Considerations for implementation of G6PD testing and radical cure in *P. vivax* endemic countries

August 2015, Geneva, Switzerland

**Background**

The current WHO *Guidelines for the treatment of malaria* (1) contain recommendations for the treatment of *Plasmodium vivax* and *P. ovale* (see Box 1A and Box 1B). These recommendations are based on the need to radically cure patients using primaquine (the only available anti-relapse medicine) while at the same time minimizing the risk of primaquine-induced acute haemolysis in those who are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD). The guidelines recommend that patients with confirmed *P. vivax* or *P. ovale* malaria who are not aware of their G6PD status be tested before the administration of radical cure with primaquine. However, given the limited availability of field-adapted G6PD tests and some performance limitations with those tests, a decision to administer or withhold primaquine may still have to be based on weighing the benefits of radical cure against the haemolytic risk posed by primaquine.

**Box 1 A. Recommendations in the WHO Guidelines for the treatment of malaria (1)**

<table>
<thead>
<tr>
<th>Preventing relapse in <em>P. vivax</em> or <em>P. ovale</em> malaria</th>
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<tbody>
<tr>
<td><strong>The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.</strong></td>
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<tr>
<td><strong>Good practice statement</strong></td>
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<td>To prevent relapse, treat <em>P. vivax</em> or <em>P. ovale</em> malaria in children and adults (except pregnant women, infants aged &lt; 6 months, women breastfeeding infants aged &lt; 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) with a 14-day course (0.25-0.5 mg/kg bw daily) of primaquine in all transmission settings.</td>
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<tr>
<td><strong>Strong recommendation, high-quality evidence</strong></td>
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<td>In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced haemolysis.</td>
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<tr>
<td><strong>Conditional recommendation, very low-quality evidence</strong></td>
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<tr>
<td>When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.</td>
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<td><strong>Good practice statement</strong></td>
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<td><strong>Pregnant and breastfeeding women</strong></td>
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<td>In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.</td>
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<tr>
<td><strong>Conditional recommendation, moderate-quality evidence</strong></td>
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This document was prepared as a pre-read for the meeting of the Malaria Policy Advisory Committee and is not an official document of the World Health Organization.

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Box 1 B Further guidance provided in the WHO Guidelines for the treatment of malaria (1)

- In patients known to be G6PD deficient, primaquine may be considered at a dose of 0.75 mg base/kg bw once a week for 8 weeks. The decision to give or withhold primaquine should depend on the possibility of giving the treatment under close medical supervision, with ready access to health facilities with blood transfusion services.
- Some heterozygote females who test as normal or not deficient in qualitative G6PD screening tests have intermediate G6PD activity and can still haemolyse substantially. Intermediate deficiency (30–80% of normal) and normal enzyme activity (> 80% of normal) can be differentiated only with a quantitative test. In the absence of quantitative testing, all females should be considered as potentially having intermediate G6PD activity and given the 14-day regimen of primaquine, with counselling on how to recognize symptoms and signs of haemolytic anaemia. They should be advised to stop primaquine and be told where to seek care should these signs develop.
- If G6PD testing is not available, a decision to prescribe or withhold primaquine should be based on the balance of the probability and benefits of preventing relapse against the risks of primaquine-induced haemolytic anaemia. This depends on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes and on the capacity of health services to identify and manage primaquine-induced haemolytic reactions.

These recommendations on the radical cure of P. vivax infections are reiterated in Control and elimination of Plasmodium vivax malaria – A technical brief (2), a WHO publication that deals exclusively with the control and elimination of P. vivax malaria (see Box 2).

Box 2. Recommendations in Control and elimination of Plasmodium vivax malaria – A technical brief (2)

- Where feasible, all patients should be tested for G6PD deficiency before administering primaquine. Testing for G6PD deficiency in vivax malaria cases should be considered an integral part of ensuring universal access to diagnosis and treatment.
- G6PD testing should be incorporated into treatment guidelines, and services made available as tools are developed (possibly with referral of patients from lower to higher level health facilities).
- Where no G6PD test is available, it is difficult to generalize on the correct approach to patient management, because each individual assessment depends on the risk of adverse consequences (related to the likely dose of primaquine required, the prevalence and severity of G6PD deficiency in the area, the degree of anaemia and the availability of blood transfusion) and the potential benefits (related to the probability of relapse). In some circumstances, the assessment will favour withholding primaquine, and in others it will favour starting radical treatment after educating the patient about the possible risks, and informing the patient that they should stop the drug if they become ill or their urine becomes red or black.
The P. vivax recommendations were launched on 29 July 2015 at a global meeting held in New Delhi. The launch was followed by a 2-day meeting in which participating countries from all WHO regions other than the WHO African Region deliberated on the translation of the guidelines into policy and strategy in their programmes. As an outcome of those discussions, countries asked WHO to provide further guidance on how best to manage the challenging implementation issues they anticipate facing in an effort to comply with the recommendations for P. vivax radical cure. The main issues in implementation are the following:

