Implementation of G6PD testing and primaquine for \textit{P. vivax} radical cure: operational perspectives from Thailand and Cambodia

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Abstract

Following progressive success in reducing the burden of malaria over the past two decades, countries of the Asia Pacific are now aiming for elimination of malaria by 2030. \textit{Plasmodium falciparum} and \textit{Plasmodium vivax} are the two main malaria species that are endemic in the region. \textit{P. vivax} is generally perceived to be less severe but will be harder to eliminate, owing partly to its dormant liver stage (known as a hypnozoite) that can cause multiple relapses following an initial clinical episode caused by a mosquito-borne infection. Primaquine is the only anti-hypnozoite drug against \textit{P. vivax} relapse currently available, with tafenoquine in the pipeline. However, both drugs may cause severe haemolysis in individuals with deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD), a hereditary defect. The overall incidence of malaria has significantly declined in both Thailand and Cambodia over the last 15 years. However, \textit{P. vivax} has replaced \textit{P. falciparum} as the dominant species in large parts of both countries. This paper presents the experience of the national malaria control programmes of the two countries, in their efforts to implement safe primaquine therapy for the radical cure, i.e. relapse prevention, of \textit{P. vivax} malaria by introducing a rapid, point-of-care test to screen for G6PD deficiency.

Keywords: glucose-6-phosphate dehydrogenase, Greater Mekong subregion, malaria, \textit{Plasmodium falciparum}, \textit{Plasmodium vivax}, primaquine

Background

Towards the elimination of \textit{P. vivax} malaria

\textit{Plasmodium vivax} malaria remains an important public health problem in many parts of the world. The World Health Organization (WHO) estimates that \textit{P. vivax} was responsible for 8.5 million cases of malaria globally in 2015. Outside of the African continent, \textit{P. vivax} accounted for approximately 41% of malaria cases. Most cases of \textit{P. vivax} malaria occur in the WHO South-East Asia Region (58%), followed by the WHO Eastern Mediterranean Region (16%) and the WHO African Region (12%).

Two sets of guidance – the Global technical strategy for malaria 2016–2030 and Control and elimination of \textit{P. vivax} malaria: a technical brief – were published by WHO in 2015. They marked not only an important step in the transition from malaria control to an elimination strategy but also a recognition of radical cure for \textit{P. vivax} infection as a key determinant for successful elimination of all malaria. At the 9th East Asia Summit in November 2014, 18 heads of government declared support for malaria elimination in Asia Pacific by 2030. In the WHO South-East Asia Region, malaria-endemic countries have already set some elimination targets, either nationwide or subnationally. Countries are making efforts to fulfil the regional commitment to malaria elimination.

Radical cure for \textit{P. vivax} malaria

Prioritization of radical cure for \textit{P. vivax} malaria has become better recognized recently, along with malaria elimination. Treatment with a 14-day course of primaquine is the only currently available therapy known to be effective against \textit{P. vivax} liver-stage hypnozoites, thus preventing relapses and providing radical cure. Tafenoquine is an investigational medicine under development as a single-dose radical cure for \textit{P. vivax} malaria, however, primaquine and tafenoquine are known to cause haemolysis in individuals with inherited deficiency of glucose-6-phosphate dehydrogenase (G6PD) enzyme. More emphasis has recently been placed on safe primaquine therapy guided by testing for G6PD status before prescription and the most recent WHO treatment guidelines indicated that it is good practice to use a patient’s G6PD status to guide primaquine administration. The availability of rapid, point-of-care (PoC) G6PD test kits is encouraging but also increases the complexity of factors facing national malaria control programmes.
control programmes (NMCPs), in terms of product choices, current technical limitations and appropriate approaches for test introduction and programme implementation.

**G6PD testing**

The introduction of PoC G6PD testing in the rapid-test format in 2013 has increased opportunity for access to routine screening prior to primaquine prescription. Cost has been cited as a concern for some countries with a high malaria burden; thus, economic modelling has been advocated to synthesize the evidence on the epidemiology of *P. vivax* and the prevalence of G6PD-deficiency variants, to provide the most cost-effective option for different settings. Some countries, including Thailand and Cambodia, have experienced a significant reduction in the burden of malaria. Given the smaller case-loads remaining, cost has been less of a concern, as these countries have been keen to focus on *P. vivax*, in order to accelerate elimination.

