Vox Sanguinis (2006) **90**, 77–84

DOI: 10.1111/j.1423-0410.2006.00733.x

REVIEW

Malaria and blood transfusion

A. D. Kitchen[1] **& P. L. Chiodini**[2]

[1] *National Blood Service, London, UK*
[2] *The Hospital for Tropical Diseases, London, UK*

Vox Sanguinis

The transmission of malaria by blood transfusion was one of the first recorded incidents of transfusion-transmitted infection. Although a number of different infections have been reported to be transmitted by transfusion since then, on a global scale malaria remains one of the most common transfusion-transmitted infections. Transfusion-transmitted malaria can have serious consequences, as infection with *Plasmodium falciparum* may prove rapidly fatal. Ensuring that, in non-endemic countries, the blood supply is free from malaria is problematical, especially as travel to malarious areas is increasing and there is some spread of the disease into new areas, as well as a resurgence of malaria in areas where previously it had been eradicated. In non-endemic countries, donor deferral can be effective, but clear guidelines are needed. In endemic countries the problem is far greater as the majority of donors may be potentially infected with malaria parasites. In both situations, the simple deferral of donors may be wasteful and can eventually erode the donor base. Thus, other strategies are needed to ensure safety with sufficiency. However, the screening of donations for evidence of malaria is not without its problems. Although the examination of blood films is still the basis for diagnosing acute malaria, in most situations it is not sufficiently sensitive for blood bank screening. In non-endemic countries, donor deferral in combination with screening for specific antimalarial immunoglobulin provides an effective means of minimizing the risk of transmission. In endemic countries, more specific donor questioning, consideration of seasonal variation and geographical distribution may help to identify the population of donors who are most likely to be infected. In addition, the administration of antimalarials to transfusion recipients may help to prevent transmission. Nonetheless, no matter what strategy is adopted, it is likely that cases of transfusion-transmitted malaria may still occur, so malaria must always be considered in any patient with a febrile illness post-transfusion.

Key words: antibody, blood transfusion, deferral, malaria.

Received: 6 April 2005,
revised 27 October 2005,
accepted 27 October 2005,
published online 11 January 2006

History

The first case of transfusion-transmitted malaria (TTM) was reported in 1911, when intercontinental travel was an unattainable dream for most of the world's population, and well before commercial air travel became established. Since that time, international travel has become commonplace, and effectively, ignoring any restrictions caused by conflict or political forces, there is no part of the world that is not accessible. With this freedom to travel, however, comes the risk of exposure to the diseases endemic in different parts of the world. The major one of these is malaria. Globally, malaria presents a significant disease burden with estimates of up to 150 million infections annually with 1–2 million deaths per year, mainly in sub-Saharan Africa. Although vast sums of time and money have been spent in trying to control malaria, the results of this have been variable, with instances of control programmes failing as a result of the breakdown of public health systems, caused, for example, by conflict, the general lack of resources needed to sustain them, or the migration of populations. Furthermore, the spread of chloroquine- (and,

Correspondence: A. D. Kitchen, National Blood Service, North London, London NW9 5BG, UK
E-mail: alan.kitchen@nbs.nhs.uk

later, multidrug-) resistant *Plasmodium falciparum* malaria, coupled with an ever-increasing number of travellers to its areas of endemicity, has led to an increasing proportion of malaria caused by *P. falciparum* among international travellers returning from trips to malarious areas. In 2004 there were five reported deaths in a total of 1660 cases of imported malaria in the UK (HPA Malaria Reference Laboratory, London, UK).

Review of worldwide data recorded from 1911 to 1979 by Bruce-Chwatt [1,2] found that the reported incidence of TTM increased from six to 145 cases per year. In the early years, *P. vivax* was the most frequently reported species, but by the 1950s *P. malariae* predominated, followed by *P. vivax*, *P. falciparum*, mixed infections and *P. ovale*. In the 1970s, *P. vivax* was again the commonest, followed by *P. malariae* and *P. falciparum*, although, ominously, the proportion of the last had risen substantially.

To reinforce this, the last five cases of TTM reported by the UK Blood Services (all in the southeast of England) were caused by *P. falciparum* [3–5]. This can be seen directly in the figures for malaria imported into the UK in recent years. Before 1986, there were more cases of *P. vivax* than *P. falciparum*, but since then *P. falciparum* has been the single most common imported species. Indeed, the total for *P. falciparum* now exceeds that of the other three species combined. In 2004, 74% of imported malaria was caused by *P. falciparum* (HPA Malaria Reference Laboratory). The figures for imported malaria from 1985 to 1995 reported by other European centres also show a substantial proportion caused by *P. falciparum* – 82·2% in France and 59·4% in Italy – compared with 38·5% in the USA over the same period [6].

