Stronger research capacity for malaria to counter critical challenges: the Ethiopia experience

Plasmodium vivax infection is conspicuously absent in most of Africa – except in Ethiopia where it accounts for a significant proportion of malaria morbidity. MMV reports on the collaborations under development to counter the problem

New antimalarial medicines and the clinical trial capacity to develop them are urgently needed in malaria-endemic countries, particularly those just south of the African Sahara where the burden of this disease is heaviest. In this region, malaria has historically been almost exclusively attributed to *Plasmodium falciparum* (*Pf*), while *Plasmodium vivax* (*Pv*) or relapsing malaria, has been conspicuously 'absent'.[1] One possible reason is that most populations in sub-Saharan Africa are negative for Duffy antigen expression. As a result, their blood lacks the Duffy antigen that allows the *Pv* parasite to establish erythrocitic infection and so prevents *Pv* from establishing stable transmission.[2]

Ethiopia, however, presents a different case. The country has to deal with a huge burden of *Pv* in addition to high rates of *Pf* morbidity. This may in part be explained by the relatively higher proportion of people that are positive for Duffy antigen expression in Ethiopia compared to other African countries.[3] Both *Pf* and *Pv* are prevalent in a ratio of approximately 75:25 in the country.[4] Ethiopia together with India, Indonesia and Pakistan account for more than 80% of estimated *Pv* cases in the world.[1] While the risks of severe disease and case fatality rates for *Pv* have not been firmly established, *Pv* clearly accounts for a significant proportion of malaria morbidity and the overall burden of disease.

Challenges to effective case management

Globally, thanks to the scale-up of control measures like insecticide-treated bed nets, in-door residual spraying and artemisinin combination therapies, overall malaria cases and deaths have declined over the last decade.[1] Yet, as we see *Pf* cases declining we are seeing a relative increase in the number of cases of the less-researched and harder-to-control parasite, *Pv*. The drive towards malaria elimination in Ethiopia and other countries where both species are prevalent is significantly hindered by the lack of adequate treatment options for *Pv* parasites that lie dormant in the liver.

The only medicine effective against these liver-stage malaria parasites, primaquine, has to be taken for 14 days, a regimen often not completed. This treatment can also be associated with haemolytic side-effects in patients with a deficit in the enzyme glucose-6-phosphate dehydrogenase (G6PD), which in rare cases can be fatal. Ethiopia has limited documentation of the distribution and clustering of G6PD deficiency (small studies suggest that prevalence is between 1.4 and 6.7% among some minority groups).[5] Given these compliance and safety issues, Ethiopia takes the cautious approach and recommends

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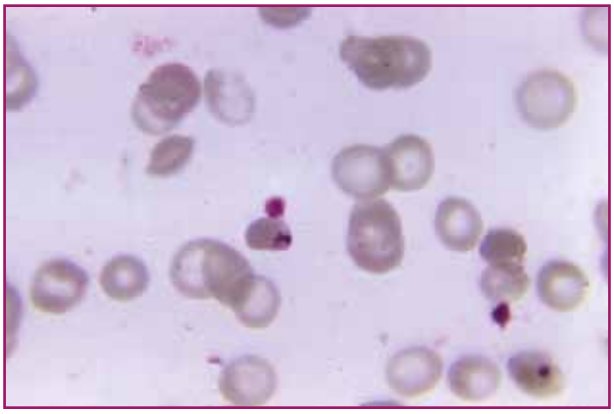
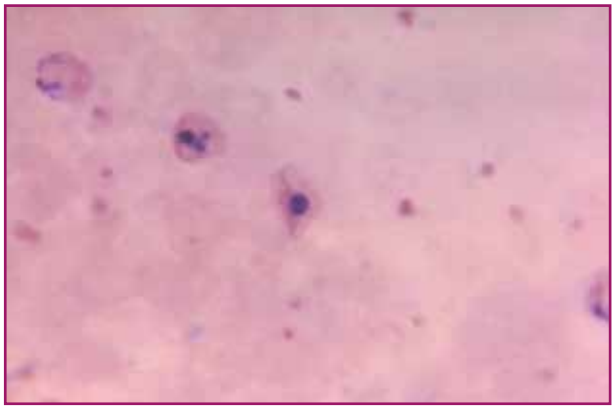


Plasmodium falciparum malarial parasite, which was found in a blood sample from a patient who had begun therapeutic treatment (Photo from the CDC PHIL website)



Under a magnification of 1125x, this thick film photomicrograph revealed the presence of a rounded, compacted and mature Plasmodium vivax trophozoite (Photo from the CDC PHIL website)

the use of chloroquine for *Pv* treatment (although treatment failure on or before day 28 has been observed) and artemether-lumefantrine to treat *Pf*.[6]

Another major challenge in the management of malaria is the tendency of patients in many endemic countries to self-treat themselves either with medicines that are not effective, or with effective drugs at sub-curative levels. Taking lower doses to save cost typically eliminates signs and symptoms of malaria, but does not fully eliminate the parasites and leads to suboptimal plasma exposure to the drug, which can result in the development of drug resistance.

