frontiers | Frontiers in Tropical Diseases

TYPE Editorial
PUBLISHED 18 April 2024
DOI 10.3389/fitd.2024.1394693

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 01 March 2024
ACCEPTED 05 April 2024
PUBLISHED 18 April 2024

CITATION
Pucca MB, de Sousa TN, Cardoso de Melo GC and Viana GMR (2024) Editorial: Challenges for diagnosis, treatment, and elimination of malaria.
Front. Trop. Dis 5:1394693.
doi: 10.3389/fitd.2024.1394693

Editorial: Challenges for diagnosis, treatment, and elimination of malaria

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KEYWORDS

malaria, *Plasmodium*, eradication, malaria transmission, diagnosis, treatment

Editorial on the Research Topic
Challenges for the diagnosis, treatment, and elimination of malaria

Malaria is a major cause of death in many tropical and sub-tropical countries, presenting about 627,000 deaths and 241 million cases in the world. Malaria is still an important public health problem that needs to be more effectively controlled. Delays in diagnosis and treatment are responsible for most deaths in many countries. Moreover, in most malaria-endemic countries, the lack of resources is a huge barrier to reliable and timely diagnosis. It is a global priority to reduce the high malaria burden and to achieve long-term malaria eradication. In this Research Topic, constituted by 10 papers, we review and discuss the current challenges of malaria transmission, diagnosis, treatment, control, and future eradication.

Challenges for diagnosis, vaccines, and treatment

Vector-targeted interventions are highly effective in preventing malaria transmission and are an essential component of elimination strategies. The detection of *Plasmodium* infection in mosquitoes can be used to estimate exposure and transmission intensity and is a critical part of the management of malaria. Hugo et al. have successfully unveiled a groundbreaking diagnostic test designed for the rapid detection of *Plasmodium falciparum* in mosquitoes, which can achieve results in less than 30 min. This test is specifically tailored for low-resource settings, offering an invaluable solution to address the challenges posed by limited infrastructure. The methodology integrates a swift and uncomplicated sample preparation procedure with isothermal amplification by utilizing recombinase polymerase amplification (RPA). This is coupled with a subsequent lateral flow detection (LFD) step. The synergy of these elements enables the test to deliver efficient and timely outcomes. Remarkably, the developed RPA-LFD test exhibits analytical sensitivity which is at par with the gold standard,

PCR. This signifies its efficacy as a reliable tool for the surveillance of mosquito populations carrying the *P. falciparum* parasite. The rapidity, simplicity, and accuracy of this diagnostic method make it a promising asset in the ongoing efforts to monitor and control malaria in resource-constrained environments.

On the other hand, the study developed by Costa et al. aimed to describe the development of seven specific qPCR assays for the diagnosis of *Plasmodium vivax* and *P. falciparum*, targeting coding and non-coding mitochondrial genomic regions as well as evaluating the possible pitfalls associated with the development of these assays. Although qPCR assays with the tested mitochondrial targets reduced the occurrence of non-specific amplifications, they were not able to eliminate them, in addition to hindering the efficiency of specific amplifications. A Cq (quantification cycle) cutoff value could not exclude false-positive findings for most assays, except for PV_CYTB and PF_CYTB, which presented a cutoff value with good specificity. As noted, although mitochondrial targets are considered the most sensitive, they often lose specificity due to their high sequence conservation (*P. vivax* and *P. falciparum* have at least 90% of mtDNA conservation). Therefore, in the panorama of molecular assays with mitochondrial targets to identify *Plasmodium* sp., it is crucial to include a screening phase to evaluate the possibility of cross-reaction between species of the genus *Plasmodium* or even nonspecific amplification in a panel of samples free of human malaria.