In the USA, there are ≈ 1000 reported cases of imported malaria per annum, compared with ≈ 2000 in the UK [6]. In 1990–1999, the USA reported 14 cases of TTM, 10 (71%) of which were caused by *P. falciparum* [7].

Transmission of malaria has been reported to occur mainly from single-donor products [8]: red cells, platelets, white cell concentrates, cryoprecipitate and from frozen red cells after thawing and washing. Transmission from single-donor fresh-frozen plasma has not been reported. Transmission from cryoprecipitate is rare and likely to reflect the preparation method and the degree to which the starting plasma is cell free.

Malarial risk-reduction strategies

There are two main aspects to bear in mind when considering malaria risk and transfusion: first, the malaria risk associated with any individual donor; and, second, the ability of the systems to identify and manage the donor and any donation. It is here that there are fundamentally different approaches taken by different blood transfusion services: differences in the overall approaches taken between endemic and non-endemic countries; and differences in the approaches taken between individual non-endemic countries.

Endemic countries

Differentiation of cases of TTM from natural infections is very difficult in endemic areas as malaria occurring post-transfusion can be the result of natural infection via a mosquito bite, rather than from the transfusion received. Furthermore, in endemic areas, many of the donors and patients are already infected with, or are at high risk of, malaria infection. Identifying low-risk individuals is virtually impossible. One approach is to use Giemsa-stained thick films or rapid diagnostic tests (RDTs) for malarial antigen to identify those donors with higher levels of parasitaemia. However, it is clear that this approach only identifies the proportion of individuals with a parasitaemia above the detection limit for these techniques. It does not, however, prevent transmission from units of blood with parasitaemia too low to detect by microscopy or RDTs. There are additional strategies that can be implemented, depending upon the geography of the country, the periodicity of malaria (seasonal or year round), the type and age of the donors, and the age, gender and underlying condition of the patients, together with their existing malaria status. For example, the segregation of donations collected from low- and high-risk localities (e.g. lowlands and highlands), with specific targeting of the donations from low-risk donor groups to low risk and the most vulnerable recipients. Routine antimalarial treatment of transfusion recipients is also performed in some areas. Such strategies are pragmatic approaches that are not absolute in their effectiveness, but can help to lessen the risk of TTM in such situations. It has been argued that many recipients in endemic areas will be immune to the plasmodium species present where they live, and therefore less likely to be adversely affected if they are transfused with blood from an infected donor [9]. However, it must be remembered that, paradoxically, many transfusions in these countries are to children with acute severe anaemia caused by malaria. These children are unlikely to have yet become semi-immune, and thus must be considered to be susceptible to TTM.

However, there remains the fact that, despite the different strategies adopted, it is virtually impossible to safeguard the blood supply from malaria in endemic countries [10,11], and often the transfusion of blood, together with the judicial use of antimalarial drugs, is necessary to minimize the occurrence of TTM in the recipient. In addition, promoting the appropriate clinical use of blood also has a role in minimizing TTM, by ensuring that patients are not exposed unnecessarily.

Non-endemic countries

Whilst overall, at any one time, the number of individuals with any malaria risk represents only a small proportion of

the overall number of donors, the number of these donors is cumulative as, year-on-year, donors either visit malarious areas for the first time or individuals originally from malarious areas present as donors for the first time. Thus, there is a high reliance upon appropriate donor-deferral guidelines, and on the accuracy and clarity of the information gleaned from the donors about their travel and any consequent malaria risk.

One simple approach taken by many countries is to identify and defer permanently any 'malaria-risk' individuals. This approach has the advantage of clarity in action, but poses a number of problems – one is that of identifying reliably the 'malaria-risk' individuals and another is the cumulative nature of malaria in a world where people are travelling further and more frequently, and malaria is spreading into countries previously considered malaria free. Permanent deferral of an increasing donor group may very quickly reduce the overall donor base. Few countries can afford to lose donors in such numbers and on a continual basis, especially when most of these donors have not been infected and could be reinstated as active donors.