The prevalence and distribution of G6PD mutants vary geographically and among ethnicities. While extreme concern surrounding prescription of primaquine persists in some countries (e.g. Cambodia), owing to fears about fatal haemolysis, primaquine has been used for decades elsewhere without G6PD testing and with no severe adverse events recorded, including in South America, the Democratic People’s Republic of Korea and the Republic of Korea. However, it should be noted that the absence of recorded incidents does not necessarily equate to an absence of severe adverse events.

In some situations, such as in Viet Nam, continuation of prescribing primaquine without G6PD testing seems to be preferred because of the local confidence in its safety, based on decades of use and the generally low prevalence of severe G6PD-deficiency variants. Primaquine treatment without G6PD testing is viewed as a contributory factor to the successful progress towards malaria elimination in northern Viet Nam. Therefore, introduction of G6PD testing is not being considered, on the grounds that it would unnecessarily increase not only the cost of malaria case-management but also the administrative and logistic complexities of a programme that is already functioning.

The G6PD gene is located on the X chromosome; thus, females can be homozygous or heterozygous, but males can only be hemizygous. The PoC qualitative G6PD tests that are currently available can reliably distinguish individuals with true normal enzyme level from hemizygous males (characterized by very low enzyme levels). However, they can be problematic in individuals with intermediate enzyme levels, usually heterozygous females, because the subpopulation of healthy erythrocytes may show normal G6PD activity. Incorrect classification of G6PD status in those women (from G6PD deficient to normal) may result in them being mismanaged and at risk of haemolysis, despite having been tested. Currently available PoC qualitative G6PD tests are also limited because they provide no control line and no control solution to monitor test validity, and the results are sometimes ambiguous. Owing to the imperfect products available, there is an ongoing debate as to whether NMCPs should proceed with the introduction of currently available PoC qualitative G6PD tests, or should delay until a quantitative PoC assay becomes available.

This paper describes the malaria situation in Thailand and Cambodia and the countries’ efforts to introduce routine G6PD testing along with radical cure for *P. vivax* malaria. The two countries differ in their general malaria situations; malaria control and elimination strategies; regulatory requirements for pharmaceutical products and diagnostics; public health organization and infrastructure; and availability of health-care resources. Enabling factors and limitations are identified in this study and potential solutions are discussed as to how safe radical cure for *P. vivax* can be made widely available to the malaria-endemic communities.

**Current malaria status in Thailand and Cambodia**

The overall burden of malaria has significantly declined in both Thailand and Cambodia over the last 15 years. *P. falciparum* used to be the most common species. However, *P. vivax* has replaced *P. falciparum* as the dominant species in large parts of both countries. A summary of the malaria situations and factors related to radical cure for *P. vivax* by country is presented in Table 1.

Both countries have adopted malaria elimination in their national strategic plans. Thailand and Cambodia aim to achieve zero indigenous case status (i.e. no local transmission) by 2024 and 2025, respectively. Both plan to introduce or revise guidelines for safe, effective radical cure for *P. vivax* malaria with routine G6PD testing.

Thailand is gradually reorientating its malaria programme towards elimination, and increasing the integration of malaria services with the general public health system. The remaining vertical part of the malaria control operations is budgeted for, and being implemented in, districts that remain endemic for malaria (248 out of the total 878 districts). There are 161 vector-borne diseases control units and 286 malaria clinics in these districts, under the technical support and coordination of the Bureau of Vector Borne Diseases at the central level and 12 offices of disease prevention and control at the peripheral level. Surveillance is being strengthened in districts that are already free of malaria, where specific malaria interventions are being transferred to the general health services, under the responsibilities of provincial public health offices and district health offices for continuing operation. This includes implementation of the elimination campaign and accountability for its progress.

According to the *National strategic plan for elimination of malaria in Cambodia (2011–2025)*, the Government of Cambodia aims aggressively to reduce malaria morbidity and mortality and to extend case-management to patients in high-risk areas, with emphasis on adherence and follow-up to ensure complete cure. Cambodia’s National Centre for Parasitology, Entomology and Malaria Control (CNM) is a unit in the Ministry of Health responsible for malaria control activities at the national level. The programme is decentralized, with the provincial health departments and operational districts involved in planning and implementation activities. Village malaria workers, village health volunteers, migrant malaria workers and local health authorities form part of the network to expand the availability of malaria services and improve their accessibility to those at risk.
Table 1. Summary of malaria status and factors related to the introduction of radical cure for *P. vivax* malaria by country

