Wednesday, 12 September 2012

Time	Session	Purpose of session, target outcomes and questions for MPAC	Type
09:00	Session 5 Primaquine single dose for *P. falciparum*/Presentation/ update **(N White)**	Report back from ERG (13-15 August meeting); Policy Recommendation	**open**
10:30	**Coffee/tea break**		
10:45	Session 6 Developing the malaria strategy mix for 2015 – 2025 **(R Newman)**	For discussion and decision on process	**open**
12:30	**Lunch**		
13:45	Session 7 Policy setting landscape for vector control/Presentation **(A Mnzava)**	For discussion and decision on process	**open**
15:15	**Coffee/tea break**		
15:30 16:15	Session 8 Developing a *P. vivax* strategy **(R Newman)** Chemotherapy TEG/Presentation **(P Olumese)**	For discussion and decision on process For discussion – TEG draft ToR	**open**
17:00	**End of day**		

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

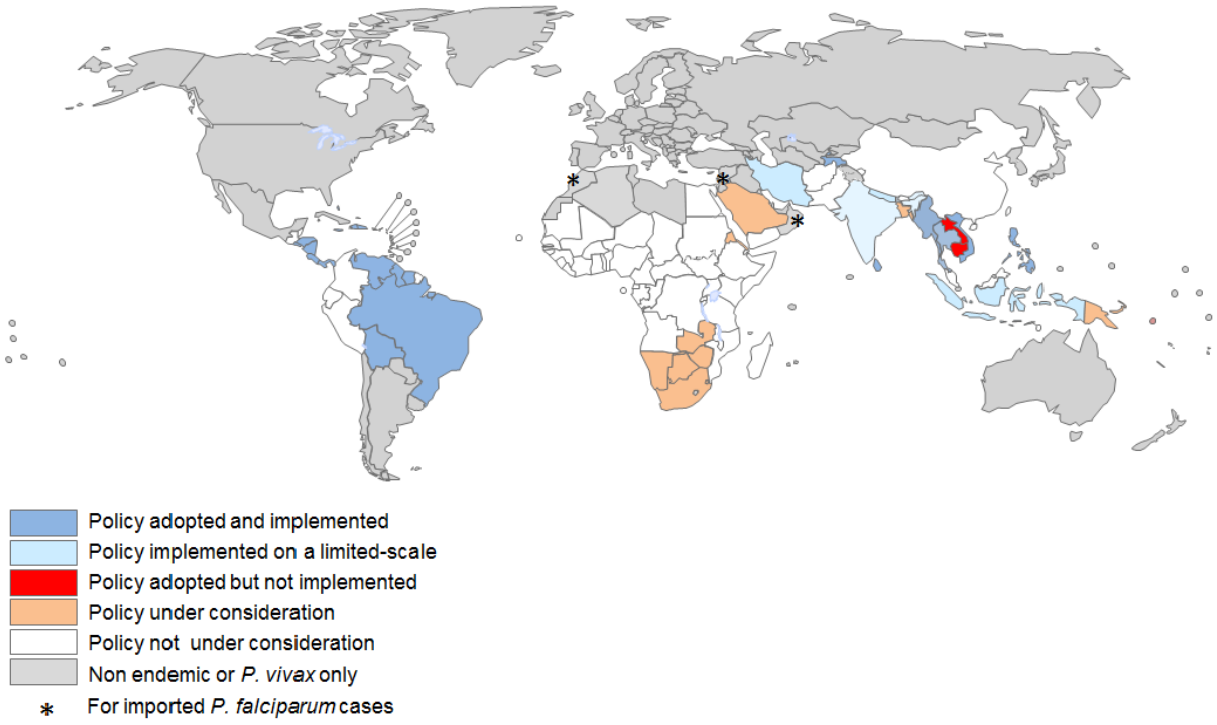
POC: Point of care

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 are 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 pre-requisite 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.

