G6PD testing in Cambodia and Laos – piloting and implementation

This brief was developed by CHAI and reviewed and approved by National Malaria Programmes in Cambodia and Laos

Both Cambodia and Laos have experience implementing qualitative G6PD Rapid Diagnostic Tests. Since late 2020, both National Programmes in Cambodia and Laos, have either started extensive roll out of G6PD analyzers, or are currently in preparation for roll-out this year. Here we discuss how the roll outs are being implemented, and how we can apply lessons learned to improve future implementation of analyzers.

Cambodia – moving from qualitative to quantitative G6PD testing

The Government of Cambodia, through the Cambodia National Center for Parasitology, Entomology, and Malaria Control (CNM), aims to eliminate all forms of malaria by 2025. However, G6PD deficiency is an issue in Cambodia in managing vivax malaria cases. Research has estimated the prevalence of G6PD normal males in Cambodia is around 85 to 92 percent[1].

What was the previous experience with G6PD testing?

Between 2019 and 2020 in Cambodia, CNM piloted the use of qualitative G6PD Rapid Diagnostic Tests (RDTs) used by health center (HC) and hospital staff, in 88 health facilities (HFs)[2] in 4 provinces to determine whether men [3] could safely receive low-dose primaquine 14-days (phase 1 implementation). Only males who were over or equal to 20 kgs would be tested with G6PD tests, and patients with G6PD normal would be treated with radical cure. Patients with *P. vivax* identified by the village malaria workers (VMWs) in the community were also referred to the HFs for testing. All patients were followed up by health center staff via phone calls on day 3, day 7 and day 14 to check adherence and side effect.

An evaluation of the pilot found 29.6% of all patients with *P. vivax* and mixed infections tested G6PD normal and received radical cure (see figure 1). A total of 3,239 *P. vivax* and mixed infections were diagnosed in selected facilities from November 2019 to December 2020. Among these, 88% (n=2,861) met the eligibility criteria for G6PD testing. However, only 45% (n=1,282) of eligible patients received a G6PD test. Among all who received a G6PD test, 971 patients (76%) tested G6PD normal, and among those with G6PD normal results 959 patients (99%) received radical cure.

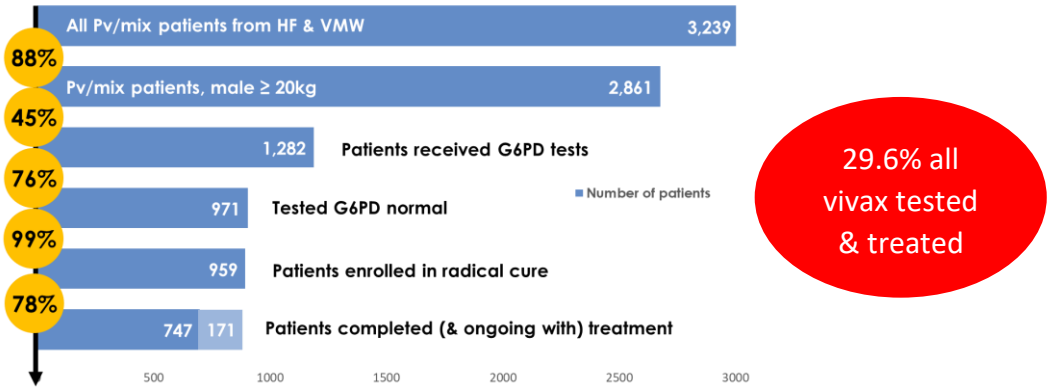
Of the 959 patients enrolled for radical cure, 747 patients (78%) completed the 14-day treatment – in conclusion, during the 14-month period, the coverage of radical cure was 29.6% (959 out of 1,282 patients) of the total patient population diagnosed with *P. vivax* and mixed infections in the four provinces.

1 Malaria Atlas Project, Oxford University. 2012.

2 Health facilities refers to both health centers and hospitals

3 Qualitative G6PD RDTs detect either G6PD deficient or G6PD normal patients above a threshold of 30% AMM. However, women can have intermediate G6PD activity that is not detected using the qualitative RDT. Because of this, and a concern for safety, the CNM decided that the qualitative RDT should be used only for men for the pilot implementation.