<table>
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<tr>
<th>Factors related to malaria</th>
<th>Thailand</th>
<th>Cambodia</th>
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| Malaria cases in 2016      | Fiscal year: October 2015 to September 2016:<sup>a</sup>  
• Total: 18 136 cases:  
  – *P. falciparum* = 3422 (18.9%)  
  – *P. vivax* = 13 006 (71.7%)  
  – Mixed infections = 123 (0.7%)  
  – Others = 1583 (8.7%) | January to December 2016:<sup>b</sup>  
• Total 23 367 cases:  
  – *P. falciparum* = 12 144 (52.0%)  
  – *P. vivax* = 9623 (42.0%)  
  – Mixed infections = 1400 (6.0%) |
| Implementation of radical cure for *P. vivax* | PQ for radical cure has been used for more than three decades with no reports of serious adverse events. Counselling on compliance and on the adverse effects of PQ by health-facility staff is encouraged. Follow-up with blood smear on days 14, 28, 60 and 90 is recommended.<sup>23</sup> | As of July 2017, PQ radical cure is not yet implemented in the country. |
| Malaria situation | Characterized by border malaria. High-risk groups are refugees in camps and workers in rubber plantations and fruit orchards, most of whom are migrants from neighbouring countries. Non-Thais account for about half of reported cases. Cases on the western border with Myanmar have declined by 50% in the last 5 years but epidemics on the other borders led to case increment in those areas. The increase on the eastern border with Lao People’s Democratic Republic and Cambodia is associated with illegal logging and forest-related activities, while the increase along the southern border is due to poor access to malaria control services as a result of insurgency.<sup>21,23</sup> | An overall decline of over 50% in the incidence of malaria has been observed in the past 5 years. The burden of malaria is prominent in ethnic minority groups and mobile, migrant and cross-border populations. The incidence is highest in the north-eastern parts of the country and lowest in the western provinces. Artemisinin resistance and migrant populations are key challenges to successful control and elimination.<sup>24,25</sup> |
| Elimination efforts | A consolidated malaria elimination strategy and an operational manual for malaria elimination, encompassing all essential activities required at each decision/implementation level, has been published.<sup>26</sup> Reorientation of the national control programme towards malaria elimination is ongoing, aiming at the integration of malaria services with the general public health system, thus reducing specialized field malaria services. | The Cambodia Malaria Elimination Action Framework 2016–2020 has been launched.<sup>27,28</sup> Pilot elimination is being conducted in selected endemic areas in the north and north west. |
| Relapse | There is a relapse rate of 50%, with a mean interval of 3 weeks to the first relapse if rapidly eliminated antimalarial drugs are given. Second-relapse recurrences of parasitaemia occur ~6 weeks after chloroquine treatment.<sup>30</sup> | There is a lack of data on studies aiming specifically at the characteristics of *P. vivax* relapses in Cambodia. However, relapse is probably “rapid and frequent”, as is typical in the tropics. The majority of *P. vivax* infections arising after treatment of *P. falciparum* malaria probably originate from relapsing liver-stage parasites.<sup>30</sup> |
| G6PD test | National treatment guidelines: “[patients] should be screened to determine G6PD status (where possible)”, but G6PD testing is not mandatory.<sup>21</sup> The Thailand NMCP is piloting PoC G6PD testing at selected malaria clinics (results pending). | National treatment guidelines indicate that a patient is to receive PQ radical cure only if they have been determined to be G6PD non-deficient.<sup>13</sup> G6PD testing is not available at most peripheral health facilities in endemic areas. Following the CNM Diagnosis and Treatment Working Group meeting in November 2016, recommended pilot-testing with CareStart™ rapid diagnostic tests in male *P. vivax* malaria patients before radical treatment with primaquine (0.25 mg/kg daily for 14 days) is conducted. Female patients will not be included, owing to the known limitation of the current PoC test in detecting G6PD deficiency in heterozygous females. |
| Characteristics of G6PD deficiency | Prevalence ranges are 10–17% in men and 6–15% in women, depending on factors such as geographical region.<sup>33–34</sup> Reports, most with limited sample sizes and ethnic components, roughly show Mahidol, some Chinese and Viangchan variants to be most common. In general, the Mahidol variant is dominant, especially in the west and the north west near the Myanmar border, while the Viangchan variant has been reported from the north east near the borders with Lao People’s Democratic Republic and Cambodia. The common presence of Mahidol, which is a less severe variant, in a large part of Thailand, may partly explain the more favourable experience with PQ use in the country.<sup>32–34</sup> | Prevalence ranges are about 8–15% in men and 3–8% in women.<sup>15</sup> Predominantly the Viangchan variant (known to be associated with severe haemolysis). Severe deficiency is more prevalent in western Cambodia, where *P. vivax* has recently become the dominant species. It is not known whether this could explain the historical observation of cases with dark urine that resulted in the negative attitude in the country towards PQ use. |

CNM: National Centre for Parasitology, Entomology and Malaria Control; G6PD: glucose-6-phosphate dehydrogenase; NMCP: national malaria control programme; PoC: point-of-care; PQ: primaquine.

