

# Village malaria workers for the community-based management of vivax malaria

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## Summary

In Cambodia, malaria cases are on a trajectory towards the goal of malaria elimination by 2025. Vivax malaria is difficult to eliminate because of hypnozoites that can cause relapse. Primaquine, an 8-aminoquinoline, clears hypnozoites but requires testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency. Routine primaquine treatment of vivax malaria has recently been implemented in Cambodia in which Village Malaria Workers (VMWs) diagnose vivax malaria by rapid diagnostic test and refer patients to health centres for G6PD testing and further treatment. Patients are referred back to the VMWs for monitoring adverse symptoms and treatment adherence. This article explores how VMWs' roles might be optimized for the community-based management of vivax malaria. With sufficient training and supervision, the role of VMWs might be expanded to include G6PD testing, making referral to the health centre superfluous. Community-based management of vivax malaria could increase the coverage of radical cure and accelerate vivax malaria elimination.

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## Introduction

Cambodia aims to eliminate malaria by 2025.<sup>1,2</sup> The ambitious elimination effort was initially triggered by the emergence and spread of artemisinin resistance in *Plasmodium falciparum* more than a decade ago, followed by increasing artemisinin-based combination therapy (ACT) treatment failure caused by subsequent resistance to ACT partner drugs.<sup>3,4</sup> With the incidence of falciparum malaria now reduced to just a few hundred cases per year, *Plasmodium vivax* has become the prominent species causing malaria in Cambodia.<sup>5</sup> The proportion of vivax malaria has increased steadily over the last few years, from 84% in 2019, to 90% in 2020 up to 93% in 2021.<sup>6</sup> Vivax malaria is more difficult than falciparum to eliminate because of the hidden parasite reservoir of dormant stages in the liver of the patient. These 'hypnozoites' can reactivate after a period of months to years, causing a relapse.<sup>7,8</sup>

The radical cure of vivax malaria is the elimination of both blood-stage and hypnozoite stage parasites, and thus requires treatment with 8-aminoquinolines in

addition to regular blood-stage antimalarials. On a population level, the burden of vivax malaria will reduce gradually without radical cure, but the implementation of the radical cure could be the critical factor for accelerating the elimination of vivax malaria.<sup>9</sup> The radical cure is currently only partially implemented in Cambodia.<sup>6,7,10</sup> An important barrier to the wider implementation of the radical cure is the concern for intravascular haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) treated with 8-aminoquinolines, which makes it necessary to assess G6PD enzyme activity prior to the prescription of treatment.<sup>5</sup> Currently, G6PD testing is only provided at the health centre or hospital, requiring referral and travel for a patient to the higher level of the health system. In practice, successful referral is not achieved consistently, resulting in inadequate coverage of the radical cure and continued transmission of vivax malaria. A more promising strategy could be community-based management of vivax malaria in which VMWs use point of care devices for quantitative G6PD measurement followed by the provision of radical cure treatment.

In this article we discuss core elements for community-based malaria worker networks to enable community-based management of vivax malaria.<sup>11–13</sup>

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## Radical treatment of vivax malaria and G6PD testing

Current drugs for radical cure include primaquine and tafenoquine, which have oxidative properties potentially causing intravascular haemolysis in G6PD deficient individuals.<sup>14</sup> The gene coding for the G6PD enzyme resides on the X-chromosome and about 140 gene mutations have been described, mostly resulting in functional enzyme variants with reduced activity.<sup>15</sup> Males are hemizygous for the G6PD gene and can either have normal gene expression or be G6PD deficient. Females, who have two copies of the G6PD gene on each X chromosome, can have normal gene expression or be heterozygous for the gene mutation resulting in intermediate levels of enzyme deficiency. Identification of heterozygous women at risk for haemolysis requires quantitative assessment of G6PD activity.<sup>16</sup> Current qualitative point of care tests are not reliable in identifying this group.<sup>17</sup> For the purpose of radical cure, current Cambodian guidelines recommend a 14-day course of primaquine in a dose of 0.25 mg/kg per day or, for G6PD deficient individuals, a dose of 0.75 mg/kg/weekly for 8 weeks. Quantitative assessment of red blood cell G6PD enzyme activity is required to decide on the primaquine regimen. Conventional quantitative tests, such as spectrophotometry, requires the use of a well-equipped laboratory with trained staff.<sup>18</sup> However, point of care quantitative tests are becoming increasingly available in the format of user-friendly biosensors.<sup>18,19</sup> Since 2021, Cambodia has started deployment of G6PD biosensors at the health centre level. At the VMWs level, several groups in Cambodia and elsewhere are currently assessing the performance and operational aspects of the SD biosensor.<sup>5,20–22</sup>

