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*

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- Dr. Elizabeth ASHLEY (Co-Rapporteur)
- Dr. Judith RECHT (Co-Rapporteur)
- Dr. Dennis SHANKS
- Dr. Olugbemiro SODEINDE
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- Professor Florencia LUNA
- Professor Lucio LUZZATTO
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**OBSERVERS**
- Dr. Germana BANCONE
- Dr. Bob TAYLOR

**WHO SECRETARIAT**
- Dr. Andrea BOSMAN

**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- Review evidence from published literature as well as unpublished studies on the efficacy and safety of single dose primaquine when used as a *P. falciparum* gametocytocide.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
Single dose primaquine as a *P. falciparum* gametocytocide
Agreements and disagreements with other studies or reviews

The findings of this review provide very little support for current WHO treatment guidelines (WHO 2010). While there is good evidence that PQ reduces gametocyte prevalence, density and AUC, there is no evidence that it is effective in reducing transmission. If PQ is given only to the fraction of infected people attending for treatment, it may not be covering enough of the infectious population to make any difference to the overall human infectious reservoir.

We found insufficient reliable evidence to recommend PQ in primary treatment for reducing transmission in a community.
Authors' conclusions

Implications for practice

Single dose or short course PQ should not be added to routine treatment of P. falciparum with ACTs until
1) it has been demonstrated that reducing infectivity of treated people in a variety of endemic situations reduces transmission on a community basis;
2) further research is done on safety and the adverse hematological effects for both G6PD and non-G6PD carriers;
3) we understand more about the proportion of gametocyte carriers who present to receive treatment in a given population and time period
4) the cost of the policy balanced against the potential benefit is explored. In any case, patients should be screened for G6PD deficiency and those with variants predisposing to haemolysis should not be given PQ.
## Outcomes and impact

<table>
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<th>Transmission intensity</th>
<th>Infectiousness Day 8</th>
<th>Potential infectiousness</th>
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<td>24-27% reduction</td>
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<td>1 study</td>
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<tr>
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<td>N=219</td>
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<td>moderate quality evidence</td>
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Community based trials

- Clyde 1962 Tanzania: AQ+PQ to all
- Hii et al 1987 Malaysia: SP+PQ+ITN vs SP+PQ
- Doi et al 1989: SP+PQ to all
- Kaneko et al 1989: SP+PQ vs SP; non-randomised; 1 cluster per arm, primary Rx + ACD
- Kaneko et al 2000 Vanuatu: weekly CQ+SP+PQ to all, ACD, ITN, fish
- Song et al 2010 Cambodia: ART+P to all
- In progress?
The gametocyte "wave"
**Plasmodium falciparum gametocytes**

(a) Early stage gametocytes  
(b) Mature stage

- **Sequestration time:** 7.8 (7.5–8.2) days
- **Mean circulation time:** 6.4 (5.2–10.6) days
- **Half-life:** 4.4 (3.8–7.3) days
- **Asexual: sexual conversion rate:** 1: 156 (7.4 to 3700)

*Smalley ME, Sinden RE. Parasitology 1977;74:1–8*
Who transmits?

P. falciparum gametocyte prevalence and density **highly** dependent on
1. Transmission intensity - immunity
2. Treatment seeking and availability
TOTAL PARASITES

Asexual stages

Transmissible Gametocytes

WEEKS

10^{12}

10^{10}

10^{8}

10^2

10^1

0
TOTAL PARASITES

- Asexual stages
- Transmissible
- Gametocytes

Recrudescent infections
- Transmission
- Drug resistance
Total gametocytes

Gametocytes/μL

Mosquito feed 1-3μL

Probable

Possible

Impossible
Very variable at an individual level

Jeffrey & Eyles 1955

Bousema & Drakely 2010

Gametocyte densities

Observed Fitted values

Proportion infected mosquitoes, %

Gametocyte density/μL

• Observed   ———— Fitted values
Plasmodium falciparum gametocytes

All effective drugs

Artemisinins

Primaquine
Patients with gametocytaemia (%)