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The international borders of the Greater Mekong subregion are well known for their significance as risk areas for malaria. In Thailand, specific malaria outreach activities aimed at remote endemic communities and migrant populations, especially along the Thailand–Myanmar border, are currently implemented through nongovernmental organizations and the government’s 25 border malaria posts and 327 malaria posts. These activities have been supported by the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM). However, current GFATM support will end in 2017, and a different funding channel will be needed to sustain these services. On the eastern side of the Thai borders and the border of Thailand–Lao People’s Democratic Republic–Cambodia, occasional malaria outbreaks occur, often due to increased forest-related activities among migrants. The situation is complicated by weak capacity for rapid surveillance and effective responses.

Despite efforts to provide access to health services according to basic human rights, migrants remain high-risk populations in such border areas. Their mobility is a challenge to reliable assessment of their treatment outcomes and drug side-effects, especially for the radical cure of P. vivax malaria, which requires a 14-day course of treatment. Some cross-border collaboration activities in the Greater Mekong subregion were initiated in response to artemisinin resistance in recent years. Cross-border coordination was one of the key action plans for the emergency response to artemisinin resistance in this subregion. However, actual on-the-ground activities need to be stepped up for more fruitful outcomes.

**Radical cure for P. vivax malaria in Thailand and Cambodia**

**Use of primaquine**

Primaquine therapy for P. vivax malaria is included in the national treatment guidelines of both countries. However, the actual implementation differs, largely due to the inability to determine a patient’s G6PD status at the point of care in remote settings.

Thailand shares with Cambodia the problem of artemisinin-resistant P. falciparum malaria. However, P. vivax is still highly susceptible to chloroquine, which is the first-line therapy for all confirmed P. vivax cases in Thailand. Uncomplicated P. vivax cases are treated with chloroquine and a 14-day course of primaquine, on an outpatient basis. If a patient is known to be G6PD deficient, he or she is referred for treatment by medical practitioners in hospital, but access to G6PD testing is generally limited in the rural areas. No serious adverse effects have been reported, although compliance has not been ascertained. However, in a clinical research environment, where patients are kept hospitalized, haemolysis due to primaquine has been recorded.

In Cambodia, primaquine was used during the era of malaria eradication from the late 1950s to the early 1960s and thereafter up to 1985. However, in the 1980s, a mass treatment with primaquine (unknown dose regimen) was thought to have caused severe and fatal haemolysis, thus precipitating complete abandonment of the drug in malaria control. Cambodia started replacing chloroquine with an artemisinin-based combination therapy, dihydroartemisinin–piperaquine (DHA-PPQ), for the treatment of P. vivax malaria from 2009, following documented chloroquine resistance.

The 2012 version of the national treatment guidelines introduced a standard course of primaquine in addition to DHA-PPQ as the first-line treatment for radical cure of P. vivax malaria. These guidelines recommended the use of G6PD testing, depending upon availability. If G6PD testing was not available, the guidelines recommended directly observed therapy and termination of primaquine if signs of haemolysis developed. In the 2014 revision, the recommendation on primaquine treatment for P. vivax malaria was revised to recommend its use only if the patient was determined to be G6PD non-deficient.

In 2016, an artemunate–mefloquine fixed-dose combination replaced the first-line therapy for both P. falciparum and P. vivax in 11 provinces of Cambodia considered to be the core areas of P. falciparum resistance to artemisinin (as well as PPQ), namely, Battambang, Kampong Thom, Kampong Speu, Kampot, Kratie, Oddar Meanchey, Pailin, Preah Vihear, Pursat, Siem Reap and Stung Treng. Directly observed therapy for antimalarial drugs is documented in the guidelines but in practice this is not done, except in the context of clinical research studies or pilot implementation. In early 2017, artemunate–mefloquine replaced DHA-PPQ countrywide.

**Making medicines and medical devices available**

The Association of Southeast Asian Nations (ASEAN) harmonization scheme adopted in recent years has eased the pharmaceutical regulatory procedures across south-east Asia. Some specific procedures still vary by country but these are unlikely to be an obstacle for the registration of new diagnostic devices/drugs that are important for malaria elimination, including PoC G6PD test kits.