Thus, an increasing number of non-endemic countries, and indeed some endemic countries, are implementing selective screening strategies for 'malaria-risk' donors, utilizing specific *in vitro* screening to look for any evidence of malarial infection. This approach still relies upon specific donor-selection criteria and the use of a limited deferral period, but does then enable the reinstatement of those donors who have no evidence of infection. In both approaches, the need for a set of clear and reliable donor-deferral criteria is paramount. These criteria are the same regardless of whether there is to be permanent deferral or screening and reinstatement; the most important aspect is that all donors with any malarial risk are identified at the point of donation and the appropriate action can then be taken.

Donor and donation screening

Screening of donors

Screening of donors by questionnaire is thus the first, and in many countries the only, step in the prevention of TTM. The development of donor-deferral criteria that are appropriate to the country and to the donor population is central to donor screening. It must be understood, however, that complete prevention of TTM may not be possible [12]. Any strategy developed must focus on minimizing the risk of introducing malaria parasites into the blood supply, but without excluding unnecessarily any potential donors, especially as many donors deferred for any significant period of time do not return.

Determining reliable deferral guidelines is an area of some debate, but there is a lot that can be learnt from any reported cases of TTM. Aside from cases where errors allowed clearly identifiable 'malaria-risk' donations to be released for clinical use, the analysis of cases of TTM has facilitated the identification of specific 'high risk' donor groups and weaknesses in guidelines, and the subsequent amendment of the deferral criteria to close the gaps [5].

Semi-immune donors

The main risk of introducing malaria parasites into the blood supply in most non-endemic countries comes from semi-immune individuals. Semi-immunity develops in those individuals who generally live in areas with high entomological inoculation rates (EIR), and are thus multiply exposed to malaria. The EIR is an indication of the daily infectious bite rate over a period of time, expressed as the average number of infective bites per person per unit time, a factor of importance when assessing risk in both residents and travellers. In Africa, for example, the EIR ranges from 1 to 1000, and even in areas with a low EIR, the prevalence of *P. falciparum* can exceed 40%; in the majority of areas with an EIR of 200 or more, the prevalence rate is at least 80%. A dynamic balance develops in the individual, whereby they are generally well and asymptomatic despite the simultaneous presence of both high-titre antibody and low-level parasitaemia in their peripheral blood. Whilst those who are semi-immune were often born in and former residents of malaria-endemic areas, it is important to note that expatriates resident for long periods of time in malarious areas can also become semi-immune. For example, a case of TTM caused by *P. falciparum* was thought to have arisen from blood donated by a person who had worked in Africa for 10 years, had a history of falciparum malaria, and failed to give a history of malaria or foreign residence when they donated [3,13]. In contrast, those donors without significant malarial immunity are likely to be symptomatic if they have malaria parasites in their blood and thus are unlikely to attend a donor clinic or, should they attend, be rejected when questioned about their health [4,13]. The potential role of semi-immune individuals as a source of TTM is further illustrated by Mungai *et al.* [14] who analysed the characteristics of donors implicated in cases of TTM in the USA from 1963 to 1999. Whereas from 1963 to 1969, 45% of the 11 donors, and from 1970 to 1979, 38% of the 24 donors, were former residents of malarious areas or recent visitors to their country of origin (itself malarious), these figures increased to 100% of the 17 donors from 1980 to 1989, and to 91% of the 12 donors from 1990 to 1999.

Acutely infected donors

Although cases of acute malarial infections in travellers from non-endemic countries are not uncommon, such cases tend to be symptomatic, medical advice would normally be sought and the donors would be identified by history taking prior to

donation. Furthermore, the vast majority of *P. falciparum* infections in such individuals present within 6 months of leaving a malarious area, a time period during which these individuals would be excluded from donation.

Deferral guidelines

The primary approach to donor screening is therefore that of history taking to identify any possible malaria risk associated with travel or residency. Important questions to be answered are the geographical location (i.e. whether or not a potential donor has visited or lived in a malarious area), the length of time in any malarious area, the length of time since last being in a malarious area, and any previous history of malaria.