ACT +

No primaquine
Primaquine

Bousema & Drakely 2010

ACT + No Primaquine
ACT + Primaquine

Days of follow up

Days since start treatment

Smithuis et al 2010
The effects of a gametocytocide on transmission depend on what proportion of all transmission occurs after its administration. For example, if primaquine reduces transmissibility by 95%.
Because of the non-linear relationship between reduction in transmission and reduction in the force of infection (redundancy in the reservoir of infection) the addition of transmission blocking drugs has little effect on the incidence or prevalence of falciparum malaria in areas of high stable transmission.
Coverage

Reduction in transmission (%)

Proportion of transmission from asymptomatics

- 50% coverage
- 80% coverage
Schuleman et al 1926

**Fig. 1. Structural Formula of Pamaquin (Plasmochin)**

General formula of 8-(ω-aminoalkylamino) quinolines

Alving et al J Clin Invest 1948
THE EFFECT OF SMALL DOSES OF PLASMOCHIN ON THE VIABILITY OF GAMETOCYTES OF MALARIA AS MEASURED BY MOSQUITO INFECTION EXPERIMENTS

By M. A. Barber, Special Expert, W. H. W. Komp, Associate Sanitary Engineer, and B. M. Newman, Scientific Assistant, United States Public Health Service
### Case No. 1

**Subject:** Malaquías Carbojal. Entered hospital Jan. 3, 1929, at 1 p.m.
**Race:** White (Costa Rican). **Diagnosis:** Estivo-autumnal malaria. Case No. 24082.
**Age:** 24. **Weight:** 104 pounds (47.2 kgs.).

<table>
<thead>
<tr>
<th>Date (1929)</th>
<th>Day</th>
<th>Treatment</th>
<th>Hour mosquitoes fed</th>
<th>Results of mosquito dissections</th>
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<tr>
<td></td>
<td></td>
<td>Plasmo-chin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jan. 3</td>
<td>First</td>
<td>None</td>
<td>10 grains (65 cg.)</td>
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<td>Jan. 4</td>
<td>Second</td>
<td>None</td>
<td>30 grains (195 cg.)</td>
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<tr>
<td>Jan. 5</td>
<td>Third</td>
<td>2 cg.</td>
<td>13 1/4 grains (66 cg.)</td>
<td>97 5 5 100.0 10</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>8 3/4 grains (56 cg.)</td>
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<tr>
<td>Jan. 6</td>
<td>Fourth</td>
<td>None</td>
<td>10 grains (65 cg.)</td>
<td>100 17 0 0.0 0</td>
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<tr>
<td>Jan. 7</td>
<td>Fifth</td>
<td>None</td>
<td>10 grains (65 cg.)</td>
<td>12 m 5 p.m.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10 grains (65 cg.)</td>
<td></td>
</tr>
<tr>
<td>Jan. 8</td>
<td>Sixth</td>
<td>None</td>
<td>10 grains (65 cg.)</td>
<td>6 3/4 grains (56 cg.) 8 3/4 grains (56 cg.)</td>
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</tbody>
</table>

**Note 1:** The total amount of plasmo-chin, 4 cg., given on Jan. 5 is at the rate of 1.69 milligrams per kilogram of body weight.

**Note 2:** On Nov. 27, 1928, same patient was admitted to the hospital with estivo-autumnal malaria (case No. 23892). He received plasmo-chin compound, No. II, b.i.d. for 12 days, a total of 48 cg. plasmo-chin and 90 grains quinine sulphate, and was discharged with negative blood.
Plasmoquine; transmission blocking activity

have appeared in the peripheral blood. The evidence on which this belief is based is in three categories—namely, (a) observations that crescent-carriers become free from crescents after a short course of treatment with plasmoquine; (b) observations on the degenerative changes which can be seen on microscopic examination of crescents in blood films from patients treated with plasmoquine; (c) observations on the results of trials to ascertain whether mosquitoes can be infected from crescent-carrying patients treated with plasmoquine. Up to the present, most of the evidence available

them are approximately the same. They may be stated briefly as follows: (a) a single dose of 0.04 grm. plasmoquine (either two doses each of 0.02 grm. or, according to Missirolli (1932) a single dose of 0.02 grm.) will affect crescents to such a degree as to make them incapable of infecting mosquitoes; (b) the destructive effect of the dose lasts for at least three days, so that the same good result can be obtained by giving a dose of plasmoquine every fourth day as by giving a daily dose (Amies); (c) a dose of 0.02 grm. given twice a week (the interval between the doses being about three days) is also effective in preventing crescent-carriers from infecting mosquitoes (Barber and co-workers), but this is the smallest effective dose (Whitmore and co-workers).
# 8-aminoquinolines

