

**WHO Evidence Review Group:
The Safety and Effectiveness of Single Dose Primaquine
as a *P. falciparum* gametocytocide**

Pullman Hotel, Bangkok, Thailand, 13-15 August 2012

Meeting Report

Background

Deployed since the early 1950s primaquine is the most widely used 8-aminoquinoline antimalarial drug. It has been used extensively in the radical treatment of *P. vivax* and *P. ovale* malaria, and as a single dose gametocytocide in falciparum malaria. The main limitation to its use has been haemolytic toxicity. The 8-aminoquinoline antimalarials produce dose dependent acute haemolytic anaemia (AHA) in individuals who have G6PD deficiency, an inherited X-linked abnormality. The prevalence of the underlying allelic genes for G6PD deficiency varies typically between 5 and 32.5 % in malaria endemic areas of Asia and Africa.

Glossary:

G6PD: Glucose-6-phosphate dehydrogenase

G6PDd: G6PD deficient

AHA: Acute haemolytic anaemia

ACT: Artemisinin combination treatment

MDA: Mass drug administration

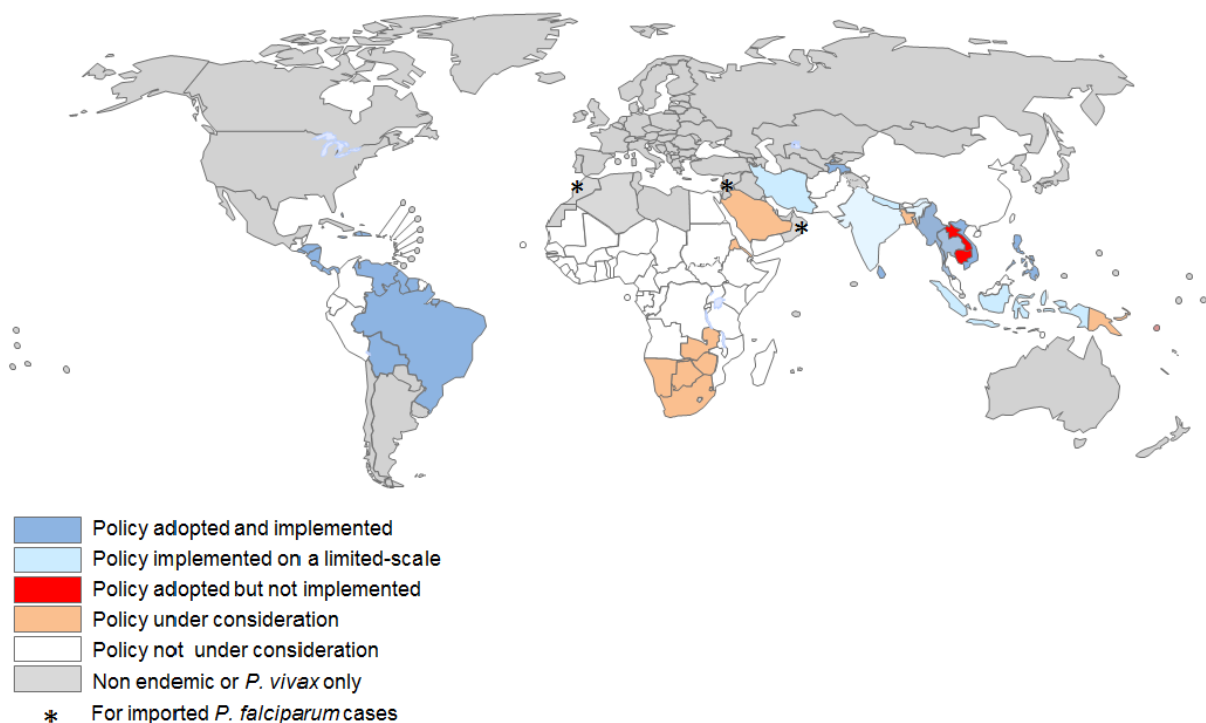
POC: Point of care

Use of primaquine as a gametocytocide has great potential to reduce the transmission of falciparum malaria in low transmission settings, and in particular to help contain the spread of artemisinin resistant falciparum malaria in SouthEast Asia. The World Health Organisation currently recommends addition of primaquine 0.75 mg base/kg (adult dose 45 mg) to treatment regimens for *P. falciparum* malaria in areas of low transmission, particularly in areas where artemisinin resistant falciparum malaria is a threat, “when the risk for G6PD deficiency is considered low or testing for deficiency is available”. Unfortunately there is often uncertainty about the prevalence and severity of G6PD deficiency, and testing for it is usually not available in these areas. In practice, the potential for developing AHA has limited the use of primaquine. Some countries recommend use of single dose primaquine as a *P. falciparum* gametocytocide, and some do not. There is also variability in the doses recommended and in their timing with respect to artemisinin combination treatment (ACT) administration.

