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New tools to stop relapse

Preventing malaria relapse for adults and children

While the incidence of *Plasmodium faciparum* malaria infections is highest, *Plasmodium vivax* is the most geographically widespread species of malaria. Although there has been a significant reduction in malaria incidence in malaria-endemic countries recently, the proportion of malaria due to *P. vivax* has been increasing. In 2019, *P. vivax* caused between 5.9 and 7.1 million clinical infections worldwide, many of which were relapses of existing infections that occurred in the absence of a new infective mosquito bite.[1] This happens because *P. vivax* parasites can lie dormant in the liver in a form known as hypnozoites, reactivating to trigger multiple episodes of malaria, weeks, months or even years after the initial mosquito bite.

Tafenoquine (*Krintafel/Kozenis*),[2] developed in partnership with GlaxoSmithKline (GSK), became the first new treatment for the prevention of relapse of *P. vivax* malaria in more than 60 years and the first ever single-dose treatment of its kind. In 2019, tafenoquine received its first *P. vivax* endemic-country market authorization approvals in Brazil and Thailand, followed by Peru in January 2021 (see interview below). A further five endemic countries are currently reviewing tafenoquine submissions.

Prior to 2019, primaquine had been the only available treatment for preventing relapses of *P. vivax* malaria. Low patient compliance with the 7–14 days treatment regimen of primaquine has been shown to compromise its therapeutic efficacy, which underscores the need for new, shorter-course treatments and strategies, such as tafenoquine.

Tafenoquine is currently approved for use in patients aged 16 years and older, however, *P. vivax* can be particularly dangerous for children, not only due to the individual periods of illness, but also to cumulative morbidity and indirect mortality. For example, in Papua, Indonesia, children under the age of five years have been shown to be at significant risk of multiple *P. vivax* relapses leading to death within one year of the initial malaria episode.[3] To help alleviate this burden, MMV and GSK have developed a new paediatric formulation for children weighing less than 35 kg. Evidence has also been generated to support the use of tafenoquine in children and adolescents under 16 years old.

The TEACH[4] study, conducted in Vietnam and Colombia, studied the pharmacokinetics[5] of tafenoquine in children and adolescents to provide information on correct dosing by weight in this age group. Tafenoquine demonstrated within this age group a pharmacokinetics and a safety profile similar to that shown in previous clinical studies. The study also revealed that 95% of the 60 participants enrolled showed no recurrence of *P. vivax* malaria during four months of follow-up. These study results supported regulatory submission to the Australian Therapeutic Goods Administration in November 2020 to extend the indication of single-dose tafenoquine to paediatric populations.

1 WHO World Malaria Report 2020: https://www.who.int/publications/i/item/9789240015791
2 Tafenoquine is marketed as *Kozenis* in Australia and *Krintafel* in the USA. Trademarks are owned by or licensed to the GSK group of companies.
3 Patriani *et al.*, Early and late mortality after malaria in young children in Papua, Indonesia. *BMC Infect. Dis.* 2019;19:922.
4 Tafenoquine Exposure Assessment in Children.
5 Duration of activity of the drug in the body.

INTERVIEW

Dr Veronica Soto Calle
Executive Director of the Directorate for the Prevention and Control of Metaxenic Diseases and Zoonoses, Ministry of Health of Peru

Dr Veronica Soto Calle discusses the challenges Peru faces in managing malaria, particularly in the context of COVID-19, and some possible solutions.

What is the main challenge Peru faces in eliminating malaria?

"The main challenge is securing political support. Malaria has existed in Peru for many years, so people assume it will always be there. Ensuring the political authorities understand that elimination is possible will be critical, because they need to commit to the elimination plans and ensure that the necessary funds are disbursed from the Ministry of Economy and Finance. Sustaining this commitment will be a huge challenge. The Malaria Zero Plan (MZP) has been programmed to last until we achieve malaria elimination, estimated to be in the next 15–20 years. With around 15,000 cases it is not difficult to justify the budget spend, but if we are successful in reducing case numbers, we will need to maintain substantial spending to ensure complete elimination of the malaria parasites. It will be a real challenge to keep the political and financial commitment for elimination when there are very few cases.

