA (1 study), or they duplicated information

from a study already included in this review (1 study). Seventeen publications [6, 7, 10, 18–31] were finally included in the review (Table 1). Three were published during the period 1980–1989, 4 were published during the period 1990–1999, and 10 were published in or after 2000. Nine of the studies were from Nigeria, 1 was from northern Nigeria, and 8 were from the south of the continent. The other studies were from Benin (1 study) Congo (1 study), Malawi (1 study), Kenya (2 studies), and Sudan (3 studies). Two studies were conducted in high malaria transmission season [6, 23], and 13 [7, 10, 18–21, 24–28, 30, 31] in both high and low seasons. In 2 studies [22, 29], the season was not stated. One study compared low- and high-endemicity regions in Kenya [19].

In all the studies except 1 [19], malaria screening was performed using microscopy. In Kenya, malaria infection was identified using an automated hematology analyzer, which detects malaria pigment in white blood cells [19]. The total number of donors (or donated blood) tested for malaria across all the studies was 33,029 (median, 444; range, 50 [23] to 12,375 [18]), with a median prevalence of 10.2% (range, 0.67%–55.0%). Malaria prevalence in donors (or donated blood) varied by geographic location and by season. Prevalence was higher in the 10 west African studies (median prevalence from Benin and Nigeria, 30.2%), compared with the 7 studies from all other countries (median prevalence, 6.4%). In Kenya, malaria prevalence in donors was 8.6% in an area of high endemicity, compared with 1.2% in a low-endemicity region. Enough studies had been conducted in Nigeria to allow an intracountry comparison of malaria prevalence in donors between high [10, 23, 25] and low [10, 25] transmission seasons. The median prevalence was 41.0% (range, 40.0%–55.0%) in high season, 22.9% (range, 19.0%–26.9%) in low season, and 26.9% (range, 4.1%–55%) in studies that covered both seasons [10, 21, 24–28].

Several studies compared microscopic evaluation with other malaria screening methods. The prevalence in Nigeria by indirect fluorescent antibody testing was 86%, compared with 7.8% for microscopic evaluation [21]. A Nigerian study found a prevalence of malaria antibody of 100% by both indirect fluorescent antibody and enzyme-linked immunosorbent assay testing, compared with a parasite prevalence found by microscopy of 41% (during high season) and 19% (during low season) [10]. Using polymerase chain reaction (PCR) as the gold standard, the sensitivity of microscopy and immunochromatography in a Sudanese study were 61.7% and 66.7%, respectively (Table 1) [29].

Twelve studies reported the type of *Plasmodium* species that was present in the donor blood. In 4 studies [10, 21, 23, 24], *Plasmodium falciparum* was the only species present, and 8 studies [6, 7, 18, 22, 25–27, 31] found >1 species of *Plasmodium* in the blood. Overall, 88.7% of infections were due to *P. falciparum,* 9.2% were due to *Plasmodium malariae,* 0.4% were due to *Plasmodium ovale,* and 0.3% were due to *Plasmodium vivax.* A total of 1.5% were mixed infections; in 1 of these mixed infections, *P. falciparum* was the predominant species identified, but other species were not specified [27] (Table 1).

Five studies provided information about the recipients of malaria-infected blood transfusions [7, 22, 23, 25, 31]. The recipients were neonates [23], children, and pregnant women [25], and the reasons for transfusion were anemia, septicemia, bleeding [31], or heart surgery. Only 1 study [31] determined the prevalence of malaria among recipients of blood transfusions (Table 1). In this study, 397 patients who tested negative for malaria by microscopic evaluation before transfusion received a total of 1354 units of blood. Fourteen patients (3.5%) had malaria when tested by microscopic evaluation 4 days after transfusion. Eight patients had received a single transfusion, and the remainder received multiple transfusions. Posttransfusion malaria was observed in all 12 patients (100%) who received blood known to contain malaria parasites. Interestingly, 2 of the patients who received multiple transfusions developed malaria, although no parasites had been detected in the blood that they received. Overall, posttransfusion malaria accounted for 31.3% of cases of posttransfusion fever.

Authors of the 17 studies made 34 recommendations about reducing transfusion-transmitted malaria in countries where malaria is endemic, of which 20 were based on study findings. The recommendations covered policies, universal or targeted screening of blood, and universal or targeted treatment of either recipients or donated blood (Table 2).