In order to review the WHO policy on single dose primaquine as a gametocytocide in *P. falciparum* malaria, an Evidence Review Group (ERG) was convened. The ERG reviewed evidence from published literature and unpublished studies on the efficacy and safety of primaquine and other 8-aminoquinolines when used as antimalarials, with special focus on

single dose gametocytocidal use. The aim of the ERG was to provide and review the evidence base and formulate possible recommendations to the WHO GMP malaria policy advisory committee (MPAC) on the use of primaquine as a gametocytocide. This takes into account the different areas where primaquine is currently recommended at 0.75 mg base/kg single dose, in areas where it is not currently implemented but there is an intention to implement soon, and more urgently the need to contain the emergence and spread of artemisinin resistance in Cambodia and other areas of Southeast Asia.

Figure 1. Global distribution of country policies regarding deployment of primaquine as a single dose gametocytocide (updated 22.8.2012)



Objectives

The specific objectives of the meeting of the Evidence Review Group were to:

- Review evidence from published literature as well as unpublished studies on the efficacy and safety of single dose primaquine when used as a *P. falciparum* gametocytocide.
- Develop draft responses to key questions identified by the WHO secretariat and the MPAC on primaquine use.
- Formulate recommendations for a policy statement on primaquine use as a single dose gametocytocide given with ACTs.
- Identify the critical gaps in knowledge and prioritise the research agenda

Process

The ERG was approved by the MPAC in February 2012. Two researchers (EA, JR) reviewed systematically all published evidence and archival material in the WHO headquarters pertaining to use of 8-aminoquinolines. Standard database (PubMed, EmBase) searches were conducted but much of the evidence on plasmoquine (primaquine's predecessor) was published before 1950 and required direct access to archive material. These data were reviewed together with those provided by the meeting participants and form the basis for the recommendations summarised at the end of this document.

Evidence reviewed

Transmission blocking effects

All the effective antimalarial drugs kill early developing gametocytes (stages 1 to 3) of *P. falciparum* and all blood stages of the other human malarias. Artemisinin derivatives substantially reduce transmissibility in falciparum malaria largely by killing younger gametocytes, but patients who already present with transmissible densities of infectious mature gametocytes may continue to transmit despite receiving ACTs. Several antimalarials (e.g. antifols and hydroxynaphthoquinones) also interfere with parasite development in the mosquito (sporontocidal activity) but, of currently available medicines, only the 8-aminoquinolines and methylene blue have been confirmed to kill mature *P. falciparum* gametocytes. Reduction in gametocytaemia has been used as an effect measure in trials assessing antimalarial drug effects on transmission but the relationship between gametocyte density and transmissibility is non-linear, complex, and affected by several different covariates. Moreover, this relationship varies substantially between individuals, as patients may have high densities of young stage 5 gametocytes which are not infectious. Definitive assessment therefore requires direct evaluation of infectivity to mosquitoes.

Studies of the effects of 8-aminoquinoline antimalarials on the infectivity of *P. falciparum* to anopheline mosquitoes were first reported in 1929. Detailed information from published studies is available on 159 subjects assessed in different locations with different vectors and different 8-aminoquinoline drug exposures. This includes studies from China on 78 subjects who received different doses of primaquine and other antimalarial drugs (kindly provided by Professor Gao Qi), studies on 31 subjects who received plasmoquine (before 1950), and 50 subjects who received primaquine. [1,2,3,4,5,6,7]. Published studies listed (reviewed in [8]) assessed the infectivity to mosquitoes from oocyst counts and sporozoite rates in the malaria vectors and in some cases through the evaluation of the success of fed mosquitoes in generating secondary infections in healthy volunteers (infectivity).