## Transmission blocking in *P. falciparum* malaria

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. subjects</th>
<th>Drug</th>
<th>Location</th>
<th>Patients</th>
<th>Malaria</th>
<th>mg base/kg</th>
<th>mosquitoes</th>
<th>oocysts</th>
<th>sporozoites</th>
<th>Infectivity</th>
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<td>Barber et al 1929</td>
<td>4</td>
<td>Plmq</td>
<td>Panama</td>
<td>Natural</td>
<td>wild</td>
<td>0.2-1.4</td>
<td>A. albimanus</td>
<td>Y</td>
<td>N</td>
<td>N</td>
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<td>Green 1929</td>
<td>5</td>
<td>Plmq</td>
<td>Malaya</td>
<td>Natural</td>
<td>wild</td>
<td>0.2-1.4</td>
<td>A. maculatus</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>Amies 1930</td>
<td>8</td>
<td>Plmq</td>
<td>Malaya</td>
<td>Natural</td>
<td>wild</td>
<td>0.7-0.10</td>
<td>A. maculipennis</td>
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<td>Y</td>
<td>N</td>
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<td>Jerace &amp; Giovannola</td>
<td>27</td>
<td>Plmq</td>
<td>Italy</td>
<td>Natural</td>
<td>wild</td>
<td>0.37</td>
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<td>Y</td>
<td>N</td>
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<td>Chopra &amp; Basu 1937</td>
<td>2</td>
<td>Plmq</td>
<td>India</td>
<td>Cairns</td>
<td>Military</td>
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<td>A. stephensi</td>
<td>Y</td>
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<td>N</td>
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<td>Volunteers</td>
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<td>S.Carolina</td>
<td>Panama</td>
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<td>Young 1959</td>
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<td>Prq</td>
<td>S.Carolina</td>
<td>Neurosyphilis</td>
<td>Panama strain</td>
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<td>A. quadrimaculatus</td>
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<td>Burgess &amp; Broy 1961</td>
<td>12</td>
<td>Prq</td>
<td>Liberia</td>
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<td>Gunders 1961</td>
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<td>Illinois</td>
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<td>Camp</td>
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Gametocytes/μL

Before 24h post PQ

Before 24h post PQ

Oocysts (%)

Gametocytes/μL

5000

500

50

0

100

50

Before

24h post PQ
Individual transmission blocking effects are underestimated substantially from assessments of gametocytaemia only
Infection (%)

920 gametocytes/μL

Sporozoites

Oocysts

MacErras & Ercole 1947
Dose-response
The effects of reducing gametocyte densities and viability on transmission from a population may be underestimated from studies of gametocytaemic individuals.
FIG. 1
RESULTS OF STUDIES ON VOLUNTEER 1

ASEXUAL PARASITES
(per mm³)

GAMETOCYTES
(per mm³)

[Graph and data table]

Oocysts

Sporozoites

FIG. 2
RESULTS OF STUDIES ON VOLUNTEER 2

ASEXUAL PARASITES (per mm$^3$)

GAMETOCYTES (per mm$^3$)

DAY OF PATENCY

PRIMAQUINE
45 mg base

Oocysts

Sporozoites

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<td>9</td>
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</table>
RESULTS OF STUDIES ON VOLUNTEER 3

ASEXUAL PARASITES (per mm$^3$)

GAMETOCYTES (per mm$^3$)

DAY OF PATENCY

MOSQUITO FEEDS
TRANSMISSION SUCCESSFUL
TRANSMISSION UNSUCCESSFUL

PRIMAQUINE 45 mg base

Oocysts
Sporozoites

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<th>25</th>
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<th>35</th>
<th>40</th>
<th>45</th>
<th>50</th>
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<td>8</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>6</td>
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<td>3</td>
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<td>0</td>
<td>0</td>
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RESULTS OF STUDIES ON VOLUNTEER 3

ASEXUAL PARASITES (per mm³)

GAMETOCYTES (per mm³)

DAY OF PATENCY

PRIMAQUINE 45 mg base

Oocysts

Sporozoites
Fig. 13. Results of studies with Volunteer 17.