In the realm of vaccination, the absence of an effective malaria vaccine stands out as a crucial gap in current strategies. This gap becomes even more pressing with the emergence of drug-resistant *P. falciparum* strains and the resistance of mosquitoes to insecticides, presenting formidable challenges to malaria treatment and elimination. The study of Waweru et al. aimed to bridge this gap by targeting the PfRh5 complex, a pivotal player in the erythrocyte invasion process. This complex comprises Pf-reticulocyte binding homolog 5 (PfRh5), Pf-interacting protein (PfRipr), Pf-cysteine-rich protective antigen (PfCyRPA), and Pf-P113 protein. Antibodies targeting these proteins have been proven effective in inhibiting parasite invasion, rendering them promising candidates for a blood-stage vaccine. However, the hurdle lies in the genetic polymorphisms within these genes, which pose potential obstacles to vaccine development. To unravel these complexities, the researchers conducted whole-genome sequencing of *P. falciparum* isolates from high-transmission regions in Kenya, with a specific focus on the PfRh5 complex. The study unveiled a total of 58 variants within the PfRh5 complex, with PfRh5 exhibiting the highest degree of polymorphism. Significantly, the Lake Victoria parasite population displayed low polymorphisms, suggesting the plausible candidacy of PfRh5 components for a malaria vaccine. These findings underscore the imperative for further exploration into the specific impacts of mutations on the parasite invasion process, offering valuable insights to propel the advancement of malaria vaccine development.

Malaria in pregnancy (MiP) presents a multitude of risks to the well-being of both mothers and their unborn infants. While the connection between severe pregnancy outcomes, including miscarriage and stillbirth, and MiP is firmly established, there is a pressing need for a more comprehensive understanding of adverse pregnancy outcomes and their prevalence in malaria-endemic regions. Acquiring such knowledge is crucial to evaluate the effectiveness of implemented strategies aimed at preventing MiP, notably the safety and efficacy of MiP vaccines. Berhe et al. reviewed the primary adverse effects associated with MiP and delineated the existing strategies to mitigate its impact. The authors underscore the significance of thoroughly assessing this information as a prerequisite to initiating clinical trials for MiP vaccines. This emphasis on pre-trial evaluation ensures a well-informed approach to vaccine development and implementation, thereby maximizing the potential for success in combatting the adverse effects of malaria during pregnancy.

Prevention and control

Malaria continues to be a major global health concern, particularly in resource-constrained settings, significantly impacting children under 5 years old. Long-lasting insecticide-treated nets (LLINs) are a key intervention endorsed by the World Health Organization (WHO) to combat malaria, which show a potential to reduce cases by 50%. In Ghana, where malaria is hyper-endemic, primarily caused by *P. falciparum*, the transmission is year-round, which peaks from June to October. Dako-Gyeke et al. lead efforts to combat malaria through mass LLIN distribution campaigns. Despite progress, challenges persist in achieving strategic plan targets, with identified barriers to LLIN use in various studies. In response, a community health advocacy team (CHAT) was collaboratively created in six Ghanaian communities, which aimed to promote LLIN use through a person-centered approach, thus leveraging the Community Health Planning and Services (CHPS) program. The qualitative study delves into the opportunities and barriers during the pilot implementation of CHATs, which involved 43 members across six communities in Ghana's Eastern and Volta regions. While CHATs effectively sensitized communities and positively influenced behavior change, the challenges included a lack of financial support for transportation and outreach activities.

Despite global efforts, regions like Djibouti and Ethiopia continue to report substantial transmission rates of malaria, which were exacerbated by disruptions from the COVID-19 pandemic. Moreover, studies across sub-Saharan Africa reveal varied knowledge, attitudes, and practices regarding malaria prevention. Factors such as education, income, age, and cultural beliefs may also influence prevention measures. In this context, the study by Addis and Wondmeneh focused on Ada'ar woreda district, in the pastoral region of Afar, Ethiopia, where malaria data is lacking. The research involved 422 households, revealing diverse knowledge, attitudes, and practices. Individuals with poor knowledge tend to practice inadequate prevention methods, and young adults exhibit suboptimal healthcare-seeking behaviors. The study highlights ongoing challenges in awareness and adherence to malaria control measures in the Afar region. The findings offer valuable insights for public health strategies in the Afar region, emphasizing the need for community-specific approaches to combat malaria.