These studies show clearly that both plasmoquine and primaquine rapidly and potently reduce the infectivity of *P. falciparum* malaria. The reduction in transmissibility assessed from oocyst numbers and morphology, and consequent sporozoite numbers (and in two series the

infectivity to other volunteers) significantly *precedes* the effect on gametocyte densities. Thus changes in gametocyte densities underestimate, and are therefore a poor short term indicator of, the transmission-blocking effects of 8-aminoquinoline antimalarials.

Dose-response relationship

Characterisation of the dose-response or concentration-effect relationship is a necessary prerequisite for dose optimization. Data from studies of the transmission blocking effects of plasmoquine suggested that low doses (10-20mg) provided potent transmission blocking activity. Pooling published data on primaquine together with results of unpublished studies conducted in China (kindly provided by Professor Gao Qi) provide 128 individual patient data sets (78 of whom received primaquine doses of between 3.7 and 15mg base). The dose response relationships show that artemisinin derivatives potentiate the transmission blocking effects of primaquine and that primaquine doses as low as 0.125 mg base/kg (adult dose 7.5 mg) when given with an artemisinin derivative, still provide near maximal transmission blocking effects. This supports use of a single 0.25mg base/kg dose as a gametocytocide.

Safety

The main safety concern for primaquine administration is the risk of AHA in G6PD deficient (G6PDd) individuals (reviewed in [9]). G6PDd individuals are uniquely vulnerable to oxidative stresses as their erythrocytes do not have alternative pathways for G6PD-dependent NADPH production, and NADPH is essential to maintain their two main anti-oxidant defences- reduced glutathione and catalase.

The severity of AHA depends on many different factors:

- (1) The dose of primaquine
- (2) Pre-existing or co-existing morbidities, particularly fever and pre-existing anaemia
- (3) Age. Severe AHA tends to be more life-threatening in children
- (4) The specific G6PDd variant involved.

G6PD variants arise from different mutations in the *G6PD* gene; therefore the extent of enzyme deficiency is more extreme with some than with others. In addition, since the mutant enzymes undergo intra-erythrocytic decay more rapidly than the normal enzyme, older red cells are more vulnerable to oxidant haemolysis. With some variants this result in self-limiting AHA upon repeat drug challenge, as the newly produced erythrocytes with higher enzyme activity are more resistant to drug-induced oxidant stress. This is not relevant to administration of a single primaquine dose.

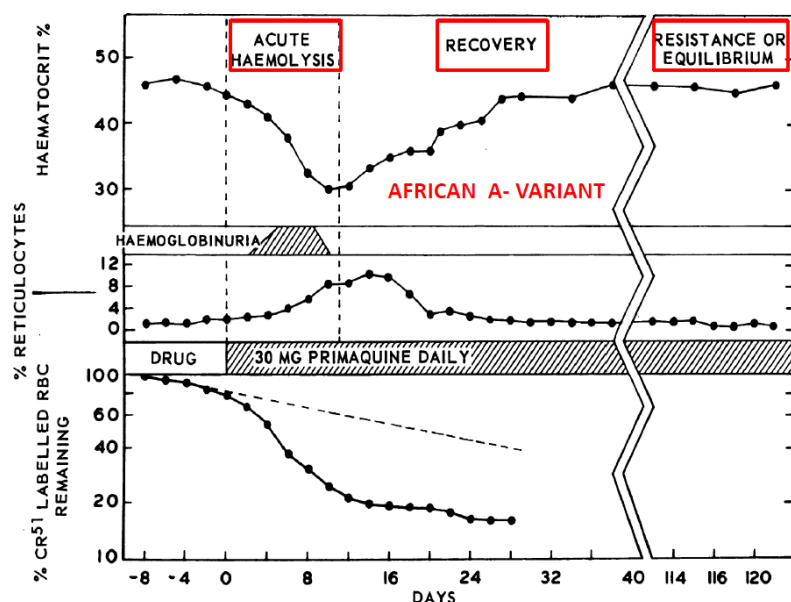


Figure 2. Characterisation of haemolysis phases in “primaquine-sensitive” (probably G6PD A-) individuals. Haemolysis in healthy African-American subjects, probably G6PDd variant A-, given a course of 30 mg primaquine daily reported by Alving *et al* in 1962 based on this groups’ studies [10,11,12,13,14,15,16,17]. The haematocrit usually starts falling on the second day. Haemolysis can be divided in 3 phases: 1) an acute phase lasting 7-12 days in which the haematocrit falls to its lowest level and ~30% of the red cell mass is destroyed, the urine is dark and sometimes black in colour, and bilirubin levels rise to 3-5 mg/dL (55 to 105 µmol/L). If primaquine is stopped during the acute phase, erythrocyte destruction

ceases within 48-96 hr 2) but even if primaquine is continued a recovery phase occurs between days 10-40, in which there is reticulocytosis reaching a peak of 8-12%, and the haematocrit slowly return to normal levels by the fourth or fifth week 3) then there is an equilibrium phase in which haemolysis is balanced by increased erythrocyte production and this continues as long as primaquine is given.

