P. vivax malaria: Transforming treatment & revitalizing elimination efforts

Why is *P. vivax* malaria of pressing concern now?

P. vivax malaria is a major public health and economic challenge and presents a major obstacle to achieving malaria elimination goals in countries in Latin America, the horn of Africa and Asia-Pacific. In some regions, as *P. falciparum* malaria is declining, *P. vivax* is becoming the most dominant parasite. For example, in Southeast Asia, the species is responsible for one-third of malaria cases.[1] Its ability to relapse from dormant liver stage parasites known as 'hypnozoites' make it much harder to eliminate, while also exerting a repeated and debilitating impact on those infected, as well as their communities, health systems and regions.

Current treatment options are often only partially implemented because of cost, difficulty identifying which patients should receive treatment, and long treatment regimens that lead to poor adherence.

What is the role of VivAccess?

VivAccess aims to support the adoption and use of new tools to improve case management, reduce individual suffering and the global disease burden, and support the elimination of relapsing *Plasmodium vivax* malaria. Diagnosis, appropriate treatment, and effective radical cure of *P. vivax* malaria require concurrent availability and coordinated use of

1. a malaria blood-stage diagnostic (either a rapid diagnostic test [RDT] or microscopy),
2. a G6PD diagnostic test,
3. a blood-stage antimalarial, either chloroquine or an artemisinin-based combination therapy (based on respective national strategies), and
4. tafenoquine or primaquine (PQ) to clear parasites from the liver.

VivAccess supports countries in the delivery of these four key elements in multiple *vivax*-endemic countries across Latin America, the Asia-Pacific and in sub-Saharan Africa.

What new tools exist for radical cure?

Tafenoquine (TQ) is the latest addition to the relapsing malaria armoury and could help transform treatment of *P. vivax* malaria by potentially providing effective elimination of the hypnozoite stage or 'radical cure' in a single dose, thereby overcoming adherence issues. The medicine is the first for this indication in more than 60 years and could thereby support elimination efforts. It was approved by Stringent Regulatory Authorities[2] in 2018. However, TQ (like PQ) can also have potentially harmful side effects in people who have low and intermediate activity of an enzyme known as glucose-6-phosphate dehydrogenase (G6PD).

G6PD diagnostic tools are vital to accurately measure patients' G6PD enzyme activity, guiding treatment decisions so that they receive the correct type and dose of anti-relapse drug. Among commercially available point-of-care G6PD diagnostics is a new quantitative test, STANDARD™ G6PD, which measures enzyme activity. In 2019, the STANDARD™ G6PD received a conditional approval (category 2) from the Expert Review Panel for Diagnostics. As such, the product is now available for procurement through the Global Fund.

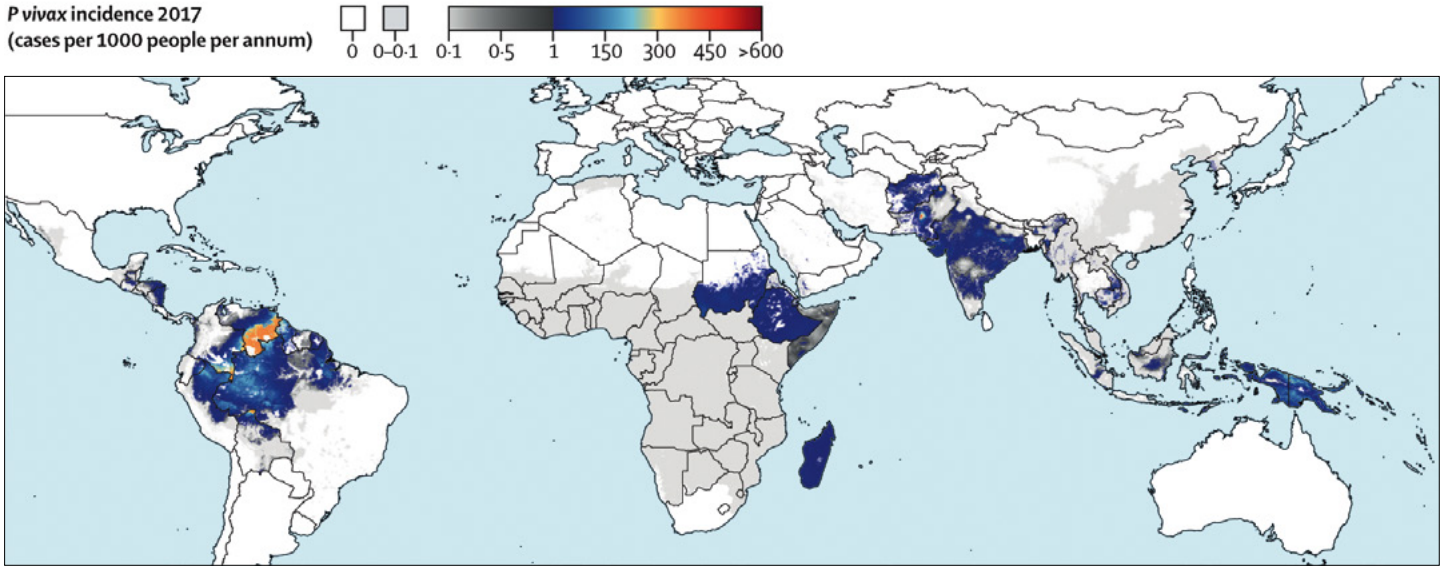
1. WHO World Malaria Report 2018: https://apps.who.int/iris/bitstream/handle/10665/275867/9789241565653-eng.pdf?ua=1
2. The United States Food and Drug Administration (US FDA) and the Australian Therapeutic Goods Administration (AU TGA)