- Location. In general, countries are identified as being malaria risk or not. However, some transfusion services subdivide countries according to geographical zones within each of them, but this results in a substantial increase in the complexity of the assessment and in the risk of errors being made. Similarly for seasonality, such distinctions are not absolute, and even in the 'non-malarial' season there may still be some residual transmission, albeit at a significantly lower level, but nonetheless the risk remains.
- Period of residence in a malarial area. The longer the period of residence, the greater the risk of an individual becoming semi-immune and thus asymptomatic whilst parasitaemic. The residency status applies regardless of whether the individual was resident as a child or as an adult, because long-term exposure as an adult can also result in an individual becoming semi-immune to *P. falciparum*.
- Period since last in a malarial area. Any visit to a malarious area could result in infection, and sufficient time must be allowed to elapse both for the malarial infection to become clinically evident in non-immunes and for any immune response to an acute infection to develop. Deferral for at least 6 months following the last visit to a risk area will allow sufficient time for either symptoms or an antibody response to develop.
- History of malaria. Although permanent deferral is commonly adopted, alternative strategies may be appropriate depending upon the time since the last symptoms/treatment.

Donor deferral is thus based upon the risk factors identified in relation to the four key factors identified above, with different countries developing their own specific criteria based upon their specific needs, resources and the numbers of donors involved. For example, since July 1995, the guidelines operating in Canada have required that donors reporting a history of diagnosis or treatment of malaria at any time in the past be permanently deferred from donating components for direct transfusion [12]. In the USA, prospective donors who have had a diagnosis of malaria are deferred for 3 years after becoming asymptomatic [14]. In the UK, prospective donors who have had a diagnosis of malaria are permanently excluded from donation in the absence of a validated malaria antibody test, but can be reinstated if malarial antibody negative for at least 6 months after the cessation of treatment or symptoms [15].

It is recognized that any such policies will invariably result in some unnecessary deferrals in some donor groups. It is common to find a 'history of malaria' in individuals from malaria-endemic areas, as fevers are often labelled as malaria on clinical grounds without laboratory confirmation [12]. Nevertheless, permanent deferral, in the absence of any donation screening, does provide a useful margin of safety as this group of potential donors is likely to contain the semi-immune individuals. Furthermore, a 3- or even a 5-year deferral would not totally exclude semi-immune individuals, as cases of TTM have been linked to donations taken more than 5 years after the last potential exposure of the donor to malaria. For example, in a United States series covering 1963–1999 [14], the longest interval between travel to a malarious area and transmission of malaria via a blood transfusion was 5 years for *P. falciparum*, 2·5 years for *P. vivax*, 7 years for *P. ovale* and 44 years for *P. malariae*. In the UK, a recent case of *P. falciparum* transmission involved a semi-immune donor who had last been in a malarious area 8 years previously [5].

It must also be recognized that cases of TTM will still occur, albeit rarely. Although no set of guidelines is perfect, appropriate deferral strategies will reduce risk to a minimum, providing that they are properly applied. However, given the fact that donor deferral relies heavily on questionnaire and interview techniques, significant failures can still occur. Donors may give inaccurate information intentionally or unintentionally, because they misunderstand the question posed, or because they are unaware or have forgotten that they previously have had malaria [12]. Furthermore, the interviewing staff may have failed to implement the guidelines as intended. In a series of cases of TTM from the USA, it was found that the guidelines had only been applied correctly in 23 out of 60 (38%) cases, four of them caused by *P. falciparum* and 15 by *P. malariae* [14]. In contrast, among the 37 cases in which the guidelines had not been correctly implemented, 22 were caused by *P. falciparum* but only three by *P. malariae*. This suggests that the potentially very long persistence of *P. malariae* at low levels in the blood makes it a more difficult species to exclude, but that correctly followed time-exclusion guidelines, even in the absence of antibody screening, are more effective in excluding *P. falciparum* as a source of TTM.

Screening of donations

The ability to screen the donations, as well as the donors, can decrease significantly any risk of TTM. The overall effectiveness

of any donation-screening programme does, however, depend on the correct application of the donor-deferral criteria. There are four specific targets for donation screening: intracellular parasites; plasmodial antibodies; plasmodial antigen; and plasmodial DNA. Although there has been some debate over which is the most effective, donor deferral plus malarial antibody screening provides the most effective strategy in non-endemic countries. In endemic countries it is clear that different strategies are needed, and that these need to be developed locally according to needs and resources.

Direct parasite detection

The most widely applied diagnostic test for malaria is examination of Giemsa- or Wright's-stained thick and thin blood films [16]. The worldwide application of this method as a 'gold standard' diagnostic assay is primarily a result of its ability to allow speciation, quantification of parasitaemia and assessment of the distribution of parasite forms. These latter two functions can help in the assessment of disease severity and sometimes influence the choice of therapy. The sensitivity of the method varies, depending on the expertise of the microscopist. In experienced hands, sensitivities of between 5 and 50 parasites/μl can be achieved, but in routine situations most laboratories achieve a lower sensitivity of around 500 parasites/μl [17,18]. The time required to read individual films (20 min for a negative thick film), plus the lack of sensitivity, makes this approach non-viable for blood screening in non-endemic areas.