DISCUSSION

The aim of this review was to synthesize existing knowledge about the prevalence of malaria in blood donors in malaria-endemic countries in SSA, the effectiveness of malaria screening methods used by transfusion services in SSA, and the risks to recipients. All the studies that met the criteria for inclusion in the review were conducted in the high malaria transmission season or during both low and high seasons, and overall, the median prevalence of malaria in blood donors or donated blood was 10%. Because of the wide seasonal and geographic variation (from <1% in Nairobi, Kenya, to >50% in Nnewi, Anambra State, Nigeria), this median prevalence should be interpreted with caution and cannot be extrapolated across the region.

This review demonstrates that malaria is one of the most important transfusion-transmitted infections in SSA. For example, among donors, the prevalence of human immunodeficiency virus in the region ranges from 0.5% to 16%, the prevalence of hepatitis C virus infection ranges from 0.5% to 12.3%, and the prevalence of hepatitis B virus infection ranges from 2.5% to 20% [32]. Compared with other transfusion-transmitted infections, the very high prevalence of malaria among blood donors has been almost totally ignored.

Table 1. Characteristics of Studies Included in the Review

Country	Year of publication	Malaria prevalence among blood donors, %		No. of donors or donated units screened for malaria	Transmission season	Malaria species (distribution of parasite species, %)	Was infected blood transfused?	Reference
		By microscopic evaluation	By tests other than microscopic evaluation					
Benin	2000	33.5	Not done	355 donors	High	*Plasmodium falciparum* (97), *Plasmodium vivax* plus *Plasmodium ovale* (3.3)	Not stated	[6]
Congo	1993	8.5	Not done	12,375 donors	High and low	*P. falciparum* (92), *Plasmodium malariae* (7), *P. ovale* (3)	Not stated	[18]
Kenya	1987	1.7	Not done	4,470 units	High and low	*P. falciparum* (88), *P. malariae* (12)	Yes	[7]
Kenya	2005	Not stated	0.67 (low-endemicity area) and 8.6 (high-endemicity area) [a]	2387 units (low-endemicity area) and 2168 units (high-endemicity area)	High and low	Not stated	Not stated	[19]
Malawi	2007	5.9	Not done	1714 donors	High and low	Not stated	No	[20]
Nigeria	1987	7.8	86 (by IFA test)	115 donors	High and low	*P. falciparum*	Not stated	[21]
Nigeria	1989	4.6	Not done	480 donors	Not stated	*P. falciparum* (73), *P. malariae* (23), *P. falciparum* plus *P. malariae* (5)	Yes	[22]
Nigeria	1995	41.0 (high season) and 19.0 (low season)	100 (by IFA test) and 100 (by ELISA)	224 (high season) and 192 (low season)	High and low	*P. falciparum*	Not stated	[10]
Nigeria	1996	40.0	Not done	50 donors	High	*P. falciparum*	Yes	[23]
Nigeria	1997	4.1	Not done	364 donors	High and low	*P. falciparum*	Not stated	[24]
Nigeria	2005	55.0 (high season) and 26.9 (low season)	Not done	444 donors	High and low	*P. falciparum* (77), *P. malariae* (23)	Not stated	[25]
Nigeria	2006	40.9	Not done	325 donors	High and low	*P. falciparum* (98), *P. malariae* plus *P. falciparum* (2)	Not stated	[26]
Nigeria	2007	10.2	Not done	1018 donors	High and low	*P. falciparum* "predominantly"	Not stated	[27]
Nigeria	2008	51.5	Not done	200 donors	High and low	Not stated	Not stated	[28]
Sudan	2004	6.5	Not done	1564 donors	High and low	*P. falciparum* (98), *P. vivax* (2)	Yes [b]	[31]
Sudan	2005	13.0	21 (by PCR) and 18 (by rapid test)	100 donors	Not stated	Not stated	Not stated	[29]
Sudan	2005	6.2	Not done	4484 units	High and low	Not stated	Not stated	[30]

NOTE. ELISA, enzyme-linked immunosorbent assay; IFA, indirect fluorescent antibody; PCR, polymerase chain reaction).

[a] Automated analyzer used to detect malaria pigment in white blood cells.

[b] Four days after transfusion, 3.5% of recipients had parasites found by microscopic evaluation, including 100% of those who received malaria-positive blood.