Primaquine has been available in Thailand for a long time. It used to be available as 5 mg and 15 mg tablets manufactured locally by the Government Pharmaceutical Organization. Recently, these have been replaced by imported 7.5 mg tablets. A qualitative PoC G6PD test product (CareStart™ G6PD test, Well Bio Inc., Republic of Korea) has already been registered with the Medical Device Control Division, Food and Drug Administration, Thai Ministry of Public Health, and is available commercially. Unlike Cambodia, registration and import of G6PD test kits in Thailand have been processed for commercial purposes by a local company, independently of the NMCP.

To be in alignment with the government’s goal of malaria elimination, Cambodia added primaquine to its essential drug list in 2015, allowing health centres to request supplies of this drug from the government’s central medical supplies unit as needed. The Cambodian Department of Drugs and Food (DDF) is the responsible agency for registration of drugs, diagnostics and cosmetics. A registration licence is required for import of products. Normally, the dossier format follows that of the ASEAN common technical dossier, and dossier files should contain clinical evaluation results to be assessed and approved by the DDF. It is not necessary for the clinical trials to have been conducted in the country, but inclusion of local data, if available, is encouraged. Drug samples have to be analysed by the National Health Products Quality Control laboratory and the registration approval process takes 8–12 months. Fast track is available, especially for WHO-prequalified products (for public use only); it may take less than 3 months from the time of DDF submission to approval.
Kitchakarn et al.: G6PD testing and primaquine for P. vivax radical cure: perspectives from Thailand and Cambodia

Primaquine phosphate tablets, equivalent to 15 mg primaquine base (manufactured by Sanofi Canada Inc., Laval, Québec, Canada), were registered with the DDF in September 2016. This is one of the two sources of primaquine in the List of malaria pharmaceutical products classified according to the Global Fund Quality Assurance Policy. Through the support of the GFATM, the first purchase order of 56,000 tablets arrived in Phnom Penh in January 2017. A pilot study with PoC G6PD screening and 14-day primaquine therapy is being planned. However, since only 15 mg tablets are available in the country, issues of inconvenience and accurate dosing, e.g. for children, need to be resolved.

In the case of tafenoquine, it is envisaged that CNM would hold the licence, if it applies for registration, probably through a fast-track channel. Since CNM is part of the Ministry of Health, the product will not be available to private providers. For both countries, import of tafenoquine in the future could be indirectly facilitated by prior clearance of the product by stringent regulatory agencies such as the United States Food and Drug Administration and the Australia Therapeutic Goods Administration.

In both countries, registration of medical devices is usually faster than for drugs. In Thailand, only the certificate of free sale from the country of origin is required, although risk assessment of diagnostic products will be needed and the process will be more complex in the near future. Dossier submission will be based on the ASEAN harmonization scheme (Common Submission Dossier Template [CSDT] of the ASEAN Medical Device Directive [AMDD]). The quality standard/requirement for registration of the G6PD test has been developed. In Cambodia, product prequalification by WHO would be helpful but is not essential. Application for registration is required the first time a medical device product is imported. Requirements for registration of new medical devices include International Organization for Standardization (ISO) certification (for quality management system in manufacturing) and a free sale certificate from the country of origin. Registration of the PoC G6PD test kits is expected to be initiated by the NMCP for primary use in the malaria programme.

Some considerations for the implementation of routine G6PD testing in P. vivax malaria

Which G6PD test?
There are several ways to determine a person’s G6PD enzyme status. Key methods are based on an estimation of the remaining G6PD enzyme activity, which is a reliable assessment of the G6PD-deficiency phenotype. Their benefits and limitations have been reviewed elsewhere. Two main quantitative testing methods – spectrophotometric assay and cytochemical assay – provide precise measurements of G6PD activity. However, these two diagnostic tests are costly and not suitable for use in field settings, as they require a functioning cold chain, laboratory equipment and skilled workers. Until recently, the fluorescent spot test has been the recommended qualitative screening method for G6PD deficiency, since it is affordable and provides qualitative visual results within minutes. However, it requires skilled staff and specialized equipment; thus, it is unsuitable as a PoC test in the field.

PoC G6PD test products have been reviewed by Ley et al. Future products will probably include a quantitative G6PD test with digital reading. Addition of a haemoglobinometer as a companion test would be an advantage. This has important implications for implementation because anaemia is common in malaria-endemic areas and the relative proportion of younger red cells (which have higher activities of G6PD enzyme) associated with anaemia may give a false-normal test result.

