The Partnership for Vivax Elimination (PAVE): Supporting radical cure for *P. vivax* malaria in endemic countries



ABOUT PAVE

PAVE supports countries in adopting new and existing tools and approaches to achieve universal access to the best clinical practices for *Plasmodium vivax (P. vivax)* case management. Our goal is to support countries in accelerating the elimination of *P. vivax* malaria. PAVE engages with National Malaria Programs to increase knowledge of tools, support policy change, procurement, and roll-out of products, such as glucose-6-phosphate dehydrogenase (G6PD) diagnostics, rapid diagnostic tests for malaria, primaquine (PQ) and tafenoquine (TQ). PAVE works with partners at global, regional, and country levels to jointly develop and implement strategies supporting the elimination of *P. vivax*.

The project supports partners and representatives from the global malaria community by providing evidence-based information relevant for decision-making processes. In Latin America, PAVE's work has been focused on Brazil, Colombia, and Peru and the current portfolio is aimed at generating evidence and coordinating with governments on their requirements regarding the potential future adoption of TQ and a semi-quantitative point-of-care G6PD test. At the global level PAVE is coordinating operational research and feasibility studies in a number of endemic countries to generate high-quality evidence on *P. vivax* case

management that can be considered by normative agencies and national governments in making policy decisions and guiding implementation. PAVE is also advancing the development of quality-assured, child-friendly treatments for relapse prevention.

PAVE facilitates access to new and existing malaria diagnostics and treatments for *P. vivax* elimination.

PAVE consolidates its project work from multiple funders and is aligned with country partners and the World Health Organization (WHO) to accelerate progress. This project is led by <u>Medicines for Malaria Venture</u> (MMV)¹ and <u>PATH</u>², in close partnership with Ministries of Health, country partners, and other not-for-profit organizations. PAVE combines investments from <u>Unitaid</u>, the Bill & Melinda Gates Foundation, the UK Foreign, Commonwealth and Development Office (FCDO) and MMV core funding, among others.

TAFENOQUINE

The WHO's treatment guidelines for *P. vivax* malaria recommend a three-day treatment with chloroquine (CQ) or artemisinin-based combination therapies (ACTs) to eliminate the parasite's blood stage form. PQ is currently the only treatment recommended by WHO to prevent relapse. It treats the liver stage of the disease. There is a broad consensus that patient compliance with 7- and 14-day PQ treatment regimens is poor.

Given the challenge in ensuring treatment compliance and the resulting risk of malaria relapse, the PAVE team envisions that TQ, a non-patented new single-dose medicine to treat the liver stage of *P. vivax* malaria, could play a significant role in the pathway toward elimination. First synthesized in 1978 by U.S.'s Walter Reed Army Institute of Research, and later co-developed by GlaxoSmithKline (GSK) and MMV, the drug in combination with CQ reduces the risk of recurrence of *P. vivax* malaria at 6 months in about 70% compared to placebo³. As

a single-dose medicine, TQ has the potential to improve patient adherence to treatment.

TQ is the first medicine approved by the U.S. Food and Drug Administration agency (FDA) for the treatment of *P. vivax* malaria in over 70 years, an important milestone in *P. vivax* malaria treatment. The drug has also received regulatory approval by Australia's Therapeutic Goods Administration (TGA). National regulatory authorities in Brazil, Thailand and Peru have also approved TQ. Registration is pending approval in Colombia. An application to extend the indication of single-dose tafenoquine to paediatric populations has been made to TGA and approval is pending. The application was supported by a Phase 2b clinical study (TEACH)⁵ that evaluated dosages of tafenoquine based on weight for children between the age of 6 months and weighing at least 5 kg, up to 15 years.

^{1.}A not-for-profit Swiss Foundation working to develop new antimalarial drugs for vulnerable populations.

^{2.} PATH is a global nonprofit dedicated to achieving health equity. PATH develops and scales up innovative solutions to the world's most pressing health challenges

^{3.} Lacerda MVG et al., Single-Dose Tafenoquine to Prevent Relapse of Plasmodium vivax Malaria. N Engl J Med. 2019 Jan 17;380(3):215-228. doi: 10.1056/NEJMoa1710775.

