PAVE
Partnership for Vivax Elimination

New treatment for *P. vivax* malaria may benefit Brazilian public health

Study led by researchers from Fiocruz and Institut Pasteur provides new positive data

Summary

A population-level transmission dynamics modelling study by Nekkab et al. on the estimated impact of tafenoquine (TQ) — a new single-dose treatment for the prevention of relapse of *Plasmodium vivax* malaria — on control and elimination in Brazil was recently published. It is the first study to show how rolling out TQ in populations can improve case management of *P. vivax*, reduce transmission, and prevent a substantial number of cases, even in settings with high rates of effective case management with primaquine (PQ). Its main finding was that, compared to Brazil's current standard regimen, PQ over 7 days, the use of TQ following a glucose-6-phosphate-dehydrogenase (G6PD) screening test has the potential to improve effective radical cure rate from 42% to 62% through increased treatment adherence and protection from new infections. Thus, with the new treatment, transmission could be reduced by 38% over a 5-year period in Brazil across mixed transmission settings.

Background

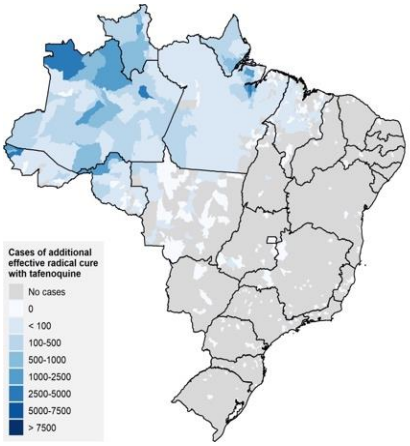
P. vivax malaria infection occurs through the bite of an infectious mosquito. Once in the bloodstream, the *P. vivax* parasite infects the blood and causes an acute malaria episode. Some parasites lie dormant in the liver, from where they can periodically reactivate, causing disease relapse despite successful treatment of the acute blood-stage infection. Hence, a single *P. vivax* infection can cause multiple episodes of malaria, even in the absence of a new mosquito bite. Relapses can occur weeks, months, or even years after the initial infection. Radical cure entails treating the malaria infection in both acute blood-stage and dormant liver-stage to prevent relapse.

The current standard of care for the dormant liver-stage is PQ, requiring a 14-day course of treatment, as per World Health Organization (WHO) guidelines. Brazil's treatment guidelines recommend administering low doses of PQ over 7 days[i,ii,iii]. TQ, a new non-patented drug developed by GSK and Medicines for Malaria Venture (MMV), belongs to the same class of antimalarials as PQ but is a single-dose treatment for the dormant liver-stage of *P. vivax* malaria. Like PQ, TQ can cause adverse effects (e.g., hemolysis) in patients with lower-than-normal levels of the G6PD enzyme. Consequently, it should be administered only to patients confirmed to have over 70% of G6PD activity—that is, normal enzymatic activity.

Effective radical cure with PQ or TQ as part of *P. vivax* case management provides both a direct benefit to the treated patient by preventing future relapse infections and an indirect benefit by preventing onward transmission in the community. In addition, TQ, as a single-dose antimalarial, has the potential to improve treatment adherence, and thus, its effectiveness.

The study

Public health modelling studies are powerful tools that use mathematical models to measure potential outcomes of implementing health care policies that may be impossible or impractical to measure in real-life settings. This study, led by Fiocruz and Institut Pasteur, modelled the introduction of TQ after screening for G6PD deficiency as a routine treatment for *P. vivax* malaria in Brazil. It looked at the impact this was likely to have on both radical cure rates and onward transmission over a 5-year period across the *P. vivax*–endemic region with mixed transmission settings.