Fig. 14. Results of studies with Volunteer 18.
These data suggest that doses much lower than the currently recommended WHO dose of 0.75mg base/kg would be effective in blocking the transmission of falciparum malaria.
Risks

A

National allele frequency
- 6 - 1%
- 1 - 3%
- 3 - 7%
- 7 - 16%
- 10 - 13%
- 13 - 17%
- 17 - 20%
- 20 - 23%
- Malaria free

B

G6PDd males (1,000s)
- <50
- 50 - 100
- 100 - 500
- 500 - 1,000
- 1,000 - 2,500
- 2,500 - 5,000
- 5,000 - 10,000
- >10,000
- Malaria free
Primaquine causes haemolysis in \textit{all} G6PD deficient individuals.

\textbf{Mortality}

1 in 692,307

(upper 95\% CI: 1 in 448,500)
Primaquine

DAILY dose

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>45 mg</th>
<th>30 mg</th>
<th>15 mg</th>
<th>&lt;15 mg</th>
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<tr>
<td>Haemolysis</td>
<td>Dangerous haemolytic anaemia</td>
<td>Severe</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Dangerous haemolytic anaemia</td>
<td>Acute</td>
<td>Mild</td>
<td>None</td>
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<tr>
<td>Half-life of Cr\textsuperscript{51} RBCs (days) *</td>
<td>0-10</td>
<td>5-10</td>
<td>10-20</td>
<td>20-25</td>
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</table>
Haemolytic risk is related to the degree of G6PD deficiency, the dose of drug, and the number of doses. A single primaquine dose of 0.25mg base/kg is unlikely cause clinically significant haemolysis in subjects who are G6PD deficient.
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”.

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 \textit{P. vivax} is a co-dominant infection.

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.

The population benefits of reducing malaria transmission by gametocytocidal drugs require that a very high proportion of patients receive these medicines.
All efforts should be made to contain the spread of artemisinin resistance.
Reducing transmission of the treated infection is imperative. 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.

Pre-elimination and elimination areas which have not yet adopted 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.
Community-wide malaria drug chemoprevention and treatment strategies are likely to play an important role in control and elimination of artemisinin resistant falciparum malaria. The Evidence Review Group strongly recommends a review of policies related to these.
<table>
<thead>
<tr>
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<th>Indication</th>
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<tbody>
<tr>
<td>Thyroxine (1891)</td>
<td>Myxoedema</td>
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<tr>
<td>Insulin (1922)</td>
<td>Diabetic ketoacidosis</td>
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<td>Vitamin B12 (1926)</td>
<td>Pernicious anaemia</td>
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<tr>
<td>Sulphonamides (1937)</td>
<td>Puerperal sepsis</td>
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<td>Penicillin (1941)</td>
<td>Lobar pneumonia</td>
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<td>Defibrillation (1948)</td>
<td>Ventricular fibrillation</td>
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<tr>
<td>Streptomycin (1948)</td>
<td>Tuberculous meningitis</td>
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<td>Ganglion blockers (1959)</td>
<td>Malignant hypertension</td>
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<td>Heimlich manoeuvre (1975)</td>
<td>Laryngeal obstruction by a foreign body</td>
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<td>Cisplatin plus vinblastine and bleomycin (1977)</td>
<td>Disseminated testicular cancer</td>
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<td>Acetylcysteine (1979)</td>
<td>Paracetamol poisoning</td>
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<td>Ganciclovir (1986)</td>
<td>Cytomegalovirus retinitis</td>
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<td>Imatinib (2002)</td>
<td>Chronic myeloid leukaemia</td>
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Table 3: Some interventions with effectiveness established through historical controlled trials