^{4.}World Health Organization. Guide to G6PD deficiency rapid diagnostic testing to support P. vivax radical cure. 2018. https://bit.ly/3wPpohb

^{5.} Tafenoquine Exposure Assessment in CHildren (TEACH) was an open-label, non-comparative, multi-centre Phase 2b study to assess the pharmacokinetics (PK), safety, and efficacy of single-dose tafenoquine in the treatment of paediatric subjects with *P. vivax* malaria. To learn more about the study please visit this link.

G6PD DIAGNOSTICS

G6PD deficiency is a condition that affects over 400 million people worldwide and its prevalence varies in malariaendemic countries. TQ and PQ have the potential to cause harmful side effects in people with lower-than-normal levels of G6PD enzyme activity. As a result, testing for G6PD deficiency prior to the use of PQ for radical cure of *P. vivax* malaria is recommended by <u>WHO</u>⁴. Currently, reliable, quantitative, point-of-care G6PD testing is not available in most health facilities in malaria endemic countries. To support access to G6PD testing, PATH has partnered with <u>SD Biosensor</u> for the development of a new G6PD semi-quantitative, point-of-care test. The device makes it easier to identify patients with low levels of G6PD enzyme activity informing health providers on treatment options according to their G6PD deficiency results. All patients should have a systematic follow-up visit the day following treatment with TQ or after the last dose of PQ to detect any adverse reactions to the drug.

The effort to develop a new G6PD diagnostic test accounted for real-world conditions typical of malariaendemic areas, such as rural and remote regions of tropical countries, with high temperatures and high humidity. The STANDARD[™] G6PD Test developed by PATH and SD Biosensor works in a wide range of temperatures, is battery-powered, portable and generates diagnostic results within 2 minutes.

The STANDARD[™] G6PD Test has received regulatory approval from both Brazil's ANVISA and Colombia's INVIMA. DIGEMID, Peru's health regulatory agency, has approved the device and quality controls, while registration of the test strips is pending. The device has received Australian TGA marketing authorization and has been submitted for WHO pre-qualification.

EVIDENCE-BASED DECISION-MAKING

Clinical evidence from the TQ's Phase III program already supports the risk/benefit profile of TQ for the management of *P. vivax* infection. Along with National Malaria Control Programs and following the granting of marketing authorization for both products in a particular country by the regulatory authority, PAVE will evaluate the operational feasibility of introducing TQ and the STANDARDTM G6PD Test in real world settings and determine the health system's ability to support the introduction.

By providing decision makers with this evidence, countries will be able to consider policy change aimed at optimizing *P. vivax* treatment schemes most appropriate for their local contexts.

CONTINUOUS DIALOGUE

Since 2016, PAVE partners have been working with National Malaria Programs from Brazil, Colombia and Peru, as well as regional and global organizations committed to malaria elimination, such as the Inter-American Development Bank (IDB) and under normative guidance from the Pan-American Health Organization (PAHO). Through this continuous dialogue, PAVE can better engage in understanding national and regional malaria prevention, control and treatment programs and priorities, and support countries' efforts in their respective strategies for *P. vivax* elimination.

The development of paediatric primaquine and planned feasibility studies described for Peru are supported with funding from Unitaid



ONGOING & AVAILABLE STUDIES IN THE REGION

Safety and Efficacy

- Phase III studies for single-dose tafenoquine: DETECTIVE (Efficacy study in Brazil, Peru, Ethiopia, Thailand, Philippines and Cambodia): <u>carried out between</u> <u>2014 - 2016</u>
- GATHER (Safety study in Brazil, Colombia, Peru, Thailand and Vietnam): <u>carried out between 2015 2016</u>
- Tafenoquine pediatric dose: <u>carried out between 2017</u> and 2020

Operational feasibility

- Feasibility (Peru): protocol development stage
- Feasibility (Brazil): initiated in Q3 2021; preliminary results expected in Q1-Q2 2022
- SafePrim (Brazil): published May 2021

Clinical Validation for SDB test

• "STANDARD[™] G6PD Test" Clinical Evaluation (Brazil and the US): <u>published August 2021</u>

Health Economics

- Cost-Effectiveness (Brazil): initiated in 2019. Results expected in early 2022
- Budget Impact Analyses (Brazil): initiated in 2021; results expected in early 2022
- Cost-Effectiveness and Budget Impact Analyses (Colombia): initiated in 2021; results expected in early 2022

Epidemiology

Modelling – public health impact (Brazil): <u>published April</u>
<u>2021</u>







You can find more resources and news about relapsing malaria at *P. vivax information hub.*

PAVE thanks all it's donors for their continued support.