Detailed prospective studies of primaquine induced haemolysis were conducted in Italy and USA in the 1950s and 1960s. In Italy the most common type of G6PD deficiency is called G6PD Mediterranean, whereas in Africa and in African-Americans the less severe A- variant (mean G6PD activity about 13% of normal) predominates. The University of Chicago-Army Medical Research Unit at the Illinois State penitentiary (Stateville) conducted a series of studies on African-American hemizygous male healthy volunteers and classified the degree of haemolytic anaemia with daily dosing as follows.

Table 2. Degree of haemolysis and anaemia in African-American primaquine-sensitive males depends on daily primaquine dosage

Primaquine DAILY dose	45 mg	30 mg	15 mg	<15 mg
Haemolysis	Dangerous haemolytic anaemia	Severe	Moderate	Mild
Anaemia	Dangerous haemolytic anaemia	Acute	Mild	None
Half-life of Cr ⁵¹ RBCs (days) *	0-10	5-10	10-20	20-25

Data from [18] RBC= red blood cell, * Half-life without primaquine is >25 days

Deaths associated with primaquine

Thirteen deaths associated with primaquine administration have been reported over the last 6 decades ([19] and references therein). Four of these were in G6PD deficient Sri Lankan children [20]. The exact dose of primaquine administered could not be ascertained but they were likely to have been overdosed. Five deaths of patients in Turkey who had been treated for vivax malaria were described very briefly in an internal WHO report in 1978 [21]. One death from hepatic necrosis was reported in association with primaquine from the UK, notified through the national yellow card reporting scheme [22]. Two deaths in G6PDd Brazilians due to primaquine induced AHA were diagnosed based on autopsy findings [23]. One additional death in the USA was reported in 1997 to the Uppsala Monitoring Centre (no details are available, [24]). Using a population denominator of all patients given any dose of primaquine in published studies or MDAs (see below) this would set the risk of death associated with primaquine ingestion at approximately 1 in 692,307 (upper 95% CI: 1 in 448,500). These data suggest that the mortality associated with severe haemolysis is low, although it is possible that other deaths have not been reported.

Severe adverse events associated with primaquine

The definition of severe adverse event used in this report to evaluate all studies, MDAs, and case reports, was any adverse event occurring after drug treatment that led to one of the following: (a) death; (b) threat to life; (c) hospital admission; (d) severe anaemia with Hb <5g/dL; or, (e) any adverse event reported as 'severe' by the authors. In 69 studies excluding MDAs (20 that included G6PDd individuals and 49 in which G6PDd status was unknown or G6PDd subjects were excluded) and in separate case reports, no severe adverse events were reported in individuals known to be G6PD normal (with the possible exception of one psychotic reaction in a subject with undetermined G6PD status). A total of 191 severe adverse events were reported in studies or case reports but not including MDAs, 25 were in individuals whose G6PD status was not determined, and 166 were in G6PDd subjects. The majority (87.4%) of all severe adverse events were reported in confirmed G6PDd subjects, some of whom had malaria. Of all the severe adverse events, 11.5% occurred after a probable overdose of primaquine, 75.9% after daily doses of either 15 or 30 mg primaquine administered mostly for vivax malaria, and 12.6% were reported from administration of 40 or 45 mg primaquine as a single dose or in weekly regimens. Although most treatment studies were conducted exclusively in adults, almost all severe adverse events from reports in which primaquine might have been administered in greater than recommended doses were in children (95.5%). The lack of paediatric tablets may have been a contributory factor. From the MDAs which included millions of patients, e.g. in the former USSR and North Korea, the incidence of severe adverse events

was very low for either primaquine daily regimens of 15 mg PQ base usually given for more than one week (2.9 per million) or single/weekly dose of 45 mg PQ base (only one severe anaemia reported). From all severe adverse events reported for the MDA studies which gave daily primaquine regimens, 61.5% were haemolysis resulting in an estimated incidence of severe haemolysis of 1.8 per million (upper 95%CI: 1 in 225,753)

From the smaller detailed prospective safety studies the incidence of severe adverse events for primaquine daily regimens was 0.26% compared with 0.42% for single or weekly doses. For the latter category, 43.8% of all severe adverse events were in children younger than 12 years old. All severe adverse events consisted of AHA. There were 108 severe adverse events from the case reports for a daily primaquine regimen, and 8 for single dose administration of 30 or 45 mg.