Resistance to artemisinin, the cornerstone of currently recommended first-line treatment for *Pf* malaria has already emerged in Southeast Asia. So far, there have been no proven cases of artemisinin resistance in Ethiopia or anywhere else in Africa. Yet, the looming possibility that artemisinin resistance might also emerge in Africa without the availability of alternative medicines, is of huge concern and warrants regular surveillance, and confirmation should the first cases be seen.

Building research capacity to address challenges

Medicines for Malaria Venture (MMV), a not-for-profit research and development organisation is working with partners across the world on solutions to these challenges. Its focus is to develop next-generation medicines to treat relapsing malaria, tackle drug resistance, and help support the elimination and ultimate eradication of malaria.

In 2014, MMV began working in Ethiopia to help strengthen research capacity, building on facilities already established by Drugs for Neglected Diseases initiative for their leishmaniasis trials. With pharmaceutical partner GlaxoSmithKline (GSK), MMV worked with Gondar and Jimma Universities to trial a potential single-dose treatment for *Pv* malaria. Support from MMV, GSK and the Austrian Ministry of Science, Research and Economy (BMWFW) through European & Developing Countries Clinical Trials Partnership, was used to upgrade the research facilities at Gondar University to meet Good Clinical Practice (GCP) standards required by stringent regulatory authorities like the European Medicines Agency (EMA) and the US Food and Drug Administration (US FDA). This included purchasing laboratory equipment, furniture and office equipment as well as providing GCP refresher training for the teams involved in the studies.

The investigational medicine for *Pv* trialled in Ethiopia is expected to overcome the issues of compliance associated with primaquine. However, it is a member of the same chemical family as primaquine, and shares a similar risk of haemolytic side effects in G6PD deficient patients. To avoid these serious side-effects, GSK is working with PATH[7] to accelerate the development of a G6PD point-of-care diagnostic test so that patients' G6PD enzymatic status can be tested before administering either primaquine or the experimental treatment, should it be approved.

Today, with MMV funding, the sites at Gondar and Jimma are being prepared to trial a new antimalarial compound, MMV048. Discovered by an international team led by Prof. Kelly Chibale from the University of Cape Town, South Africa, MMV048 has potential not only to treat malaria, but also to prevent it and stop its transmission. By undertaking the phase IIa trials of MMV048 in Ethiopia, the intention is also to continue the African heritage of the molecule.

One of the challenges is the recruitment of malaria patients in remote regions within the catchment areas of the trial sites in Gondar and Jimma. To address this, satellite sites in Gondar and Jimma have been identified where a new inpatient/outpatient clinical research laboratory will be constructed. The patient and staff transport capacities are currently being improved through the purchase of a vehicle dedicated to malaria research, while the technical expertise of staff will be strengthened. Those involved in the trial will receive refresher GCP training and advanced diagnostic and laboratory techniques. These efforts will enable us to bring the research closer to people most affected by malaria, thereby improving the quality of care they can receive and supporting the long-term sustainability of the projects.

Prior to these projects with MMV, international interest in malaria research in Ethiopia largely consisted of minor epidemiological studies (frequently student projects) or the exploration of traditional

herbal medicines conducted by a number of universities. Although small in scale, these projects remain valuable as they also help build research capacity, which is currently still limited, especially in terms of laboratory/diagnostic facilities in endemic areas beyond the capital, Addis Ababa.

Today, the support from DND*i*, MMV, BMWFW and GSK is enabling Phase II and III clinical trials to be run in Ethiopia to international standards, making the medicines developed in these facilities eligible for registration by the EMA, the US FDA or WHO's Prequalification Programme. These standards provide assurance that the development of these medicines is underpinned by rigorous safety and efficacy data derived from the same patient population for whom the registered drug is intended.

The Ethiopia experience is a major step forward in creating sustainable capacity for research in sub-Saharan Africa to not only help develop projects for both *Pf* and *Pv* malaria but also for other diseases, such as HIV and tuberculosis. MMV aims to continue to create sustainable capacity for malaria research in Ethiopia and other African countries, building a base for the next generation of researchers to develop the next generation of medicines.

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