- The limited availability of a robust, easy-to-use, point-of-care G6PD test restricts the ability to deploy primaquine for radical cure at lower levels of the health system. Promoting referral to higher level facilities will be problematic where referral services are weak (as is the case in most endemic countries) and it threatens early treatment of blood-stage infection if patients are referred to a higher level for both G6PD testing and P. vivax treatment.
- Some countries, particularly (but not only) in the Region of the Americas, are currently implementing radical cure for all patients at health facility level without necessarily testing for G6PD. This approach is justified on the basis that the G6PD deficiency allele frequency is very low (and the variants are generally considered to be mild) or absent, and therefore the benefits of providing radical cure for all P. vivax patients in whom the G6PD status is unknown exceeds the risk of primaquine-induced haemolysis. Hence, full compliance with the recommendation of testing before treatment could prevent expansion or could reverse implementation in settings where, before this recommendation, primaquine was being administered without first determining the G6PD status. In other settings, the risk–benefit analysis may be more challenging and guidance is needed to conduct the risk–benefit assessment and monitor the impact.

The above issues call for WHO to provide practical guidance to:

- countries on how they could move steadily towards introducing quality G6PD testing with currently available tools in all P. vivax patients before providing radical cure, while at the same time not compromising early P. vivax diagnosis and treatment programmes in settings where current G6PD tests cannot feasibly be deployed; and
- national malaria programmes on how to perform a risk–benefit analysis to inform decision-making on administering or withholding radical cure when a patient’s G6PD status is unknown, assessing the prevalence and type of G6PD deficiency alleles prevalent in the country, testing for and interpreting G6PD tests, and managing the risk of haemolysis when primaquine is administered when G6PD status is not known.

The following are proposed:

- WHO recommendations made on preventing relapse in the current WHO Guidelines for the treatment of malaria (1) and in the Control and elimination of Plasmodium vivax malaria – A technical brief (2) remain unchanged.
- In translating these recommendations to action plans in countries, the following (or similar) guidelines be provided by WHO in (or as an addendum to) the P. vivax technical brief (2).

Where feasible, all patients with confirmed P. vivax and P. ovale should be tested for G6PD deficiency before administration of 14-day radical treatment with primaquine. There is limited experience in programmatic settings with currently available point-of-care, rapid diagnostic format tests for G6PD. Also, these tests may not be appropriate for use at the lower levels of the health system by health workers with limited skills and training, because the performance
of these tests is sensitive to temperature, the visual read out is more subjective than for malaria rapid diagnostic tests (RDTs) and there is a lack of integrated controls and quality control materials to allow for performance monitoring. Other potentially more robust point-of-care technologies have recently been commercialized but have not been independently assessed or achieved stringent regulatory approval; therefore, those technologies cannot be recommended for use. Hence, countries may use the following guiding principles as they move towards G6PD testing and implementing radical cure with primaquine for all confirmed *P. vivax* patients in the future:

- All countries in the phases of malaria elimination or in prevention of re-introduction (or both) should incorporate G6PD testing with currently available tests into treatment guidelines, and ensure that all *P. vivax* patients who do not know their G6PD status are tested before the administration of primaquine anti-relapse therapy.
  - In these phases of the programme, the patient load is extremely low, and, by requirement, patients are treated under close surveillance and often hospitalized. Thus, G6PD testing and administration of primaquine for radical cure should be entirely feasible.

- Countries where the prevalence of G6PD deficiency is known to be very low, and where G6PD testing is not currently considered mandatory on the basis that the potential benefits (related to the probability of relapse) exceed the risk of adverse consequences of primaquine treatment, should continue, while taking all precautions to educate the patient about the possible risk. Patient counselling should explicitly state that patients should stop the medicine and seek medical care if they become ill or their urine becomes red or black. The pharmacovigilance system need to be strengthened in these countries, to report on acute haemolytic anaemia induced by primaquine.

- Where both the burden of *P. vivax* malaria and the prevalence of G6PD deficiency is considerable, *P. vivax* patients should continue to be tested for malaria and treated for the blood-stage infection at all levels of the health system, particularly at the community level. A decision to administer primaquine anti-relapse therapy should be on one or both of the following:
  - individual patient assessment of the benefits of preventing relapse being assessed as exceeding the risk of giving primaquine (the risk depending on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes, and the capacity of and accessibility to the health services that can identify and manage primaquine-induced haemolytic anaemia)
  - referring the patient to a higher level health facility for G6PD testing and primaquine treatment after providing treatment for the blood-stage infection.

- WHO should provide more specific guidance to countries on:
  - making risk–benefit assessments for radical cure;
  - assessing the feasibility of managing an acute haemolytic event when the G6PD status is unknown;
  - determining the population prevalence of G6PD and variants; and
  - G6PD testing of patients, where it is feasible, and interpretation of test results.

Such guidance may include an algorithm-based decision-making scheme, and defining factors that would enable effective management of haemolysis (e.g. distance to nearest hospital and blood bank, and a checklist for patient counselling and advice).
References