Single-dose primaquine without G6PD screening- the ethical problem

Central to the consideration of recommending a policy of single dose primaquine is the fact that individuals being treated for their malaria episode with an ACT + primaquine derive no immediate individual benefit from primaquine treatment, that G6PD testing is not widely available, and therefore that individuals with undiagnosed G6PD deficiency will be put at risk of iatrogenic acute haemolytic anaemia. The justification for recommending a policy of single dose primaquine is the benefit to the population (of which the patient is a member) of reduced transmission of malaria. Indeed, as the risk of acquiring malaria in the relatively low transmission settings where primaquine should be used is unevenly distributed, treated patients are often at increased risk and more likely to be infected again. In the context of spreading drug resistance there is the potential benefit of reducing the spread of resistance and thereby reducing treatment failures. But this begs the question as to what degree of risk is acceptable? This ethical problem can be conceptualized using a public health framework. Public health policies aim to benefit populations and the impact is often not uniform across individuals affected by the policy. In general a public health policy is justified on the basis of (but not limited to) the following:

- 1) Overall benefit (acknowledging tensions because individual interests may be diminished).
- 2) Fairness in the distribution of burdens (in general the basic tenet is that burdens should be equivalent- this is not the case here where only the individuals who are G6PDd are at risk of harm).
- 3) Harm principle- the only justification for interfering in the liberty of an individual against her will is in order to prevent harm to others.

In considering use of primaquine as a *P. falciparum* gametocytocide there is no immediate individual benefit and 'acceptable risks' are hard to define. Perceptions of risk also may differ. People may be willing to take serious risks, but they should be informed properly and given the

right of refusal. As with many other public health policies it is likely that high population coverage with primaquine is needed to maximize the impact on malaria transmission, hence a high rate of individuals who withhold consent will have a negative impact on the success of the policy. For this reason, seeking individual consent, as is done for biomedical research, is not feasible. There is a principle that the more intrusive a policy, the more justification is needed. If the policy is mandatory there is no free will, although information may be given to the public. There should be community engagement in discussing these issues. When there is scientific uncertainty of the risks involved in following a certain approach, then the 'Precautionary Principle' has been applied [25]. This puts the onus on the policy maker to establish that the policy is unlikely to cause significant harm to the population to whom it will be applied to. However, at the same time, lack of scientific evidence should not be used as a justification for inaction, particularly when there may be other harms associated with inaction, e.g. in this case, the propagation of artemisinin-resistant malaria. A precautionary approach [26] may be applied to the introduction of widespread use of single-dose primaquine in areas where G6PD testing is usually not available e.g. by applying recommendations in a step-wise fashion, having a regional policy (targeting areas at highest risk of artemisinin-resistance first), reducing the dose of primaquine to one where there is less scientific uncertainty about the potential to cause harm, implementing measures to mitigate the risk (e.g. improving early detection and management of AHA, continued development of point of care G6PD tests, gathering more evidence through research). The policy can be revised later when more information is available.

Point-of-care G6PD testing:

The "gold standard" for determining the G6PD status of a person is the spectrophotometric assay of red cell G6PD content - but this can be done only in a laboratory setting. Point-of-care (POC) testing for G6PD is seldom available in the rural tropics. Several screening tests have been used in the field [27,28] but the one that has been used most extensively for diagnostic work is the fluorescent spot test (FST) based on Beutler's method from the 1960s. This detects directly the production, from NADP⁺, of NADPH which is fluorescent, and so a UV lamp is required. In general the FST classifies as deficient individuals with G6PD activity <30% normal. This threshold identifies individuals at risk of clinically significant haemolysis. A modification of the FST using dried blood samples on filter paper is often used for neonatal screening of G6PD deficiency. Implementation requires quality control of the field laboratory results and a cold chain to transport and store the reagents. These are significant obstacles for using G6PD testing at the point of care in most areas where malaria is endemic. New POC tests are in the advanced stages of development but are not yet sufficiently well validated to be recommended at this time.