Currently, CareStart™ is the G6PD rapid-test kit in a cassette format available in the market in several endemic countries. The product is not ideal, but has been shown to be a sensitive and specific qualitative test if performed under the required conditions and with caution in the interpretation of test results. However, improvements are needed in its test performance. An improved product with a control line to verify a valid reaction, and with a storage temperature up to 40 °C, is in the pipeline. Recent improvements include the availability of a visual-aid chart for comparison of colour shades in reading results.

The two countries expect the availability of PoC tests with some “ideal” characteristics in the near future, including: (i) the ability to sustain long-term storage at >35 °C; (ii) a valid assay can be performed at >35 °C; (iii) affordability (e.g. not more than a few US$ for Thailand); and (iv) a shelf-life of at least 2 years. In the absence of an established quality-assurance/quality-control mechanism, WHO has recently defined “preferred product characteristics” for qualitative PoC G6PD tests. These include (i) test sensitivity of >95% for detecting G6PD activity of <30% of normal (compared to that of spectrophotometry or equivalent quantitative tests for detecting G6PD enzyme activity); (ii) negative predictive value of >95% (i.e. providing at least 95% probability that the patient has >30% normal G6PD activity when the diagnostic test indicates that they are not deficient; (iii) stability at 30–40 °C; and (iv) a visual read-out that clearly distinguishes between “deficient” and “normal” G6PD activity.

Technical constraints
Despite its availability in a rapid-test format suitable for PoC implementation, use of the G6PD test is not as straightforward as a malaria rapid diagnostic test, because there are multiple steps of treatment algorithm to follow, including patient counselling on the safety of primaquine. Thus, there is a concern that the tool may not yet be ready for peripheral health settings, where the majority of individuals with malaria in the Greater Mekong subregion are primarily seeking treatment for their malaria. Examples of such remote settings for passive case-detection are a malaria post in Thailand and the house of a village malaria worker in Cambodia.

Unlike the Philippines and Malaysia, a national neonatal G6PD screening scheme is available in neither Thailand nor Cambodia. Both countries agree that PoC G6PD test kits should be piloted at selected facilities above the levels of village malaria workers and malaria posts. In Cambodia, initial implementation is planned for a provincial hospital or referral hospital levels. The readiness of the infrastructure will have to be re-examined in both countries.

Thailand has started piloting CareStart™ tests at 61 malaria clinics with refrigerators and air-conditioned laboratory space, to ensure the manufacturer’s required optimum storage (4–30 °C) and conditions for a valid assay (<32 °C). A new generation of PoC G6PD tests that can sustain a storage and performance environment of 35–40 °C will expand patients’ access to wider endemic areas.
Recently, a study in the Philippines suggested that CareStart™ performed more accurately with venous blood than capillary blood.\textsuperscript{53} This has raised further concern, as staff at most peripheral malaria clinics in Thailand and Cambodia are not trained to perform venepuncture. In addition, venepuncture may not be acceptable to uncomplicated malaria patients and is likely to further increase the cost of malaria case-management.

Training and preparing system readiness
To prepare for implementation of G6PD testing, the NMCP needs more than selection of what is believed to be a suitable G6PD test based on known evaluation of performance. The programme also needs to ensure testing skills; ability to interpret results reliably; correct recording of results; and staff understanding of the algorithm for primaquine prescription, case-referral and pharmacovigilance. According to WHO, the capability and readiness of the local health services in emergency handling of primaquine-induced haemolytic anaemia should be considered prior to implementation.\textsuperscript{3}

Staff must be well trained to ensure adherence to a well-designed case-management plan. Training materials must be carefully prepared and pretested to satisfaction, to avoid any misleading interpretation. Emphasis should be placed on supervised therapy when possible. Local health staff must be trained to explain clearly to patients the importance of compliance with 14-day treatment (to continue taking the medicine to finish the full course, despite feeling well several days before the end of the course) and how to observe early signs of haemolysis, such as dark urine. In addition, a plan should be made to allow an objective evaluation of pilot implementation, in order to guide decisions as to whether improvements or modifications are needed before expansion.

In Thailand, supervisor-level staff of the regional office of disease prevention and control and the central Bureau of Vector Borne Diseases unit for standards of malaria case-management work together to develop a training plan and decide on the materials needed. The regional staff will then train staff at selected malaria clinics. In Cambodia, trainers will be laboratory supervisors of the provincial health department (bachelor degree minimum), who will be initially trained by CNM’s senior technical staff (training of the trainers). The trainers from the provincial health department will then train staff of selected peripheral hospitals where PoC G6PD tests will be deployed.