Following the same context, Nigeria, which is celebrating 62 years of independence in 2022, faces a severe malaria burden, contributing significantly to the global caseload and mortality. The perspective article of Oboh et al. underscores that, despite numerous control initiatives, Nigeria consistently leads in both malaria cases and deaths. The diverse malaria transmission patterns across the country emphasize the need for tailored intervention strategies. To address this challenge, the authors advocate for a focused and research-driven approach, exploring vectorial capacity, insecticide susceptibility, hotspot identification, and the genetic makeup of *P. falciparum*. This targeted research has the potential to reveal crucial insights, including the migration of parasite populations. Achieving pre-elimination status demands prioritized efforts to comprehend the circulating *Plasmodium* strains, which will enable informed policy implementation for malaria transmission control in Nigeria.

Mozambique's National Malaria Strategic Plan targets 85% population protection through testing and treatment. However, the country faces challenges due to climatic vulnerability, frequent natural disasters, and susceptibility to climate change. The study of Armando et al. explores the spatial and temporal dynamics of malaria transmission, which integrate socioeconomic, climatic, and land use data. Analyzing data from 2016 to 2018 at the district level, the study employs a Bayesian framework to model malaria cases. The results reveal an increased malaria risk associated with higher temperatures and specific climatic conditions. Moreover, the study identifies lag patterns and establishes links between climate variables and malaria incidence. Notably, education level, access to electricity, and toilet facilities impact malaria risk. The findings provide valuable insights to design early warning systems and targeted prevention strategies to mitigate seasonal malaria surges in Mozambique, where the disease imposes a significant health burden.

In contrast, one focus of the study of Wang et al. was to present the epidemiological data of imported malaria cases in China from 2011 to 2019, i.e., before WHO has declared it to be malaria-free in 2021. This historical epidemiological pattern of imported malaria in China is of utmost importance to provide evidence-based data to prevent malaria re-establishment in this country. Prevention of re-establishment (POR) is understood as any strategy capable of preventing the emergence of malaria outbreaks/epidemics or avoiding the reestablishment of indigenous malaria in a malaria-free country. These findings revealed that the majority of malaria reported cases were from migratory volunteers, regardless of *Plasmodium* species, being imported cases mainly from West and/or Central Africa and Southeast Asia. Therefore, POR of malaria is a key strategy adopted by countries with malaria-free certification to successfully sustain the "malaria-free status."

Although the World Health Organization (WHO) has promoted "test and treat" guidelines since 2010, recommending that all suspected malaria cases be confirmed with a parasitological test, usually a rapid diagnostic test (RDT), prior to treatment, the compliance of this recommendation is not a reality, especially in malaria-endemic areas in developing countries. In these scenarios, febrile patients are presumptively treated as malaria without diagnostic confirmation. The state of the art of an observational study on private sector antimalarial sales in Uganda has been enumerated by Shelus et al. The main goal of this study was to expand the understanding and knowledge about the private sector malaria case management in Bugoye, western Uganda approximately 10 years after the Uganda Ministry of Health launched their "test, treat, and track" policy. Among the study's key findings, the authors noted that, of the 934 customers with suspected malaria who visited study drug stores during the data collection period, only 25% (233/934) purchased a RDT. Therefore, most cases used to be treated presumptively and possibly may not even have the malaria infection. This practice of irrational use of medicines can cause many organic disorders, in addition to contributing to the selection of resistant strains of *Plasmodium* sp. to antimalarials. In view of this, it is mandatory to adopt interventions in the field of pharmacovigilance, with the aim of ensuring rational use of medicines in the private sector of Bugoye, western Uganda.

Author contributions

MP: Writing – original draft, Writing – review & editing. TN: Writing – original draft, Writing – review & editing. Gd: Writing – original draft, Writing – review & editing. GV: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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