Title: Global challenges of malaria risk; perspectives from Transfusion-transmitted malaria

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Short title as running head: Challenges in transfusion malaria risk

Abstract

Malaria is a protozoan disease that is transmitted by the *Anopheles* mosquito. It can however be transmitted by blood transfusion if the blood donor is parasitaemic. Of the five species of *Plasmodium* that causes malaria, *P. falciparum* causes the most severe form of malaria. Nearly half of the world’s population is at risk of malaria. Mortality due to malaria has reduced by 48% from 839,000 deaths in 2000 to 438,000 deaths in 2015. This is largely due to a combination of two approaches, vector control and effective antimalarial drugs

There are challenges to be encountered in managing malaria risk. Some have evolved from the interventions while others may be inherent with parasite. The complex life cycle of the plasmodium parasite and the different stages it undergoes both in the mosquito and human requires a multifaceted approach to reduce or eliminate the burden of malaria.

The challenges faced in transfusion-transmitted malaria mirrors the global malaria risk. The presence of parasitaemia in blood donors represents a risk for the transmission of malaria by transfusion as well as serving as a reservoir for environmental transmission. Yet, there is no ideal method for parasite detection.

There is the need for institutions such as National Blood Services and Malaria Control programmes to collaborate and lead joint interventions that reduce the malaria risk. Such collaborations should also involve stake holders such as academia, policy makers, funders, governments and international organizations.

Introduction

Malaria is a disease caused by the *Plasmodium* parasite and is one of the most common infectious diseases worldwide. The parasite is transmitted through the bite of an infected female Anopheles mosquito or directly by blood transfusions[1]. There are five species of *Plasmodium* that cause disease in humans. These are *P. falciparum, P malariae, P, ovale, P vivax* and the recently identified *P knowlesi*. *P falciparum* is the most frequent cause of severe malaria and is largely responsible for most of the morbidity and mortality associated with malaria.

The global burden of malaria is reducing considerably [2]. Malaria cases fell from 262 million in the year 2000 to 214 million cases in 2015. A cumulative 1.2 billion fewer malaria cases and 6.2 million fewer malaria deaths occurred globally between 2001 and 2015 than would have occurred had incidence and mortality rates remained the same. Globally, mortality has been reduced by 60% from 839, 000 deaths in 2000 to 438,000 deaths in 2015 [3]. Inspite of the progress made over the years, malaria still remains a major cause of morbidity and mortality, representing a global public health concern [4].

At the World Health Assembly 2015, WHO member states endorsed the bold vision of a malaria free world, and adopted a Global Technical Strategy for malaria covering the period 2016-2030. The strategy aims to reduce the burden of malaria by 90% by 2030 [5]. It also emphasizes the importance of scaling up malaria responses and the need to urgently increase investments across all interventions. Most of the interventions require huge budgets to implement and the enormity of the challenge should not be underestimated.

There is a large heterogeneity in malaria epidemiology across regions and countries. Therefore successes of control/eradication interventions are diverse [6]. Challenges to the management of malaria risk are dependent on prevailing global or local conditions. This paper discusses some common challenges that may be encountered in malaria including the changing epidemiology, asymptomatic carriers, drug resistance and vaccine development. These challenges are then discussed in relation to transfusion-transmitted malaria.

Drug resistance

Chloroquine was a remarkable antimalarial compound and was active against all four species known to cause malaria in humans at that time. It was cheap and effective. Resistance to chloroquine was noticed from the late 1950 and subsequently spread across the world from the epicenters of Columbia and eastern Thailand [7]. The widespread emergence of resistance of *P. falciparum* to chloroquine was a major cause of the persistently high rates of morbidity and mortality by the close of the last century. Other drugs such as sulphadoxine-pyrimethamine experienced such widespread resistance and contributed to the poor outcomes of malaria. Since 2001 the WHO has recommended artemisinin-based combination therapy (ACT), a combined regimen of artemisinin and a longer acting partner drug, as the treatment of choice for falciparum malaria [8]. Since the introduction of the ACTs, there has been an improvement in treatment outcomes of malaria. Most of the successes chalked up over the past 10 years especially in sub Saharan Africa can be attributed to the successful adoption of ACT and the other programmes such as rapid diagnostic testing, indoor residual spraying (IRS) and insecticide treated bednets (ITN)[9].

Unfortunately, the old problem of resistance emerged. The first hints of resistance were observed in western Cambodia and south-eastern Thailand [10, 11]. The major challenge is to prevent the spread of resistance strains especially to Africa. If not controlled, artemisinin will suffer the same fate as chloroquine, and this will be disastrous in the fight to eradicate malaria.