Figure 1: The percentage of Pv/mixed cases identified, received G6PD tests, being G6PD normal – tested with qualitative G6PD RDT, enrolled in radical cure and completed 14-day Primaquine treatment, cases from both HFs and village malaria workers (VMW) during Nov 2019 to Dec 2020, Cambodia



After the phase 1 implementation, CNM discussed with the national Technical Working Group (TWG) and decided to switch to quantitative G6PD analyzers given health workers had difficulty distinguishing the colors on the tests and consequent difficulty reading the qualitative results. Additionally, changing to quantitative G6PD analyzers would allow the CNM to reach more patients (both males and females) and the quantitative G6PD is the only alternative on the market that is approved by Global Fund External Review Panel (GF ERP).

What is the status of G6PD testing implementation in Cambodia?

Quantitative G6PD testing is underway through health facilities, used by health facility staff who are usually medical doctors, nurses or midwives. After the phase 1 implementation with qualitative tests, during November 2019 to December 2020, CNM expanded radical cure nationwide. Training on quantitative G6PD testing commenced in October to November 2020, and distribution of the G6PD analyzers nationally was completed in February 2021 after which health centres officially began to use them in routine care.

How do we decide where to place G6PD analyzers, and for what are they used?

For the nationwide expansion, all 11 national and 25 provincial hospitals received quantitative G6PD analyzers. All 42 district referral hospitals were also provided with G6PD analyzers. A further 246 Health Centres (HC) with at least one *P. vivax* and mixed case of malaria per month in 'endemic' provinces[4] were also selected. Given the G6PD test is expensive it was decided for reasons of cost-effectiveness to select these 324 health facilities focusing the intervention in areas with a higher burden of malaria.

G6PD analyzers will be used to determine the G6PD status of patients ahead of treatment with 14-day primaquine (0.25 to 0.5 mg/kg/day). There are no current plans to extend the use of G6PD analyzers beyond diagnostic testing.

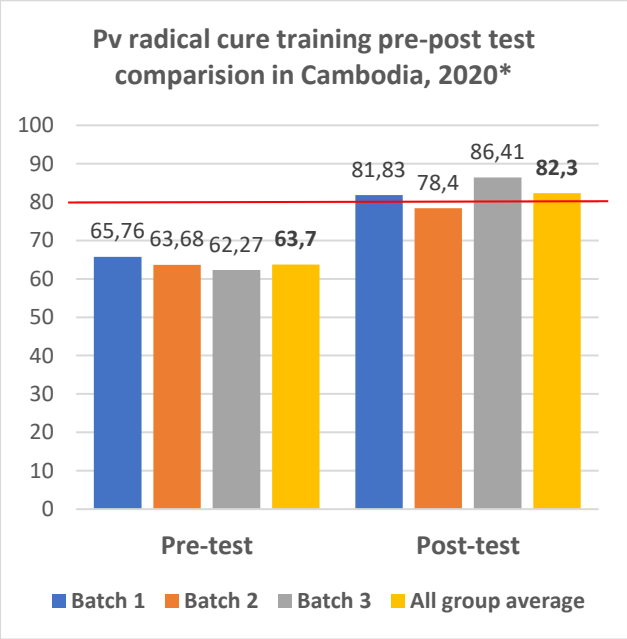
What type of training did health workers receive on quantitative G6PD analyzers?

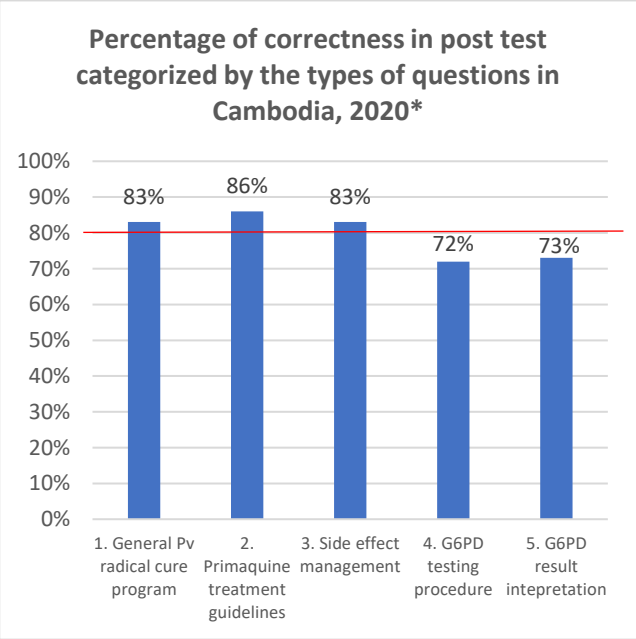
A Training of Trainers (TOT) was conducted over 2 days by CNM and *P. vivax* radical cure technical Working Group to train 36 trainers. Then, training was undertaken via 12 group trainings provided to 802 participants in total. This included provincial and district level authorities, Ministry of National Defence, national hospitals, provincial hospitals, district referral hospitals and health centers to enable the health departments to fully understand and support the national programme and ensure staff at