What additional challenges has the COVID-19 pandemic brought to malaria control in Peru in 2020 and how have you overcome them?

"One of the major challenges has been patient follow-up. It has been even more difficult during the COVID-19 pandemic in terms of reaching patients in remote areas and ensuring treatment follow-up. Many of the primary healthcare facilities closed during the pandemic, so access to medical care was greatly affected. Fortunately, community health workers have been an invaluable support, especially during 2020. They have continued diagnosing and treating patients in remote rural areas and have led the activities of the MZP. We have also been able to maintain a dedicated team for the MZP, despite many resources having been reallocated to COVID-19 activities. Keeping this dedicated human resource helped us a lot. Another challenge has been the lack of reporting in the national surveillance system. In a non-pandemic year, around 5% of cases do not get reported. Last year this number increased.

What benefit do you feel single-dose tafenoquine and the quantitative glucose-6-phosphate dehydrogenase (G6PD) test could bring to malaria control and elimination efforts in Peru?

"Most malaria patients have *P. vivax,* which means that they receive treatment for at least seven days. Currently, treatment adherence is only around 60%, partly due to patients living in remote areas far from health facilities. If we could have a single-dose treatment, it would be wonderful in terms of adherence. The next phase of the MZP aims to reduce malaria by 99%. We need tools that allow us to achieve that objective. Drugs such as tafenoquine could really boost adherence in future years, combined of course with a safety test such as the G6PD test.

Raquel da Silva's story

The burden of relapsing *P. vivax* malaria on families

Raquel and her son, Carlos

Nossa Senhora de Fatima is a remote village located in the middle of the Brazilian Amazon. In addition to being one of the most beautiful places in Brazil, the Amazonian region also accounts for 99.5% of all national malaria cases.

Raquel da Silva lives in Nossa Senhora de Fatima with her family. For Raquel, the burden of *P. vivax* malaria is heavy. Not only has she been ill with *P. vivax* malaria many times, but she has to care for each member of her family who have been infected one after the other. "My family and I had malaria five times, for 5 consecutive months last year," she says. "When I got malaria, my baby was 6 months old, so I couldn't take the full treatment regimen for 7 days. I took just enough so my symptoms would improve, so it always relapsed. My husband works so he had to leave the house and I didn't have energy to do anything. It was hard."

In addition to transmission through mosquito bites, *P. vivax* malaria can relapse causing multiple episodes of malaria from a single infectious mosquito bite. It impacts efforts to achieve global goals like zero poverty and gender equality. Research shows that each episode of malaria requires at least two days of care, the burden of which is almost always borne by women and girls, preventing them from pursuing economic and social activities like going to work and school.

There is an urgent need to improve access to new tools for relapsing *P. vivax* malaria in these remote villages so that Raquel, and women like her, are relieved of the burden of care, and children can go to school and play fearlessly.

The Ministry of Health, in partnership with MMV, plans to conduct a study to understand the feasibility of implementing quantitative point-of-care G6PD testing with tafenoquine in real-world settings before treatment is made available in Brazil. This study, known as Tafenoquine Roll-oUt Study (TRuST), is due to take place in 2021. Mathematical modelling work conducted by the Pasteur Institute in partnership with the Oswaldo Cruz Institute in Brazil estimates that single-dose tafenoquine could lead to a 38% reduction in transmission and over 214,000 cumulative averted cases within the first five years of introduction in Brazil.[6]

6 Nekkab N *et al.*, "Estimated impact of tafenoquine for *Plasmodium vivax* control and elimination in Brazil: A modelling study" *PLOS Medicine*. 18(4): e1003535 (2021). https://doi.org/10.1371/journal.pmed.1003535.