The possibility of keeping data on G6PD status, a hereditary condition, in a permanent and retrievable database should be considered, so that patients, especially men, will not have to be tested again following another episode of \emph{P. vivax} infection. The national malaria database or national pharmacovigilance database can be modified to accommodate these additional variables, but it is still debatable whether a person’s definitive G6PD status should be based upon a single PoC qualitative G6PD test result.

WHO guidelines include a recommendation for a prolonged treatment regimen (8 weeks) among those with mild or intermediate G6PD deficiency. In practice, this is usually not followed. Based on the available qualitative PoC G6PD rapid test, used in the ongoing pilot implementation in Thailand, malaria clinical staff are advised to refer such patients to a district hospital, or a higher-tier health facility. Further clarification on the guidelines is needed for consistent practice. Besides the concern that patients are unlikely to complete an 8-week course, Thailand’s decision is also based on the belief that a G6PD-deficient individual should be treated by a medical doctor. The issue will have to be re-discussed, as this is currently not practical because malaria clinics and health facilities that provide malaria treatment in remote areas are not normally staffed by doctors.

Logistics of procurement and product supply-chain system
While an optimum procurement strategy and an uninterrupted supply-chain system for G6PD test kits and anti-relapse drugs have yet to be determined, it is likely that each country would prefer to integrate them with existing systems and practices used for antimalarial drugs and rapid diagnostic tests. For now, G6PD tests and primaquine may have to be procured and distributed separately. In the future, once tafenoquine, a single-dose anti-relapse therapy, becomes available, one of the options might be co-packaging of tafenoquine and PoC G6PD tests, to avoid prescription without G6PD testing.

The country’s experience with the current procurement and distribution systems for antimalarial drugs and rapid diagnostic tests should help in designing a system for the procurement of G6PD test kits and new anti-relapse therapies. In both countries, rapid diagnostic tests and quantification of antimalarial drugs is based on calculation of the number of malaria cases in the previous year(s). To avoid too short a shelf-life, Cambodia specifies in the bidding that shipment is to be made twice per year.

Thailand’s procurement and distribution are made through a centralized government agency. Management of warehousing and the stock inventory are adequate for malaria control commodities. This is a beneficial system in terms of costs and quality assurance. In Cambodia, drugs and rapid diagnostic tests are stored at the Central Medical Store in Phnom Penh. However, storage in the periphery of the public health system, including at operational district and health centre levels, is under less stringent conditions. Temperature control is inconsistent or unavailable. Therefore, only a small amount of supplies is usually kept at the facilities below the provincial level, with a monthly inventory to determine refill needs.

For G6PD test kits, the demand scenarios are still unclear. Implementation of radical cure will probably be on a limited scale initially but with potential expansion in a later phase. Quantification will be made accordingly, based on the reported number of cases of \emph{P. vivax} malaria.

Ensuring the quality of G6PD test kits
The lack of a product prequalification scheme by WHO for PoC G6PD tests is a factor in why some countries, including Cambodia, are hesitant to adopt routine G6PD screening in a malaria programme.

Significant development has occurred since 2015 for prequalification of PoC G6PD tests. Previously, the G6PD test was not in the WHO programme portfolio for prequalification of \emph{in vitro} diagnostics. The PoC G6PD test is considered to have high public health impact but has not yet undergone a stringent regulatory assessment. Therefore the Expert Review Panel for Diagnostics mechanism was set up by GFATM and the International Drug Purchasing Facility (UNITAID), coordinated
by WHO. As a result, in February 2016, a call was made for manufacturers to submit an expression of interest for product evaluation by the Expert Review Panel for Diagnostics. This will help to identify assays meeting a minimal set of requirements, assist NMCPs in procurement decisions and facilitate procurement of G6PD tests using GFATM grant funds. As of June 2017, the WHO prequalification process for G6PD tests is under way and specifications have been set for the assessment of G6PD tests.

Assessment of community uptake
Most countries feel that more evidence is needed to improve confidence in the community, in order to enhance smooth introduction of a radical cure for \textit{P. vivax} malaria. In Cambodia, acceptance is difficult among medical practitioners, owing to the long-term belief in a haemolytic adverse effect of primaquine causing “black water fever”. It is hoped that, given the government policy, improved PoC G6PD tests and a better case-referral system, these practitioners will be willing to comply. The Cambodian NMCP bears a huge responsibility for proving to the local people the safety of primaquine administration as guided by G6PD testing.