Asymptomatic parasitaemia

The relevance of asymptomatic malaria has become increasingly critical as the world moves from malaria control to malaria elimination. In seeking to eradicate malaria, three important issues have to be answered appropriately. These include

1. Should asymptomatic individuals with parasiatemia be actively sought for?
2. What will be the best detection tool?
3. Should people with asymptomatic parasitaemia be treated?

It is clear that current diagnostic or screening test available have individual limitations. PCR is relatively expensive in developing countries but also highly sensitive and can detect very low parasitaemia. Microscopy and RDT are test methods with low sensitivity and are therefore inaccurate in the detection of low-level infections. The ability to accurately detect parasitaemia in all individuals and in all populations is fundamental to achieving elimination and eradication of malaria. There is the need for newer test methods that are sensitive enough to detect low-level parasitaemia.

*Plasmodium vivax*

*P. falciparum* is responsible for nearly 98% of malaria in Africa. *P. vivax* has a wider geographic distribution than *P falciparum*. In countries such as Mexico, Belize and large parts of China where *P. falciparum* has been successfully eliminated, *P vivax* remains a problem [12, 13]. *P vivax* is less responsive to malaria control measures. It survives better in natural conditions than *P. falciparum*. Other reasons for the non-response of *P. vivax* to control measures include the dormant liver stage of its life cycle, which results in relapse after treatment, and the production of infectious gametocytes after parasites emerge from the liver.

Currently, primaquine is the recommended drug for treating the liver stage to avoid relapse [14]. Treatment duration is up to 14 days and this long duration often results in poor adherence and lower efficacy [15]. One of the challenges therefore is to find a new drug to replace the 14-day primaquine treatment. Primaquine is also known to cause acute hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient patients. A diagnostic test is needed for point of care testing to quickly identify G6PD deficiency [6].

Mass treatment with antimalarials

The mass treatment approach has been used in other diseases. It was one of the methods used in the 1960’s and 70’s as part of efforts to eliminate malaria [16]. Despite its success in some areas, concerns exist regarding efficacy and feasibility and there is fear about accelerating drug resistance [17]. Mass treatment for malaria is not a programme that is encouraged by WHO. The current treatment guidelines recommend laboratory confirmation of parasites prior to initiation of ACT. Depending on the country status of malaria elimination, a combined mass screening and treatment method may be a preferred alternative to only mass treatment, and is used in Cambodia to contain and eliminate malaria [18].

Rigorous and detailed systematic reviews have been conducted in the area of mass drug administration. This reveal that there are still gaps in knowledge. Evidence is needed and therefore, more research should be conducted to identify optimal target population size, methods to improve coverage and primaquine safety. Mass drug administration will have a role to play in eradication of malaria but it has to be carefully managed within an overall strategy of a combined effort of malaria eradication in specific settings [17].

Vaccines

Malaria vaccines would be the ideal addition to the existing armamentarium of antimalarial tools [19]. However till date there are no universally licensed malaria vaccines. Malaria vaccine development has not progressed as rapidly as one may desire. Antimalarial immunity is poorly understood and the identification of an immune correlate of protection continues to elude malaria researchers. Other reasons for the lack of an efficacious vaccine include the genetic diversity of malaria parasites and the complex life cycle that the parasite undergoes both in man and the female anopheles mosquito[20]. These complexities have resulted in the many different approaches to the development of the malaria vaccine. Some of the major approaches used include a) a recombinant protein with adjuvant vaccine aimed at *P. falciparum* pre-erythorcytic stage, b) whole sporozoite vaccines aimed at Pf pre-erythrocytic stage, c) prime boost vaccines that include recombinant DNA, viruses and bacteria aimed at Pf pre-erythrocytic and asexual erythrocytic stages and d) recombinant protein with adjuvant vaccines aimed at Pf and P. vivax sexual erythrocytic and mosquito stages [19]. There are many clinical trials at various phases ongoing across the world with the hope that a breakthrough will occur shortly.

Early malaria vaccine development in the 1930’s focused on inactivated or killed parasites that failed to generate a protective immune response. Continued efforts led to the first immunization and field trials for malaria vaccines before the close of the century. The vaccine, SPf66, which contained sequences of 3 *P. falciparum* blood-stage antigens and the circumsporozoite protein, was successful in showing a reduction in parasitaemia in South America but did not have any protection in Africa.

