

5 Reducing the burden of relapsing malaria

The World Health Organization's (WHO's) Global Technical Strategy for Malaria 2016–2030 has set the ambitious target of eliminating malaria from at least 35 countries by 2030.¹ A major challenge in reaching this target is the elimination of *Plasmodium vivax*, a species of malaria parasite that accounts for half of all cases outside sub-Saharan Africa, and is often predominant in countries that are close to eliminating the disease, such as Thailand and Guatemala.² In fact, *P. vivax* accounts for 70% of malaria cases in countries that have fewer than 5,000 cases per year.³

P. vivax causes between 5.9 and 9.3 million clinical infections every year worldwide,⁴ many of which are relapses of existing infections that occur in the absence of a new infective mosquito bite. This happens because *P. vivax* parasites can lie dormant in the liver, reactivating to trigger multiple episodes of malaria, weeks, months or even years after the initial mosquito bite. These relapses not only cause further illness, but also perpetuate the cycle of onward transmission of parasites back into the mosquito during its next blood meal. Until recently, primaquine (PQ) was the only available treatment for preventing relapses of *P. vivax* malaria. However, ensuring patient compliance of the 7 to 14-day treatment regimen for PQ is difficult, and low compliance can compromise therapeutic efficacy. A reduced-frequency dosing schedule to improve compliance was therefore urgently needed.

Tafenoquine: preventing malaria relapses with a single-dose treatment

In 2018, tafenoquine (TQ; *Kozenis/Krintafel*),⁵ developed in partnership with GlaxoSmithKline (GSK) became the first new treatment for the radical cure (prevention of relapse) of *P. vivax* malaria in more than 60 years – and the first-ever single-dose treatment for this indication. TQ was approved by both the US Food and Drug Administration and the Australian Therapeutic Goods Administration in 2018, marking a major regulatory milestone for *P. vivax* elimination efforts. Increasing access to this essential medicine has continued to be a priority for MMV and GSK, with marketing authorization granted in Brazil in 2019 and Thailand in early 2020, and regulatory submissions made in five other *P. vivax*-endemic countries between 2018 and 2020.⁶ MMV and GSK are also seeking to expand access to TQ for one of the most at-risk patient populations (children under 16) through the TEACH⁷ paediatric study, which will support a regulatory submission anticipated in late 2020.

Both PQ and TQ belong to a class of compounds called the 8-aminoquinolines. In individuals who are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD), 8-aminoquinolines can destroy red blood cells, potentially causing anaemia.⁸ To help identify patients eligible for treatment, GSK's partner PATH⁹ has fostered development of a quantitative point-of-care G6PD diagnostic test, which is now approved in nine *P. vivax*-endemic countries.¹⁰

However, despite the relatively low ex-factory cost of TQ, the final in-country cost of the G6PD diagnostic may have an impact on the cost-effectiveness of the complete treatment package¹¹ – a challenge that MMV, together with PATH, is working to address. Preparations are currently underway to support an implementation study of TQ with the G6PD diagnostic test in Brazil (the TRuST¹² study), as well as implementation studies in Thailand and other countries, the results of which are intended to support widespread adoption of these new tools into WHO policy and National Treatment Guidelines.

To support widespread adoption of the new tools to achieve effective radical cure of *P. vivax* malaria, in April 2019, MMV and PATH announced the 'VivAccess' project – a 5-year, jointly-led initiative involving malaria control programmes and other partners in ten countries across Asia, Africa, and Latin America. MMV, PATH and regional groups such as the Asia Pacific Leaders Malaria Alliance are also collaborating to support malaria elimination efforts by developing advocacy strategies and disseminating relevant research and advocacy findings through vivaxmalaria.org. This information hub is available to all countries and is designed to increase global understanding of *P. vivax* malaria (p. 29).

1 World Health Organization. Global Technical Strategy for Malaria 2016–2030 (2015): <https://www.who.int/malaria/publications/atoz/9789241564991/en/>

2 According to the WHO 2019, Thailand reported 3,575 cases of *P. vivax* malaria in 2018 vs. 447 cases of *P. falciparum* malaria; in the same year, Guatemala reported 3,018 cases of *P. vivax* vs. 3 cases of *P. falciparum*.

3 World Health Organization. Control and elimination of *Plasmodium vivax* malaria - A technical brief (2015): <https://www.who.int/malaria/publications/atoz/9789241509244/en/>

4 World Health Organization. World Malaria Report 2019: <https://www.who.int/publications-detail/world-malaria-report-2019>

5 Tafenoquine is marketed as *Kozenis* in Australia and *Krintafel* in the USA. Trade marks are owned or licensed to the GSK group of companies.