Table 2. Recommendations from Published Studies for Reducing Transfusion-Transmitted Malaria in Endemic Countries

Recommendation	Reference(s)
Blood donation policies should incorporate malaria screening	[24, 26, 27]
Donors should be screened for malaria before donation	[10, 24, 31, 25]
Blood for neonates should be screened for malaria	[23]
All blood infected with malaria should be rejected	[22]
Blood screened for malaria should be retained but marked negative or positive	[25, 28]
All recipients of malaria-infected blood should be treated for malaria	[10, 25, 28]
All neonates should be treated after every transfusion	[23]
Antimalarials should be added to donated blood to eradicate parasites in vitro	[30]
Presumptive treatment for all recipients	[6, 21, 27]

Although healthy adults living in malaria-endemic areas have some immunity to developing clinical malaria, the recipients of blood transfusions in SSA are predominantly children and pregnant women who are likely to be immunologically compromised. We were not able to find any systematic studies that investigated the risk of developing malaria after receiving an infected blood transfusion. One study, which investigated posttransfusion parasitemia [31], found that all 12 recipients of infected blood had malarial parasitemia after—but not before—transfusion. However, because individuals living in malarious areas often harbor malaria parasites without developing symptoms, it is crucial to know whether malaria-infected blood transfusion leads to clinical malaria and whether some groups of recipients are particularly vulnerable. Without more evidence about the impact of malaria-infected blood on different types of recipients, it will not be possible to develop any rational policies about whether to screen blood for malaria in countries where it is endemic.

Despite this critical lack of evidence about the clinical impact of transfusion-transmitted malaria, international policies recommend screening blood for transfusion for malaria [33]. Because only a few parasites in a unit of blood are sufficient to cause infections in susceptible individuals, there is a need for screening tests to be highly sensitive. Our review has demonstrated that microscopic evaluation is the method used by almost all transfusion services in SSA for malaria screening. However, microscopy is far too insensitive to be recommended as the usable screening test for transfusion services in malaria-endemic SSA, and posttransfusion malaria has been reported in recipients of blood that has tested negative by microscopy [31]. Therefore, microscopic evaluation is likely to significantly underestimate the prevalence of parasitemia in blood donors. Serological screening is unhelpful, because the majority of individuals in malaria-endemic areas have anti-malaria antibodies. Alternative malaria-screening methods all have drawbacks, make them inappropriate for use by transfusion services in SSA [10, 21]. Rapid diagnostic tests have a similar sensitivity to microscopic evaluation, although sensitivity decreases when the parasite load is <100 parasites/μL [34]. PCR-based [35] diagnostic methods for malaria surpass microscopic methods in both sensitivity and specificity and may detect malaria at a parasite load of 1 parasite/μL, compared with 50–100 parasites/μL for microscopic evaluation [35]. Quantitative nucleic acid sequence–based amplification (NASBA) is 1000 times more sensitive than standard microscopic evaluation [36]. Although they are highly sensitive, genomic amplification methods, including PCR and quantitative NASBA, are not currently affordable or practical for routine malaria screening by transfusion services in resource-poor countries.

Even if appropriate screening tests were available, the wide variation in malaria prevalence in donors across SSA means that malaria-screening policies need to be tailored to the local context. In areas with a low prevalence of malaria parasites in donors, exclusion of malaria-positive donors may be a reasonable approach, because this would not have a major impact on the amount of blood available for transfusion. In contrast, even without adjusting for the insensitivity of microscopic evaluation for malaria, exclusion of malaria-positive donors would reduce the blood supply by more than one-third in high-transmission areas in west Africa. This would undoubtedly result in increased morbidity and mortality, predominantly among women and children.

Several alternatives to donor screening for reducing the burden of transfusion transmitted malaria have been published. These include adding antimalarials to the blood pack, marking units that test positive for malaria, and only screening blood destined for neonates. Treating all transfusion recipients in areas of high malaria prevalence with antimalarials is another option recommended by the WHO [37] and by other authors [6, 18, 21, 27, 28]. However, no evidence to support this recommendation is provided in the studies we reviewed, and widespread chloroquine resistance means that the more expensive combination antimalarials would be needed. Furthermore, the cost of preventing transfusion-transmitted malaria by preemptive treatment of recipients with either sulfadoxine-pyrimethamine or artemesinin-based combination antimalarial treatment is

considerably higher than that of pretransfusion screening using automated detection of malaria pigment in white blood cells [19]. There are some promising new technologies, such as pathogen reduction measures, that have the potential to reduce transfusion-transmitted malaria [38, 39]. In wealthy countries, blood is transfused as separate components. Separate components, such as plasma and platelets, may contain the exo-erythrocytic forms of malaria parasites, and *P. falciparum* in such components has been shown to be highly sensitive to inactivation by photochemical treatment with amotosalen and long-wavelength ultraviolet light [40]. However, in resource-poor countries, >95% of blood is given as whole blood, and no pathogen-reduction systems have been developed for whole blood [41]. The critical lack of evidence about the clinical impact of transfusion-transmitted malaria and the absence of an effective and feasible screening method are preventing rational decision-making about when and how to screen blood for malaria.

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