## Current management of vivax malaria at the community

Cambodia has an extensive network of 2548 VMWs and 275 mobile malaria workers (MMWs), which covers the large majority of rural villages in the malaria endemic areas.<sup>6</sup> Most of the communities they serve have few alternative health care providers and early diagnosis and treatment of malaria are thus dependent on VMWs and MMWs.<sup>23–25</sup> Vivax malaria patients identified by community-based VMWs and MMWs are referred to a health centre for G6PD testing and radical cure treatment. Apart from minimal monthly incentives, VMWs and MMWs receive additional incentive for each new cases of malaria when they diagnose, refer and follow-up in the community. In the community, VMWs/MMWs supervise radical cure, monitor clinical recovery, observe urine colour as an indicator of intravascular haemolysis, follow-up for adherence on days 3, 7 and 14, and report patient outcomes. To promote successful referral, a system of ‘assisted referral’ was recently introduced, where patients are accompanied by VMWs

or delegates to facilitate the journey from the village to the nearest health centre. However, travel to the health centre remains an important barrier. Since vivax malaria has receded to remote areas and is prevalent mostly among forest goers, patients are often unwilling or unable to travel to a health centre.<sup>26,27</sup> Reasons for this include long distances, poor road conditions, lack of money for transportation, and loss of time and income.<sup>28</sup> Preliminary reports show considerable reluctance among patients to spend time and money to visit health centres once they are diagnosed with vivax malaria. Based on a pilot study assessing the referral system for vivax malaria, less than a third of *P. vivax* patients (27.3%; range 15–38%) identified by VMWs completed referral to the nearest health facilities for G6PD testing.<sup>6,21</sup> The referral rate varied between provinces, from 21% in Kampong Speu to 54% in Kampong Chhnang. This recent study, which was confined to male patients, showed that the proportion of patients completing a 14-day course of primaquine was 23% (747 completed radical cure treatment from a total of 3239 *P. vivax* cases).<sup>6,21</sup>

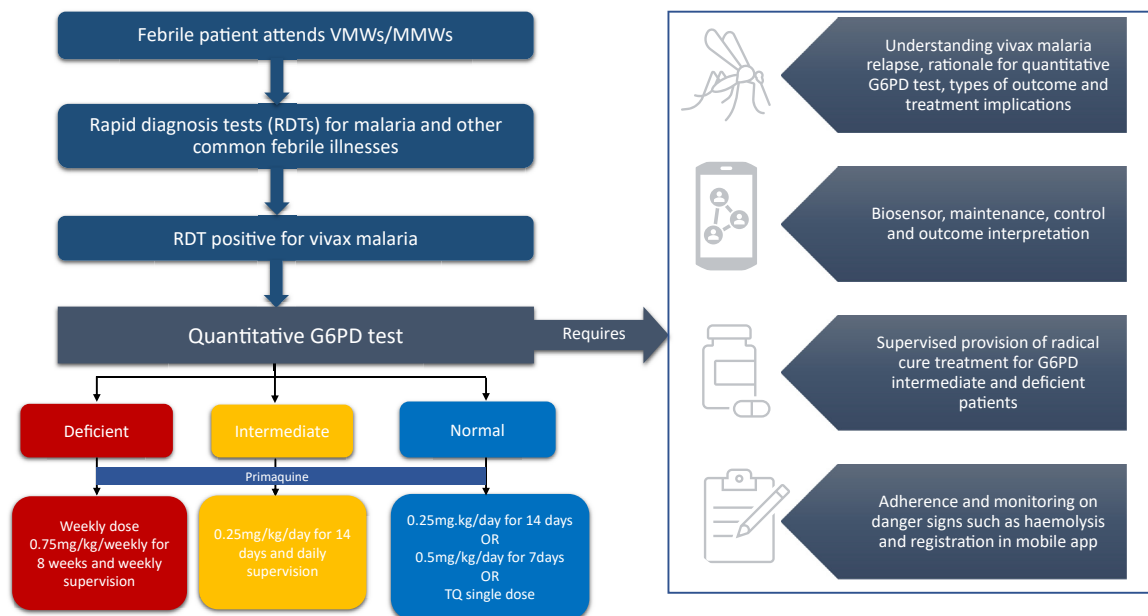
## Utilizing village malaria workers for community-based vivax malaria elimination in Cambodia

A potential approach to mitigate poor adherence to current referral system is to implement G6PD testing with a biosensor and treatment with primaquine at the community level. For this, VMWs will need to receive training and supervision for both G6PD testing and to provide the appropriate radical cure regimen to vivax malaria patients without requiring referral to the health centre.

Most VMWs have some formal education, are literate, and take on devolved health related responsibilities. Adding supplementary tasks to the current responsibilities of village malaria workers requires that these tasks are effective, economical, and acceptable to VMWs and the communities. Assessing these parameters goes beyond the usual evidence generated in clinical trials.<sup>29</sup> Studies are underway evaluating the feasibility of introducing point of care tools to identify G6PD deficiency, in particular assessing whether community health workers can identify reliably G6PD deficiency and subsequently provide appropriate treatment.<sup>20</sup>

The introduction of G6PD testing and radical cure treatment as opposed to an ACT alone, will also require VMWs to be able to understand the differences between falciparum and vivax malaria in more detail (Fig. 1).<sup>30</sup>