6 Regulatory submissions have been completed for India, Ethiopia, Colombia, Peru and Vietnam; submissions to Myanmar and the Philippines are underway as of 2020.

7 Tafenoquine Exposure Assessment in Children.

8 The current label for TQ restricts its use to patients with at least 70% G6PD activity (however, PQ can be given to people with 30–100% G6PD activity).

9 PATH: an international, non-profit global health organization based in Washington, USA.

10 India, Djibouti, Pakistan, Myanmar, Thailand, Indonesia, Philippines, Cambodia, Saudi Arabia.

11 Compared to the current standard of care in each *P. vivax*-endemic country.

12 TRuST: Tafenoquine Roll-out Study.



In 2019, MMV launched vivaxmalaria.org – a comprehensive repository of information on *P. vivax*. The website contains key insights, best practices, tools and resources that are suitable for both general and technical audiences. These are shared and uploaded by a consortium of stakeholders involved in the treatment and control of *P. vivax* malaria. The information hub is currently housed by MMV to support its work with partners on *P. vivax* malaria. Through vivaxmalaria.org, MMV aims to:

- Increase awareness of relapsing *P. vivax* malaria
- Inform stakeholders about progress in the development of new tools
- Promote global partnerships to advance the elimination of the disease

www.vivaxmalaria.org



Representatives of the Brazilian Ministry of Health's Malaria Technical Group, tell us about some of the challenges in controlling relapsing malaria in their country.

13 Pan American Health Organization.
14 Ferreira MJ, Castro MC. "Challenges for malaria elimination in Brazil." *Malar J.* 20;15(1):284 (2016).

What are the main challenges associated with malaria control in Brazil, particularly given the presence of both *Plasmodium falciparum* and *P. vivax* malaria?

While there are a number of challenges for malaria control in Brazil, the main concerns are around access to remote populations, logistical issues (e.g. car, boat and fuel) to reach certain areas during the rainy or dry season, and a lack of trained healthcare workers in the field. A major challenge with *P. vivax* malaria is ensuring that people comply with the long treatment regimen (minimum 7 days), as studies show that around 20% of people do not complete treatment. This leads to relapses and continuous onward parasite transmission.

What is the potential impact of TQ on the clinical case management of *P. vivax* in Brazil?

TQ has similar efficacy to PQ, but it's a single-dose regimen and so can improve compliance to treatment, which can potentially lead to better control of *P. vivax* malaria and perhaps even elimination in some areas. However, several challenges must first be addressed. Operationalizing quantitative G6PD testing before prescribing TQ for the population will be expensive. Furthermore, we need to ensure quality control of the tests and also train more healthcare workers, so that these can be rolled out across the country. This is why we are conducting an implementation study (TRuST).¹²

How are results from the TRuST study expected to inform policies regarding TQ in Brazil?

We expect results from the TRuST study to provide insights about the possibilities and associated challenges of TQ implementation in Brazil, particularly regarding its cost-effectiveness (given the additional expense of the G6PD test). The Ministry of Health will analyse the results to define if, when and where it will be possible to use TQ in Brazil.

What is the National Malaria Control Programme's (NMCP's) strategy for malaria elimination in Brazil?

The NMCP is developing a new elimination plan for the country using recommendations from the WHO and PAHO¹³ and will discuss it with specialists and states, as they are involved in elimination strategies in their municipalities. Ultimately, to achieve complete elimination, we need to ensure political commitment so that all such elimination plans can be implemented in a sustainable manner.

Moises's story



Tucked away in a remote corner of the Brazilian Amazon is a village called Nossa Senhora de Fatima. The only way to reach this village is by boat. Located in one of the most endemic regions for relapsing malaria, the inhabitants of this village are very familiar with their local malaria clinic, which provides front-line care. Brazil carries one of the highest burdens of malaria in Latin America, and the Amazon region within the country accounts for 99.5% of all national cases.¹⁴

This was the third time in the recent past that Moises Da Silva was seeking treatment for malaria. For a young, able-bodied man like Moises, relapsing malaria is very disruptive. Having now experienced two relapses following his initial infection, Moises can easily recall the specific symptoms. He says, "You feel cold. It's hot outside, but your body feels cold. You wrap yourself under a pile of sheets, still you shake all over."

In Amazonian villages like Nossa Senhora de Fatima, the abundant presence of mosquitoes complicates the situation further. There are times when several members of the family are suffering from malaria at the same time. Though not known to be the deadliest killer in the malaria family, *P. vivax* malaria can still kill and has devastating impacts on the social and economic lives of people. People like Moises, who live in remote endemic regions where relapsing malaria is a daily reality, are in need of medicines that can treat *P. vivax* malaria once and for all.

Source: Relapsing malaria in Brazil (film by MMV and ITN Productions)