Acceptability to patients is also a factor. Gastric irritation, for example, often discourages patients from completing the 14-day course. Advice to patients to take primaquine with a meal could improve compliance.

According to the current plan, patients will be subjected to finger pricking twice, first for malaria diagnosis and, if found to be positive for \textit{P. vivax}, then a second prick for G6PD enzyme testing. Not all patients may find this acceptable.

In Thailand, some patients may prefer to take the risk of side-effects from primaquine if advised to go to a higher-level health facility for further G6PD assessment. This has to be considered in a case-management algorithm.

Pharmacovigilance
Thailand has used primaquine in uncomplicated cases of malaria for decades but it is not known whether adverse events related to primaquine are really absent, because there is an inadequate effort to detect and report adverse effects and an inability to ascertain compliance to the 14-day regimen for \textit{P. vivax} infection. Both Cambodia and Thailand have an established pharmacovigilance system, but improvement is needed to increase emphasis on antimalarial drugs and to enable the system to capture patients at the lower level of public health, where most malaria patients seek treatment.

Nonetheless, current capabilities are encouraging. For example, the Cambodian Pharmacovigilance Centre, a unit under the Essential Drug Bureau in the DDF, has been established since 2008 and has been a full member of the Uppsala Monitoring Centre (Uppsala, Sweden) under the WHO Programme for International Drug Monitoring, since 2012. The Cambodian Ministry of Health has also established a Pharmacovigilance Advisory Committee. Monitoring of antimalarial adverse drug reactions has recently been introduced into the Cambodian Pharmacovigilance Centre system, aiming at coverage of both the public and private sector.

Primaquine, and in the near future tafenoquine, should be placed under close vigilance for any adverse outcomes. WHO recommends that, at a minimum, the pharmacovigilance report should include who the patient is (age, sex, pregnancy status, illnesses and concomitant medicines), the drug dose and duration of treatment, a description of the adverse event (symptoms, severity, times of onset) and the name of the reporter.

Capability strengthening
Both countries welcome external technical support to plan for successful implementation of G6PD testing and safe primaquine therapy. Both share the problem of limited human resources dedicated to malaria case-management. Intercountry collaboration to develop templates for standard operating procedure, training materials and other documents for sharing could accelerate successful implementation.

Conclusion
The enabling environment for malaria elimination and for tackling \textit{P. vivax} hypnozoites has reached a higher level than ever experienced before. This is a good opportunity, given the availability of certain funds.

On the negative side, the addition of routine G6PD testing may not be viewed highly by some countries, where malaria funding has to compete with other health priorities. However, this is not currently an issue for Thailand or Cambodia, owing to their smaller case-loads.

Rapid PoC G6PD tests are available but not ideal. Current PoC G6PD tests have limitations and do not confer 100% primaquine safety. They can be useful for malaria programmes if implementation is well planned and undertaken with caution. Next-generation quantitative tests, paired with a haemoglobinometer, will provide an improved level of primaquine safety. The new-generation qualitative test with a control line and storage temperature of up to 35–40 °C should also be of benefit to malaria programmes.

Policy alone is not sufficient. Programmes can only profit from policy if they have planning and implementation capability. Countries need time and specific guidance to prepare for training and other activities related to G6PD testing. Simple instructions are important, as complex instructions will be ignored. In terms of human resources, inadequacy of staff is an issue, as there is a tendency to shift staff towards more urgent tasks like outbreak responses to other tropical diseases, or to integrate malaria services with general health services, such as in Thailand. Thus, more technical support is needed for a smooth introduction of G6PD testing. Without such support, pilot implementation can turn out to be fruitless and actual integration of G6PD as a part of standard \textit{P. vivax} case-management can be a lengthy and expensive process. This is complicated by the technical constraints of current test kits, which limit accessibility for those in remote areas, where the majority of malaria cases are passively detected.

Thailand and Cambodia both have a policy for and are making efforts towards the reality of effective radical cure for \textit{P. vivax} malaria, though their strategic approaches may be different. The path to success may be easier for Thailand, given the more advanced health-system infrastructure and lower fear of haemolytic adverse effects from past experience within the medical community. The two countries would benefit from working together in planning for and sharing experience with the use of G6PD tests. This should be expanded into a
subregional effort to enhance radical cure for \textit{P. vivax} and eventually speed up malaria elimination from the Greater Mekong subregion.

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