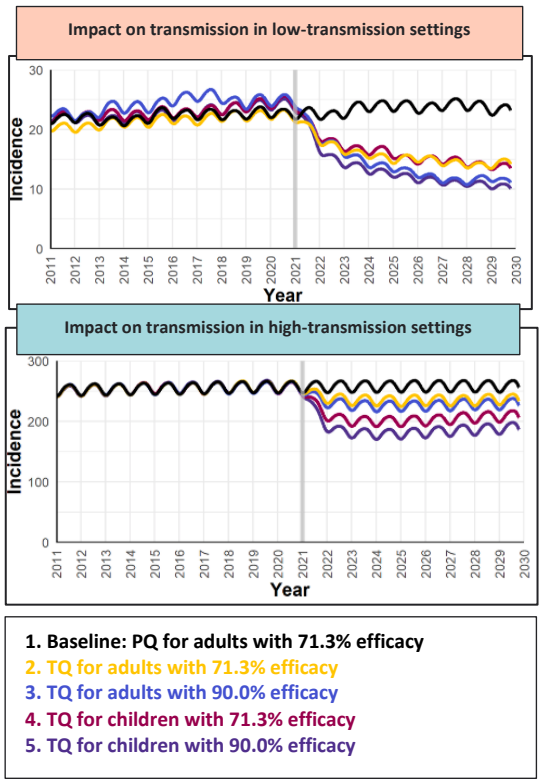
The research team gathered data from case reports from the SIVEP-Malaria database[iv] from 2018 to inform the model's parameters, calibrating it for the 126 Brazilian municipalities reporting at least 100 *P. vivax* malaria cases per year. The model considered treatment efficacy, adherence, G6PD deficiency rates, low CYP2D6 metabolization prevalence, and caseload in different transmission settings, with data obtained from nationwide malaria case reports, clinical trials, and published literature. The study assessed predicted disease impact 5 years after the concurrent introduction of TQ and G6PD testing in different epidemiological scenarios.

Main results

The main advantage of introducing TQ treatment is that its single-dose regimen ensures full compliance compared to the longer 7-day PQ regimen currently used in Brazil, resulting in an increase of the overall rate of effective radical cure.

Results from the model predicted that TQ rollout for adults would improve the mean effective radical cure rate from 42% to 62% among clinical cases, leading to a predicted 38% reduction in transmission, equivalent to over 214,000 cases averted cumulatively over 5 years of implementation.

TQ would increase the rate of radical cure by approximately 20% compared to the current treatment regimen, benefiting patients and health systems as it reduces the risk of relapse.



In addition to improved treatment outcomes, TQ would also help reduce transmission over time, considering different epidemiological contexts simulated by the model. The effect of TQ on reducing malaria transmission is predicted to be higher in settings with low transmission, suggesting that TQ can be especially impactful in settings closer to elimination.

Additionally, the study observed that impact would be more significant in settings with low preexisting PQ adherence and where there is a high proportion of working-age males who are

eligible for TQ, as there may be an additional risk of infection associated with occupational exposure in this population.

The study also highlighted the important role that paediatric TQ could play if approved by regulatory bodies and introduced. The model predicts that a paediatric formulation that reduces the minimum age for TQ treatment from 16 years to 2 years is estimated to cause larger reductions in transmission, with the median effect size increasing from 38% to 45%.

In a high-transmission setting with more infections in children and where a portion of transmission is driven by asymptomatic infection that reduces treatment-seeking behavior, TQ would still reduce new infections between 9% when administered to adults and 21% when children are also treated.

Implications for the Brazilian public health system

Results from this modelling study indicate that introducing TQ and the G6PD test in Brazil's public health system would be beneficial; it would enable access to a more-effective radical cure treatment and drive a reduction in malaria relapses and transmission, thus preventing a substantial number of cases. Additionally, the study considered epidemiological and demographic variables that influence the impact of TQ, causing outcomes to vary in different transmission settings. As such, these results can also be helpful to provide evidence to inform context-tailored interventions that would contribute to reaching malaria elimination goals.

Note: *This non-technical brief is based on a paper published in* PLOS Medicine *titled "Estimated impact of tafenoquine for* Plasmodium vivax *control and elimination in Brazil: A modelling study" by Nekkab N et al. (April 2021). For more details, please refer to the published results (https://doi.org/10.1371/journal.pmed.1003535).*

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[i] 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. *Malaria Journal.* 2010;9:308. https://doi.org/10.1186/1475-2875-9-308.
[ii] 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. *PLOS Medicine.* 2017;14(5):e1002299. https://doi.org/10.1371/journal.pmed.1002299.
[iii] 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. *PLOS Medicine.* 2017;14(8):e1002379. https://doi.org/10.1371/journal.pmed.1002379.
[iv] SIVEP-Malaria stands for Malaria Epidemiological Surveillance Information System.