The most advanced malaria vaccine is RTS,S/AS01. This is a recombinant vaccine against the pre-erythocytic stage of the parasite in which regions of *P falciparum* circumsporozoite protein are fused to hepatitis B surface antigen[21]. Phase III trials at 11 different sites involving 8922 children and 6537 young infants have been completed. Vaccine efficacy against clinical malaria in infants aged 6 to 12 weeks decreased from 27% to 18.3% at 20 months and 48months of follow up while efficacy in children (5-17 months) was 45.1% and 28.3% at 20 months and 48 months follow up respectively. In July 2015, the European Medicines Agency approved RTS,S/AS01 for vaccination in children aged 6 weeks to 17months but WHO is yet to recommend it as part of routine immunization in infants within the Expanded Programme of Immunization. There are still several follow up studies that are ongoing to evaluate the long term protective effect of the vaccine. In addition experts have recommended other exploratory studies including the four-dose options studies in three to five distinct epidemiological settings [22]. The WHO, working with malaria vaccine funders group have in 2013 published a roadmap with a strategic framework that seeks to deliver safe and effective vaccines against *P. falciparum* and *P. vivax* by 2030 [23].

In spite of the disappointing results, RTS,S represents a major milestone and scientists can build on this achievement. There are more than 20 malaria vaccine strategies currently in clinical testing[20]. One major challenge is to figure out how to improve vaccine efficacy by combining antigens that may act at different targets of the life cycle. Public-private partnership which has contributed significantly to the advancement of RTS,S must be maintained and strengthening the capacity of clinical trial sites and personnel in Africa to conduct high level clinical trails will also be important.

Transfusion transmitted malaria.

Transfusion transmitted malaria (TTM) is an area that requires critical attention since malaria elimination strategies must include, though have largely neglected, blood donors as reservoirs of transmission. The donor whose blood may have parasitaemia, the blood service that supplies that collects and distributes blood and the recipient of the blood should all be evaluated to determine the best way malaria risks can be identified. Subsequent interventions that may or may not be within country specific malaria control programmes should be implemented. Some of the challenges in the area of TTM include the following:

1. Should a routine screen for malaria be performed all blood donors?
2. Which screening test is best suited to correctly identify parasitaemia in the healthy volunteer?
3. Should all healthy asymptomatic but parasitaemic donors be treated?
4. Should all transfusion recipients be given routine antimalarial prophylaxis?
5. Should all recipients of transfusion be screened for parasitaemia?
6. What is the risk of developing clinically significant malaria from transfusion if recipients are semi-immune?
7. In malaria high endemicity areas, how to confirm that malaria in a transfusion recipient was acquired through transfusion rather than through a mosquito bite?

These are questions for which presently, there are no clear evidence based answers. If we are to make significant progress in the onward march towards eradication of malaria, these challenges have to be addressed. More research has to be conducted to generate the required data on which appropriate policy direction could be derived.

Selecting the appropriate tools for managing malaria risk and control/eradication requires an understanding of local epidemiology, geography and socioeconomic conditions. The approach in high transmission regions may be different from low transmission regions. For example the risk of malaria in healthy donor depends on the endemicity of people living in malaria endemic areas. Donors living in a malaria endemic area are often semi-immune and may be able to habour parasites without showing any signs of malaria. A highly sensitive screening method such as PCR is needed to enable donor parasitaemia to be identified. Genotyping is needed in TTM to determine whether the parasites are the same as in the blood transfused. Tests such as microscopy and RDT are not sensitive and may miss low levels of parasitaemia

 For donors living in a non endemic area, it is important to establish whether the donor has visited an endemic area or not. A visit to an endemic area may either outrightly exclude a donor or antibody testing may have to be performed to identify an exposure.

The asymptomatic blood donor is not only a risk to the transfusion recipient but is a reservoir for the community. Mosquitoes may bite them, take up gametocytes and transmit malaria to another person. The blood donors therefore represent an unexplored population in the fight against malaria and efforts and resources should be channeled to support research in this area. In malaria endemic regions, TTM should not be left to only the national blood services but there should be a close collaboration with the malaria control programmes so that there is a comprehensive approach to the asymptomatic person whether a blood donor or not. Currently there are conflicting practices and policies.

Conclusion

When the WHO announced the goal of global eradication of malaria in 2007, many diverse opinions for and against it were expressed. There is now consensus that eradication is a long term goal and requires thoughtful considerations of all risks, benefits and challenges [24]. Some of the challenges such the search for an efficacious vaccine has been yet to be overcome while the challenge of drug resistance is recurrent. It is critical that we build on the lessons from the past to shape the way we move forward. If the combined efforts and resources of all stakeholders (Governments, Non-governmental organizations, International organizations, funders academia and researchers) are maintained, then there is the hope of overcoming these challenges and the aim of malaria eradication can be achieved.

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