Fluorescence microscopy techniques based on dyes (e.g. acridine orange) with affinity for parasite nucleic acids have also been applied as diagnostic assays [19–21], but difficulty in discriminating between fluorescence-stained parasites and other nucleic acid-containing cellular debris have limited the sensitivity of such techniques to more than 100 parasites/μl. Although the processing time is reduced by comparison with routine microscopy, specialized equipment is needed. Species differentiation is often difficult and requires confirmation by alternative methods. For these reasons, fluorescent methods offer little, if any, improvement over standard staining techniques.

Despite their continued application as key diagnostic tests, microscopic techniques have several key limitations that render them inappropriate for universal or targeted donor screening. Specifically, they lack the required sensitivity to detect all infected units, are too time-consuming (generally requiring 1 h or more for preparation and detailed examination), and require significant expertise and specialized equipment when fluorescence methods are used.

Antibody testing

Following infection with plasmodial species, the immune response results in the formation of specific antibody. Although not necessarily protective, it is nonetheless an effective indicator of infection [22], although it does not necessarily indicate that the person is harbouring malaria parasites. However, a negative malarial antibody test cannot guarantee that the donor is not infected with malaria parasites, as antibody may not be detectable in the first few days of malarial illness, and infection with *P. ovale* and *P. malariae* may not be detected by *P. falciparum* and *P. vivax* antigen-based assays.

Draper & Sirr examined sera from 415 known cases of malaria diagnosed in the UK [23]. Eighty-eight were from UK residents who had travelled abroad and were suffering from their first attack of malaria, whilst 327 were from immigrants, who showed a wide range of malaria histories. One week after the onset of clinical symptoms 78% of UK residents had antibodies against *P. falciparum*, as determined by the indirect fluorescent antibody test (IFAT), but 100% of the immigrants were already seropositive. Furthermore, the immigrant patients also showed higher mean titres, longer persistence of antibodies and greater cross-reactions with other (non-falciparum) malarial antigens. Draper & Sirr went on to observe that individuals from hyperendemic areas in Africa may have high titres of antibodies reactive to all antigens, which may be associated with a low-grade asymptomatic infection that is undetectable microscopically – the scenario now referred to as semi-immune and described above.

Given the potential for malaria parasites to persist in certain patients for some years, it is important to note that in individuals who have suffered repeated attacks of malaria, antimalarial immunoglobulin may be detectable for several years. Although the persistence of antibodies long after cure of the malarial infection would lead to some individuals, who are no longer parasitaemic, being excluded as potential donors, it does provide a useful margin of safety if candidate donors, who are malaria antibody positive, are excluded from donating.

Although for many years the IFAT was still regarded as the 'Gold Standard' for malarial serology, the more recent arrival of enzyme immunoassays (EIAs) using native and recombinant antigens has provided a more sensitive and practical alternative to IFAT [4,24]. Overall, EIAs demonstrated sufficiently high sensitivity and specificity to screen at-risk donors, and the authors estimated that use of the EIA could safely retrieve up to 50 000 red cell donations each year that may otherwise be lost to the English blood service. It is important to note that the use of antibody-detection enzyme-linked immunosorbent assay (ELISA) is not recommended for the diagnosis of acute malaria, blood films still being the most sensitive method for malaria diagnosis in a clinical laboratory.

Slinger *et al.* commented that malaria antibody-detection tests lack both sensitivity and specificity [12], and that although technically useful where the prevalence of malaria

in donors is high, these tests would probably have a poor positive predictive value in the Canadian setting, resulting in the unnecessary rejection of donors with false-positive test results. However, although antibody from past infections would indeed lead to, arguably, unnecessary donor exclusion in non-endemic areas, the absolute numbers would be low – 1·5–3% of the 'malaria-risk donors' [4,24] – an acceptable level for blood transfusion services in the context of malaria screening to reinstate donors and collect donations otherwise 'lost' because of a possible malaria risk. Additionally, antibody-detection assays demonstrate high antibody levels and good sensitivity in semi-immune individuals, the very donors who are potentially at high risk of acting as a source of TTM by being asymptomatic but parasitaemic [13].