The characteristics of an ideal POC test were summarized:

1. Rapid
2. Easy to perform (few steps, no need for other equipment or electricity)
3. Easy to interpret (qualitative or semi-quantitative)
4. Quality control possible
5. Humidity and temperature stable (storage and perform)
6. Low cost

Conclusions and recommendations

The ERG addressed the following key questions which had been set at the MPAC meeting and made the recommendations below for consideration.

1. What is the adverse effect (health impact) of a single gametocytocidal dose of primaquine in heterozygous females and hemizygous males with G6PD deficiency?

In G6PD normal individuals there is a very low risk of severe adverse effects. Primaquine is well tolerated at doses up to 45 mg if taken with food.

The risk of AHA with a 45 mg dose is 100% in G6PD deficient subjects, although its severity is variable and haemolysis will be subclinical in the majority of cases. The severity of AHA is dose-dependent and varies depending on the G6PD variant; however, it is also variable in individuals with the same G6PD variant. The variability is greatest among heterozygous females, as they have a variable proportion of G6PD deficient red cells in their blood. Considering that the 15 mg per day dose given for 14 days has been also extensively used in radical cure and mass drug administration without G6PD screening, we expect that a single 15 mg primaquine adult dose (0.25 mg base/kg) will not result in clinically significant haemolysis in G6PD deficient individuals.

2. What is the clinical impact of radical curative dose regimens of primaquine in heterozygous females and hemizygous males with G6PD deficiency? 3. What is the haemolytic dose response relationship of primaquine when used for *P. vivax* radical cure?

Giving primaquine for radical cure requires at least 7 days of drug administration with a cumulative adult dose ≥ 180 mg, resulting in a correspondingly greater risk of clinically significant AHA, therefore G6PD testing is recommended. We do not have sufficient evidence to change the existing recommendation of 45 mg primaquine once weekly dose for *P. vivax* in G6PD deficient individuals with mild variants. More evidence is needed to optimize an effective and safe dose regimen for this population.

4. How can G6PD deficiency be detected in the field use of primaquine?

Currently most people who receive primaquine do not get tested for G6PD deficiency. The gold standard for the laboratory assessment of G6PD deficiency is the quantitative spectrophotometric assay. The NADPH fluorescence spot test (FST) is the current reference standard and widely used for diagnosis in field research settings. However, because the test

requires a cold chain, specialized equipment, laboratory skills, and is relatively expensive, its availability in most areas of endemic malaria is virtually non-existent. The NADPH FST may be adequate, provided it is properly calibrated to classify as G6PD deficient individuals with enzyme activity levels $\leq 30\%$. This threshold identifies G6PD deficient individuals, including heterozygote females, who are at risk of developing clinically significant AHA.

If G6PD testing is not available, the patient should be informed of the risk of AHA, instructed to monitor urine colour and to stop the use of the medicine and seek medical advice if his/her urine becomes dark.

5. How can primaquine-induced haemolysis be best assessed in the field in patients with unknown G6PD status?

1) Patient/caregiver education should be given on symptoms and signs to look for (e.g. change in urine colour). Young children should be monitored carefully.

2) Training of health workers, with the support of appropriate job-aids, to recognise symptoms and when to refer for further assessment. Symptom checklist: back pain, dark urine, jaundice, fever, dizziness, breathlessness.

6. What is the best clinical management of haemolytic reactions following primaquine exposure?

Stop the primaquine

Oral hydration

Refer to inpatient facility

Clinical assessment

Check haemoglobin or haematocrit

Check plasma or serum creatinine or urea (BUN) if possible

Give blood transfusion, if needed, as per the following guidelines:

- Hb < 7g/dL, transfuse
- < 9 with ongoing haemolysis, transfuse
- 7-9 or > 9 and no evidence of ongoing haemolysis, observe

Ongoing haemolysis with no need for transfusion careful fluid management with monitoring of urine colour

7. What is the dose response relationship for gametocytocidal activity in falciparum malaria?

Historical data on 8-aminoquinolines (plasmoquine and primaquine) suggest that doses of 15 mg primaquine alone, and 7.5 mg primaquine together with an ACT are effective as transmission blocking regimens. The individual patient data to date are shown above (Figure 3). However, 15 mg was not fully efficacious when not given with an artemisinin derivative so more data are urgently needed in areas where artemisinin resistance is emerging.