[4] Cambodia Malaria Elimination Action Framework, 2016-2020.

health facilities were able to accurately conduct G6PD testing. Each health facility had two participants. Due to limited training budget and staff availability, CNM could not train more people, but guided the trained health facility staff to train other staff. Training included technical knowledge on vivax malaria, the theoretical and practical use of the G6PD test and role play on the treatment regimen. The ratio of trainees to facilitators for TOT was 5 to 1 and at cascade training to subnational level it was 8 to 1. During the trainings there was 1 analyzer for every 3-5 participants.

Except for the TOT sessions, assessments on theoretical knowledge of vivax and G6PD analyzers were undertaken before and after each training session. Practical competency assessments in the use of the G6PD analyzers were also done after some, but not all, training sessions, but data from practical competency tests was not inputted and analysed. Pre- and post- theory evaluation results from trainings are provided in the figure below (N = 751 for pre-test and N= 817 for post-test):





***Pass >=80%**

An additional day training for provincial hospitals on side effect management and Adverse Drug Reaction form reporting was conducted with the Pharmacovigilance unit of the Department of Drug and Food (DDF) in Cambodia. This was crucial in ensuring health workers felt informed about potential side effects and how to report them.

What support is provided to health workers after training?

A supportive supervision checklist was developed by the *P. vivax* radical cure Technical Working Group, and used by CNM Monitoring and Evaluation unit, Provincial Health Department (PHD), Operational District (OD) and partners to target HFs who did not have a passing score of 80 points post-training. Included in this 'enhanced supervision' checklist is a competency assessment for G6PD tests. Plans were to undertake 3 supervision visits from CNM *P. vivax* radical cure team to around 15 HC in total where health workers scored less than 80%. The checklist is also integrated into monthly supervision from PHD to HC, and quarterly supervision from OD to HC, for assessing the radical cure implementation routinely. As of July 2021, because of the COVID situation only one supervision trip to five HCs has been possible from CNM *P. vivax* radical cure team.

Key considerations, challenges, and lessons learned in implementing improved radical cure

Training setups, supervision – human resources and time

Trainers:

- Human resource limitations for trainings meant it was difficult to ensure a low ratio of trainees to facilitators. Trainings were conducted in parallel because of a lack of trainer availability, meaning that four separate groups of trainers were required simultaneously.
- Trainer briefings and discussion conducted after each training session allowed for the improvement in quality of the next group of trainees as training was cascaded.

Practice time and participation

- Adequate practice time with analyzers was important - having 1 table, with 2 analyzers, 1 facilitator and ten trainees was all that was feasible for practice time.
- Sufficient training time is needed to ensure not only technical content, but methods to ensure effective knowledge transfer to trainees, for example, participative methods – such as use of role-play and vignettes.
- Variable use of post-training competency testing because of time, or human resource, constraints meant that the CNM did not always have information on the competency of health workers post-training to prioritise for follow-up supervision.
- Insufficient trainer time and resources meant there was no immediate remedial action possible during the training (e.g. re-do the post-test) for individual health workers who performed badly for either theory or practical tests.

Support materials

- Large print-outs of the G6PD testing procedure helped groups read and practice with G6PD analyzers during training. This was used in conjunction with a video on G6PD testing.

Supervision

- Competency testing and pre-post evaluation, when undertaken, allowed for prioritisation of supervision follow-up to health facilities where health workers may have been performing less well.
- Post-training follow-up supervision was planned 3 months after the training, but limited because of the COVID situation.