In New Zealand, only the plasma was used from donors who had visited a malarious area within the last 3 years [22], resulting in the 'loss' of 4% of all collected blood in the Auckland region alone. Using the same commercial EIA assessed by Chiodini *et al.* [4], Davidson *et al.* then investigated the prevalence of malarial antibodies in these 'malarial-risk' donors [22]. Of a group of 530 donors, 1·7% were found to be malarial antibody positive, a figure similar to that found by Chiodini *et al.* Thus, antibody testing, with the appropriate time interval after the last possible exposure episode, provides an effective means of identifying donors who have had malaria at some time and may still represent a risk of TTM.

Malarial antigen detection

Current malaria antigen-detection assays are not sufficiently sensitive to exclude totally the presence of malaria parasites in a unit of blood destined for transfusion.

Antigen detection

The detection of malarial antigen was originally intended as a more rapid and objective alternative to direct microscopy. However, although rapid and reasonably objective, their sensitivity is not sufficient for use in a screening context, as their overall sensitivity is still less than that of blood films. The assays are generally based on the detection of major specific proteins – histidine rich protein 2 (HRP-2), plasmodial lactate dehydrogenase (pLDH) or aldolase – using various rapid immunochromatographic formats, and using whole blood as the sample of choice. Assay sensitivities range from 100 to 1000 parasites/μl, depending on the species and method, in general comparable with routine microscopy, except when this is performed by experienced staff [25]. Most of these assays are in a 'dipstick' format that can be used with minimal training and provide a result within 10–20 min. Expense and relative insensitivity have restricted their application as donor screening tests.

Although some authors have proposed the combination of malarial antibody screening with antigen detection as a means of increasing the sensitivity of any screening performed [27,28], the validity of this strategy in a donor screening context is not clear as the assay combinations and samples used are not representative of blood screening. Although a combination of IFAT and antigen assay [26] would improve sensitivity over IFAT alone, IFAT has been shown to be less sensitive than a new recombinant EIA for antibody detection [24]. Furthermore, the Australian study [28] used acute-phase samples, and thus studied individuals who would not have been eligible to donate until 6 months after their return from a malarious area.

Nucleic acid testing

The detection of plasmodial DNA by molecular techniques is now well established in diagnostic situations. Polymerase chain reaction (PCR)-based amplification techniques have been developed that have been quoted to provide relatively high levels of sensitivity in a diagnostic situation [28–30], offering a rapid and sensitive means of detection of plasmodial DNA in clinical samples. However, the use of molecular techniques to detect malarial parasites in donated blood has, for some time, been an area of debate. Although PCR sensitivities as low as 0·004 parasites/μl have been quoted [31,32], the key issue is whether any of the current molecular tests can detect parasites at the low level at which they may be present and still transmit malaria, bearing in mind the size of the inoculum [33]. To illustrate whether an individual is parasitaemic at a low level, for example one parasite per ml of whole blood (below the quoted sensitivity of current PCR tests), a unit of red cells would need to contain at least 200 parasites, a level at which transmission could clearly occur. However, this level would be undetectable unless the initial extraction volume for the genomic test was at least 1 ml of blood and the whole extract was then used for the PCR of blood. Using this volume of sample starts to become problematic as large sample volumes are not ideal for routine screening tests where sample numbers are relatively high and simple streamlined and automated techniques are required. When the size of the inoculum is factored into the considerations, it is clear that the level of parasitaemia in any donation could actually be quite a lot lower, and yet the red cell products could still transmit malaria. Experiments involving the infection of mice with *P. chabaudi* demonstrated infectivity at a dose of 100 parasites [34]. Thus, in non-endemic countries the use of even the most sensitive techniques for the detection of malarial DNA would not be sufficient to ensure that a donation was free of parasites. Although it has been suggested that a combination of PCR and donor questioning is an effective way of minimizing the risk of malaria transmission by transfusion [31], a combination of questioning, deferral and antibody screening is a far more effective and reliable, and in fact cheaper, strategy [24,35].

In endemic countries, however, PCR has been suggested as a way in which infectious donations, with parasitaemia

below that detectable by standard thick films, can be identified. In comparison with thick films there is no doubt that a well-designed PCR can be more sensitive [36,37]. Moreover, routine PCR screening is not widely available in the majority of malaria-endemic countries, the cost is almost always prohibitive and the infrastructure needed is not normally available. Therefore, in malaria-endemic countries, PCR is not currently, or in the foreseeable future, a viable alternative to Giemsa-stained thick films for the screening of blood donations.