VivAccess is a PATH and MMV partnership supporting countries to eliminate *P. vivax malaria*

MMV Medicines for Malaria Venture

PATH

Predicted incidence in 2017



Battle K, Lucas T, Nguyen M *et al*. Mapping the global endemicity and clinical burden of *Plasmodium vivax,* 2000–17: a spatial and temporal modelling study. *The Lancet,* 394(10195). 332-343 (2019).
The biology of *P. vivax* means that the clinical case estimates generated here represent only a proportion of the total parasite reservoir, which includes a large proportion of asymptomatic infections' citing Teun Bousema's work: T Bousema, L Okell, I Felger, C Drakeley. Asymptomatic malaria infections: detectability, transmissibility and public health relevance. *Nat Rev Microbiol,* 12 (2014), pp. 833-840

How can these tools help transform treatment and revitalize *P. vivax* elimination efforts?

Improve patient outcomes: Multiple relapses of malaria can lead to anaemia (a decrease in red blood cells), making people weaker and more susceptible to other diseases that can be fatal, particularly in young children and the elderly. In the short term, repeated infections prevent people from attending work or school. In the long term, they can have a negative and lasting impact on physical and cognitive development leading to lower productivity later in life. Effective treatment to reduce relapses could help reverse these negative trends.

Increase healthcare workers' confidence to treat P. vivax malaria: Accurate G6PD diagnostics help ensure healthcare workers select the appropriate type and dose of anti-relapse medication. Once they know a patient has normal G6PD enzyme activity they can confidently give them a dose of TQ to treat the hypnozoites that are present and reduce relapse.

Ensure patients take their full course of treatment: Primaquine, the current WHO recommended treatment for relapsing malaria, requires patients to take daily doses for 7–14 days. Adherence to such a long treatment regimen is low unless directly observed.[3,4,5] Providing patients with a single-dose cure to reduce relapse automatically increases their adherence to treatment.

Reduce costs: Recent research has estimated that the global economic burden of *P. vivax* malaria is USD 330 million per year. These costs include repeat treatment for the same infection which not only impacts the healthcare system but also the patient and more broadly, the economy. Adopting a policy of screening for G6PD deficiency together with delivery of a highly effective radical cure is projected to save USD 45 million per year.[6]

Accelerate progress towards elimination goals: During a *P. vivax* malaria relapse, parasites re-emerge in a person's bloodstream where they can be picked up by mosquitoes and spread to other people. Ensuring appropriate radical cure of patients with *P. vivax* malaria should reduce transmission which will reduce the overall burden of the disease and help countries achieve their elimination targets.

3. Takeuchi R, Lawpoolsri S, Imwong M *et al.* Directly-observed therapy (DOT) for the radical 14-day primaquine treatment of *Plasmodium vivax* malaria on the Thai-Myanmar border. 1–8 (2010).
4. Abreha T, Hwang J, Thriemer K *et al.* Comparison of artemether-lumefantrine and chloroquine with and without primaquine for the treatment of *Plasmodium vivax* infection in Ethiopia: A randomized controlled trial. 1–17 (2017).
5. Douglas NM, Poespoprodjo JR, Patriani D *et al.* Unsupervised primaquine for the treatment of *Plasmodium vivax* malaria relapses in southern Papua: A hospital-based cohort study. 1–19 (2017).
6. Devine A. The Economics of Vivax Malaria Treatment. PhD thesis The Open University (2018): https://osf.io/wj6a8/download/

PATH and Medicines for Malaria Venture (MMV) are jointly leading an initiative called VivAccess to support countries in the elimination of *P. vivax* malaria. The goal of VivAccess is to support introduction and access to a suite of radical cure products to address the challenges associated with *P. vivax* malaria. These products include malaria diagnostics, G6PD diagnostics, blood-stage drugs, and liver-stage radical-cure drugs. Guided by the leadership of national health agencies, VivAccess will provide support in terms of market analytics, technical expertise, and product delivery coordination as countries seek to introduce effective radical cure into national malaria protocols and accelerate progress towards malaria elimination goals. This work is funded by the Bill & Melinda Gates Foundation.

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