Early implementation

- The performance of key indicators, including percentage of patients who received a G6PD test and percentage of patients finishing 14-day treatment, were lower in the first three months of the implementation due to the learning curve. Early implementation requires additional and closer supervision in the beginning of the programme.
- The quality of G6PD testing was more challenging in health centers with a higher malaria burden during phase 1 implementation with G6PD qualitative tests. Contributory factors may have included; limited time for health workers to spend with each patient, capacity of health center staff to conduct and interpret the tests, poor storage and quality concerns with the G6PD RDTs, and differences in population characteristics across provinces.

Patient follow-up and access

- Phone call follow ups for supporting patient adherence and checking for side effects are difficult to monitor and validate. Poor cellular coverage and unreachable patients were observed during supervision visits, and loss to follow up was often an issue for patients who are forest goers. In the

nationwide scaleup of radical cure, thus, CNM revised the guidance from phone call follow ups to in-person follow ups by VMWs.

- Access of radical cure at the community was another main challenge. Over half (55.2%) of the eligible *P. vivax* and mixed infections in Cambodia's phase 1 implementation did not receive a G6PD test given the low completion rates of VMW referrals for G6PD testing, while VMWs detected over 60% of total malaria cases in the country.

Safety & pharmacovigilance

- Pharmacovigilance system could be strengthened to report side effects in collaboration with DDF. With paper-based recording, PHD and OD faced challenges to follow up the examination results from provincial hospitals after patients were referred. Information of adverse events were lost during the reporting process. Further collaboration between CNM and DDF is underway for nationwide scaleup, including establishing the reporting flow between CNM, DDF and partners, setting up regular meetings to review all cases of side effects.

Laos – planning for quantitative G6PD implementation

The Government of Laos, through the Laos Centre of Malaria, Parasitology and Entomology (CMPE), aims to eliminate all forms of malaria by 2030. The current vivax radical cure treatment is 14-day Primaquine (PQ) (0.25 mg/kg/day) provided to patients who are G6PD normal and 8-week PQ to those who are either G6PD deficient or who have not received a G6PD test.

Experiences with the implementation of qualitative G6PD tests

Between 2018 and 2019, the Laos CMPE deployed qualitative G6PD RDTs to all hospitals across the country including 22 'hotspot' health centres. Similar to the CNM strategy, out of concern for the cost of the analyzers and the relative complexity of their use, G6PD analyzers are being targeted to hospitals and health centres in higher transmission strata 3 and 4, and only during the following year will they be extended to lower transmission strata 1 and 2. CMPE are currently planning for the implementation of quantitative G6PD analyzers in targeted areas of the country.

Switching G6PD tests from qualitative to quantitative

In 2020, CMPE decided to change from the use of qualitative G6PD RDTs to the quantitative G6PD analyzers because they can be used for both males and females and they are the only G6PD diagnostic tool currently approved by the Global Fund. The estimated prevalence of G6PD normal and deficient in Laos is 95% and 5% respectively[5]. Anecdotally, feedback from supervision visits found that health workers remained reluctant to treat patients with either PQ14 or 8-week PQ because of difficulty in reading test results.

Facilitating the switch – training and planning for implementation

To facilitate the change to quantitative tests, a Training of Trainers was conducted in June 2021. The trainee to facilitator ratio for CMPE TOT was 7 to 3 and at provincial/ district level it was about 8 to 1. During training practice sessions, between 3 and 5 participants shared 1 G6PD analyzer. No practical competency tests were undertaken during training and instead these are planned to be conducted during supervision visits. Cascade training of provincial and district health authorities is underway with training at health facilities expected to begin in mid-July. Quantitative G6PD testing at health facilities is planned to start in Q3 2021.

5 The assessment of the use of G6PD RDT and Primaquine 2015. CMPE

In Laos, G6PD analyzers will be placed in all provincial (17) and district hospitals (137) and all HCs in stratum 3 and 4 (228) in 2021 and will be expanding to remaining HCs in strata 1 and 2 in 2022. There are no current plans to extend the use of G6PD analyzers beyond diagnostic tests.

Applying learning

Both CNM and CMPE are aiming to ensure optimal, expanded *P. vivax* radical cure to high transmission areas in the first instance. Importantly, both countries have experience in implementation of qualitative G6PD testing, and training on the use of quantitative G6PD analyzers. Learning from these experiences is important to further improve quality of care for patients, both in Cambodia and Laos, and also in other countries in the region that are considering how to further improve vivax treatment and increase access to radical cure.

Having the time and resources to *apply these learnings* as part of programme activities is key for countries to meet their elimination goals.