Conclusions

Although cases of TTM are not common in non-endemic countries, malaria is nonetheless a significant problem in a number of these countries and a potential problem in most others. This is because malaria is a disease that is gradually spreading in terms of the numbers of individuals exposed to it. The disease itself is encroaching into new areas and back into areas from which it was previously eradicated, and there is increasing travel into malarious areas. Thus, the number of donors who have a potential 'malaria risk' is increasing, and there is corresponding pressure on the collection teams to correctly and effectively identify all such 'malaria-risk' individuals, and pressure on the recruitment staff to replace the donations lost, even if deferral is only temporary. Lengthy deferral increases the risk of donors not returning. This is clearly a cumulative problem that, if malaria risk leads to permanent deferral, is likely to erode significantly the donor base. Therefore, an effective strategy with comprehensive and effective guidelines for both the management of donors and the screening of donations needs to be put into place to safeguard both the safety and sufficiency of the blood supply in the face of an ever-growing threat. Finally, it must be recognized that cases of TTM will still occur, albeit rarely. Although no set of guidelines is perfect, appropriate deferral strategies, providing that they are properly applied, with the appropriate laboratory screening, will reduce this risk to a minimum.

References

1 Bruce-Chwatt LJ: Transfusion malaria. *Bull WHO* 1974; **50**:337–346

2 Bruce-Chwatt LJ: Transfusion malaria revisited. *Trop Dis Bull* 1982; **79**:827–840

3 De Silva M, Contreras M, Barbara J: Two cases of transfusion-transmitted malaria (TTM) in the UK [letter]. *Transfusion* 1988; **28**:86

4 Chiodini PL, Hartley S, Hewitt PE, Barbara JAJ, Lalloo K, Bligh J, Voller A: Evaluation of a malaria antibody ELISA and its value in reducing potential wastage of red cell donations from blood donors exposed to malaria, with a note on a case of transfusion-transmitted malaria. *Vox Sang* 1997; **73**:143–148

5 Kitchen A, Mijovic A, Hewitt P: Transfusion transmitted malaria: current donor selection guidelines are not sufficient. *Vox Sang* 2005; **88**:200–201

6 Schlagenhauf P, Mueutener P: Imported malaria; in Schlagenhauf P (ed.): *Travellers' Malaria*. Hamilton, BC Decker Inc., 2001:495–508

7 Mungai M, Tegtmeier G, Chamberland M, Parise M: Transfusion-transmitted malaria in the United States from 1963 through 1999. *N Engl J Med* 2001; **344**:1973–1978

8 Wylie BR: Transfusion transmitted infection: viral and exotic diseases. *Anaesth Intensive Care* 1993; **21**:24–30

9 Tegtmeier GE: Infectious diseases transmitted by transfusion: a miscellanea. *Vox Sang* 1994; **67**:179–181

10 Dodd RY: Transmission of parasites by blood transfusion. *Vox Sang* 1998; **74**:161–163

11 Dodd RY: Transmission of parasites and bacteria by blood components. *Vox Sang* 2000; **78**:239–242

12 Slinger R, Giulivi A, Bodice-Collins M, Hindieh F, St John F, Sher G, Goldman M, Ricketts M, Kain K: Transfusion-transmitted malaria in Canada. *Can Med Assoc J* 2001; **164**:377–379

13 Kitchen AD, Barabara JA, Hewitt PE: Documented cases of post-transfusion malaria occurring in England: a review in relation to current and proposed donor selection guidelines. *Vox Sang* 2005; **89**:77–80

14 Mungai M, Tegtmeier G, Chamberland M, Parise M: Transfusion-transmitted malaria in the United States from 1963 through 1999. *N Engl J Med* 2001; **344**:1973–1978

15 Current UK donor selection guidelines: http://www.transfusionguidelines.org.uk

16 Warhurst DC, Williams JE: Laboratory diagnosis of malaria – ACP Broadsheet no 148, July 1996. *J Clin Pathol* 1996; **49**:533–538

17 Moody A: Rapid diagnostic tests for malaria parasites. *Clin Microbiol Rev* 2002; **15**:66–78

18 Milne LM, Kyi MS, Chiodini PL, Warhurst DC: Accuracy of routine laboratory diagnosis of malaria in the United Kingdom. *J Clin Pathol* 1994; **47**:740–742

19 Baird JK, Purnomo, Jones TR: Diagnosis of malaria in the field by fluorescence microscopy of QBC capillary tubes. *Trans R Soc Trop Med Hyg* 1992; **86**:3–5