8. When should single dose primaquine be given?

No data are available regarding optimum timing, but public health considerations and practicalities favour directly observed therapy on the first day of ACT administration to ensure transmission blocking as early as possible during an infection as well as compliance with the single dose treatment.

9. Can the administration of single-dose primaquine be made safer?

Tolerability can be improved by taking primaquine with food and the patient should be advised to monitor signs of severe AHA such as dark urine (e.g. aided by a colour chart). A past medical history of haemolysis may be sought.

A reliable supply of a paediatric formulation is needed and a paediatric dosing schedule which should allow age and weight-based dosing.

10. Based on the review of available evidence, including unpublished reports, which key recommendations (if any) could be proposed for a GRADE assessment?

All of the data on the efficacy of the 8-aminoquinolines in blocking infectivity to mosquitoes should be submitted. It is desirable that the important data from Chinese colleagues reviewed at this meeting be published in peer reviewed journals as soon as possible, thereby permitting a GRADE assessment of likely greater impact.

11. Which priority research and development gaps need to be addressed to clarify the role of primaquine as a gametocytocide for falciparum malaria?

- 1) More data are needed urgently on
 - a. the primaquine dose-response relationship for transmission-blocking activity in different locations
 - b. measuring the severity of AHA in G6PD deficient individuals with different G6PD variants.

Efficacy and safety should also be evaluated in pregnant women, infants, HIV infected patients (including potential for interactions with antiretroviral drugs) and individuals with different variants of enzymes known to be involved in drug metabolism (e.g. CYP P450).

2) Formulation (including paediatric), supply, policy and sociological factors that can influence primaquine deployment including coverage

3) Development, optimization, and field evaluation of a rapid, easy to use and read, robust, affordable POC G6PD test.

4) More data are needed on the excretion of primaquine in breast milk.

5) Research on efficacy and safety of alternative falciparum transmission-blocking drugs, such as methylene blue and ivermectin.

6) Studies of the mechanism of action of primaquine in causing AHA and potential mitigation or potentiation of haemolytic toxicity by the use of partner drugs.

7) Research to understand the epidemiological impact of deploying gametocytocidal treatments in different population groups.

8) Detection of resistance to the gametocytocidal activity of primaquine.

Of these, we consider **1** and then **2** the highest priority.

WHO currently recommends a 0.75 mg base/kg single gametocytocidal dose should be given in addition to an ACT for falciparum malaria “when the risk for G6PD deficiency is considered low or testing for deficiency is available”. However, G6PD testing is seldom available in the field, and this has limited the implementation of this recommendation. G6PD testing needs to be deployed more widely. Gametocytocidal medicines play an important role in reducing malaria transmission, and their use would be essential in efforts to eliminate malaria, and particularly in the elimination of *P. falciparum* malaria. The population benefits of reducing malaria transmission by gametocytocidal drugs require that a very high proportion of patients receive these medicines. Based on the review of the evidence the group proposes, the following revised recommendations for the following scenarios:

Countries where primaquine as gametocytocide is currently implemented as policy for falciparum malaria:

These countries should be encouraged to continue with current policy until more information is available. G6PD testing is recommended, especially in countries where *P. vivax* is prevalent. For G6PD deficient patients, a 0.25 mg/kg primaquine single dose is recommended instead of 0.75 mg base/kg dose.

Areas threatened by artemisinin resistance where there is not high coverage of single dose primaquine as a gametocytocide for falciparum malaria:

Where G6PD testing is not available, a 0.25 mg base/kg primaquine single dose in addition to ACT on day 0 should be given to all patients with falciparum malaria except pregnant women and infants <1 year of age. All efforts should be made to contain the spread of artemisinin resistance, and reducing transmission of the treated infection is imperative.

Pre-elimination and elimination areas which have not yet adopted primaquine as a gametocytocide for falciparum.

Where G6PD testing is not available, a 0.25 mg base/kg primaquine single dose in addition to ACT on day 0 should be given to all patients with falciparum malaria except pregnant women and infants <1 year of age.

The Evidence Review Group strongly recommends that a review of policies related to Community-wide malaria drug chemoprevention and treatment strategies in the context of eliminating artemisinin resistant falciparum malaria.

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Annex 1

List of the meeting pre-reads

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