In the past, VMWs provided identical treatment with ACTs to patients with either falciparum or vivax malaria. When a referral system for vivax malaria is introduced, the importance of radical cure and G6PD testing for patients with vivax malaria needs to be clearly communicated with the VMWs and the community to avoid the



**Fig. 1:** Schematic diagram to demonstrate how village malaria workers and their network could be trained and supervised for community-based vivax malaria management.

perception that this referral is an unnecessary burden. Explaining the rationale for G6PD testing is essential when introducing the community management of vivax malaria. VMWs can be selected based on past performance and interest in taking on additional responsibilities. It will be important to avoid overburdening of VMWs and MMWs by adding extra tasks. Expanding the service package provided by VMWs has a risk of overburdening the VMWs, most of whom have many other responsibilities in addition to their malaria work. Mitigating this risk involves proper engagement with VMWs to discuss workload, and integration of the additional activities into their routine work, including providing sufficient incentives, support, training, and time allocation.<sup>31,32</sup> Continued support for the VMWs and MMWs networks will be crucial, including adequate incentives for the individual's roles, responsibilities, and values. Currently, this support is mainly provided by donors, such as the Global Fund and the President's Malaria Initiative.<sup>33,34</sup> It is predicted that over time, public funding will likely have to contribute to the larger share of the budget.

Sufficient time should be allowed for the introduction of radical cure for vivax malaria at the community level, which could include a pilot phase to assess the capability of selected VMWs or MMWs to perform G6PD testing and provide radical treatment. The provision of adequate backup (training, support and supervision) from the health centre will be important. Introduction of G6PD biosensors at the village level will also have repercussions for the supply line and stock

keeping of consumables by the VMWs and MMWs. Issues around logistics management and adjusted budgets to cover the added activities will need to be addressed. Although we did not perform a formal economic analysis, the costs of the biosensor devices might well be offset by the cost-savings from assisted referrals to the health centre, which will become redundant. In addition, community-based testing for G6PD can result in better coverage of radical treatment for vivax malaria and thus less costs for the diagnosis and management of relapse infections. At the same time, decreasing vivax malaria cases can lead to decrease in the activity of VMWs and MMWs, thus maintaining their roles in the community is crucial to ensure their presence and relevance, particularly to prevent decline in interest and investment towards the 'last mile' program in Cambodia.<sup>1,33,35</sup> It seems appropriate that the current funding sources could also be utilized to support the additional activities contributing for rapid elimination of vivax malaria.

There are potential constraints of utilizing VMWs for this additional task. VMWs/MMWs are familiar with the RDTs based diagnosis of malaria. Any new technology that requires skills beyond what is required for RDTs will need adequate training and continuous support, which was recently shown in a Cambodian study from Kravanh district.<sup>36</sup> The study conducted in Kravanh district has demonstrated the feasibility of G6PD measurements using biosensors by VMWs/MMWs at the point of care (at the community) when offered regular supervision, support and coordination by the health

centre. In this study, VMWs and MMWs convened every month at the health centre, their biosensors were calibrated, control tested, and concerns were resolved.<sup>36</sup> Regular meetings between VMWs/MMWs and the supervisory team offered an opportunity to resolve potential issues and ensured quality control of the biosensor results. One of the major implications from the study was the need to consider the limitations posed by VMWs and MMWs. The majority of VMWs have limited formal education, so any new health technology or diagnostic tools they are given must be comprehensive and practicable.<sup>36,37</sup> Community based provision of radical cure for vivax malaria requires extensive engagement and adequate investment in the training, supervision, and monitoring of VMWs/MMWs in order to build their capacity and ensure quality service delivery in the community.<sup>38–43</sup>

Expanding the skills of VMWs/MMWs to manage vivax malaria provides several benefits. Firstly, VMWs/MMWs come from the same community and thus can have an existing familiarity, links, relationship and trust with the population. Secondly, the ability to treat vivax malaria without referral to the health centre removes barriers related to travel to the health centre. Thirdly, management of vivax malaria within the community will strengthen early diagnosis, treatment and reporting. Fourthly, increasing the roles of VMWs and MMWs will capitalize on their unique and rich capabilities, intrinsic motivation, and promote a sense of contribution towards the trajectory of malaria elimination in Cambodia by 2025. Finally, training these community based VMWs and MMWs to manage malaria within their community can significantly reduce resources from both supply side (reaching out to communities for any potential outbreaks) and demand side (travel, time and money required to visit health centre). The strategy could become a template for other countries in the region.

## Conclusion

Without high coverage of radical cure, it will be difficult to reach the goal of rapid vivax malaria elimination in Cambodia and other malaria endemic countries in Southeast Asia. Implementation of community based G6PD testing and provision of primaquine for radical treatment is a promising strategy. Implementation will require adequate engagement, resourcing, training and supervision. Deployment of radical cure for vivax malaria is urgent and operational research to assess the feasibility and performance of this approach are important.

## Contributors

BA, RT, TJP, JJC, LvS, LD, and AMD discussed the concept. BA conducted the literature review and wrote the first draft under the supervision of AMD. The draft was reviewed by all the authors and approved the final manuscript.

## Declaration of interests

The authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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