20 Benito A, Roche J, Molina R, Amela C, Alvar J: Application and evaluation of QBC malaria diagnosis in a holoendemic area. *Appl Parasitol* 1994; **35**:266–272

21 Bosch I, Bracho C, Perez HA: Diagnosis of malaria by acridine orange fluorescent microscopy in an endemic area of venezuela. *Mem Inst Oswaldo Cruz* 1996; **91**:83–86

22 Davidson N, Woodfield G, Henry S: Malaria antibodies in Auckland blood donors. *NZ Med J* 1999; **112**:181–183

23 Draper C, Sirr SS: Serological investigations in retrospective diagnosis of malaria. *BMJ* 1980; 1575–1576

24 Kitchen AD, Lowe PHJ, Lalloo K, Chiodini PL: Evaluation of a malarial antibody assay for use in the screening of blood and tissue products for clinical use. *Vox Sang* 2004; **87**:150–155

25 Huong NM, Davis TM, Hewitt S, Huong NV, Uyen TT, Nhan DH, Cong le D: Comparison of three antigen detection methods for diagnosis and therapeutic monitoring of malaria: a field study from southern Vietnam. *Trop Med Int Health* 2002; **7**:304–308

26 Silvie O, Thellier M, Rosenheim M, Datry A, Lavigne P, Danis M, Mazier D: Potential value of *Plasmodium falciparum*-associated

antigen and antibody detection for screening of blood donors to prevent transfusion-transmitted malaria. *Transfusion* 2002; **42**:357–362

27 Seed C, Cheng A, Keller A: Comparison of the efficacy of two malarial antibody enzyme immunoassays for targeted blood donor screening. *Transfusion* 2004; **44**:99A [Abstract]

28 Perandin F, Manca N, Calderaro A, Piccolo G, Galati L, Ricci L, Medici MC, Arcangeletti MC, Snounou G, Dettori G, Chezzi C: Development of a real-time PCR assay for detection of *Plasmodium falciparum*, *Plasmodium vivax* and *Plasmodium ovale* for routine clinical diagnosis. *J Clin Microbiol* 2004; **42**:1214–1219

29 McNamara DT, Thomson JM, Kasehagen LJ, Zimmerman PA: Development of a multiplex PCR-ligase detection reaction assay for diagnosis of infection by the four parasite species causing malaria in humans. *J Clin Microbiol* 2004; **42**:2403–2410

30 Rubio JM, Benito A, Berzosa PJ, Roche J, Puente S, Subirats M, Lopez-Velez R, Garcia L, Alvar J: Usefulness of seminested multiplex PCR in surveillance of imported malaria in Spain. *J Clin Microbiol* 1999; **37**:3260–3264

31 Benito A, Rubio JM: Usefulness of seminested polymerase chain reaction for screening blood donors at risk for malaria in Spain. *Emerg Infect Dis* 2001; **7**:1068 [Letter]

32 Thellier M, Lusina D, Guiguen C, Delamaire M, Lkegros F, Ciceron L, Klerlein M, Danis M, Mazier D: Is airport malaria a transfusion-transmitted malaria risk? *Transfusion* 2001; **41**:301–302

33 Rickman LS, Jones TR, Long GW, Paparello S, Schneider I, Paul CF, Beaudoin RL, Hoffman SL: *Plasmodium falciparum*-infected *Anopheles stephensi* inconsistently transmit malaria to humans. *Am J Trop Med Hyg* 1990; **43**:441–445

34 Timms R, Colegrave N, Chan BHK, Read AF: The effect of parasite dose on disease severity in the rodent malaria *Plasmodium chabaudi*. *Parasitology* 2001; **123**:1–11

35 Shehata N, Kohli M, Detsky A: The cost-effectiveness of screening blood donors for malaria by PCR. *Transfusion* 2004; **44**:217–228

36 Hang VT, Be TV, Tran PN, Thanh LT, Hien LV, O'Brien E, Morris GE: Screening donor blood for malaria by polymerase chain reaction. *Trans R Soc Trop Med Hyg* 1995; **89**:44–47

37 Ndao M, Bandyayera E, Kokoskin E, Gyorkos TW, MacLean JD, Ward BJ: Comparison of blood smear, antigen detection and nested-PCR methods for screening refugees from regions where malaria is endemic after a malaria outbreak in Quebec. Canada. *J Clin Microbiol* 2004; **42**:2694–2700