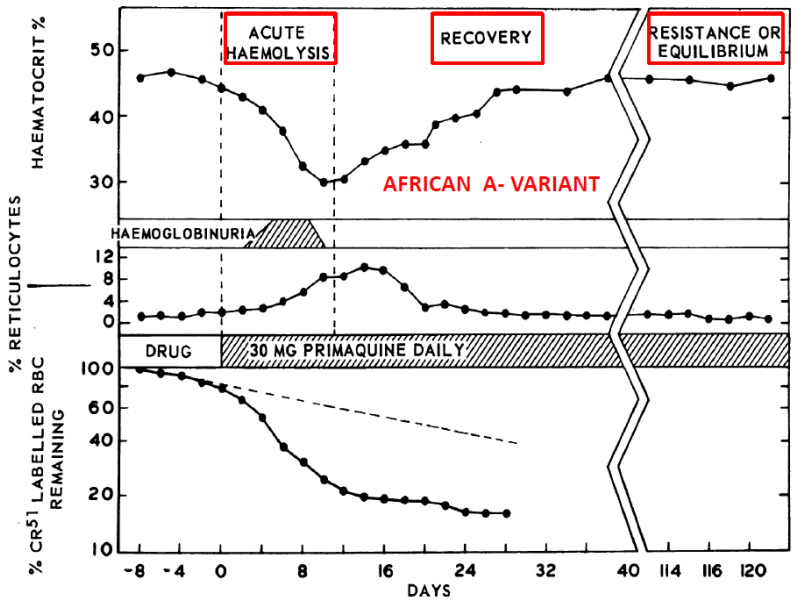


Figure 2. Characterisation of haemolysis phases in "primaquine-sensitive" (probably G6PD A-) individuals. Haemolysis in healthy African-American subjects, probably G6PDd variant A-, given a course of 30 mg primaquine daily reported by Alving *et al* in 1962 based on this groups' studies [10,11,12,13,14,15,16,17]. 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 1in 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 administrationof 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 in 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 G6PDd 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 G6PDd 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, it is 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 ≤ 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 G6PDd 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

Baird JK, Surjadjaja C. Consideration of ethics in primaquine therapy against malaria transmission. Trends Parasitol. 2011 Jan;27(1):11-6. Epub 2010 Sep 16.

Dern RJ, Beutler E, Alving AS (1954) The hemolytic effect of primaquine. II. The natural course of the hemolytic anemia and the mechanism of its self-limited character. J Lab Clin Med 44: 171-176.

Eziefula AC, Gosling R, Hwang J, Hsiang MS, Bousema T, von Seidlein L, Drakeley C. Rationale for Short Course Primaquine in Africa to Interrupt Malaria Transmission: Meeting Report 2012 (under review).

Graves PM, Gelband H, Garner P. Primaquine for reducing Plasmodium falciparum transmission. Cochrane Database of Systematic Reviews 2009, Issue 4 . Art. No.: CD008152. DOI: 10.1002/14651858.CD008152 (manuscript in preparation)

Howes RE, Piel FP, Patil AP, Nyangiri ON, Gething PW, Dewi M, Hogg MM, Battle KE, Padilla CD, Baird JK, Hay SI. A map of G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries, 2012. (manuscript in preparation)

Kondrashin AV, Baranova AM, Sergiev VM. Large scale use of primaquine and G6PD deficiency (unpublished report)

Luzzatto L, Poggi V. Glucose-6-Phosphate Dehydrogenase Deficiency. Chapter 17 in *Haematology of Infancy and Childhood.* Edited by Orkin *et al.,*7th Edn, Saunders 2009

Pamba A, Richardson ND, Carter N, Duparc S, Premji Z, Tiono AB, Luzzatto L. Clinical spectrum and severity of hemolytic anaemia in G6PD deficient children receiving dapsone**.** Blood; 2012 (in press)

Myint HY, Berman J, Magill A, Ohrt C. Primaquine/8-aminoquinoline-induced hemolysis: a review (manuscript in preparation)

Recht J, Ashley EA, White NJ. 8-aminoquinolines Safety Review for WHO Primaquine ERG, August 2012 (unpublished). *This review of 8-aminoquinoline safety was commissioned by the WHO MPAC and reviews the history of the 8-aminoquinolones and their use for transmission blocking as well as published and unpublished literature on the safety of plasmoquine and primaquine.*

White NJ. The role of primaquine in blocking the transmission of falciparum malaria. Lancet Infect Dis, in press.

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WHO SECRETARIAT

Dr Andrea BOSMAN
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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

ERG MEMBERS (*indicates MPAC members)

Dr Elizabeth ASHLEY (Co-Rapporteur)
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OBSERVERS

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WHO SECRETARIAT

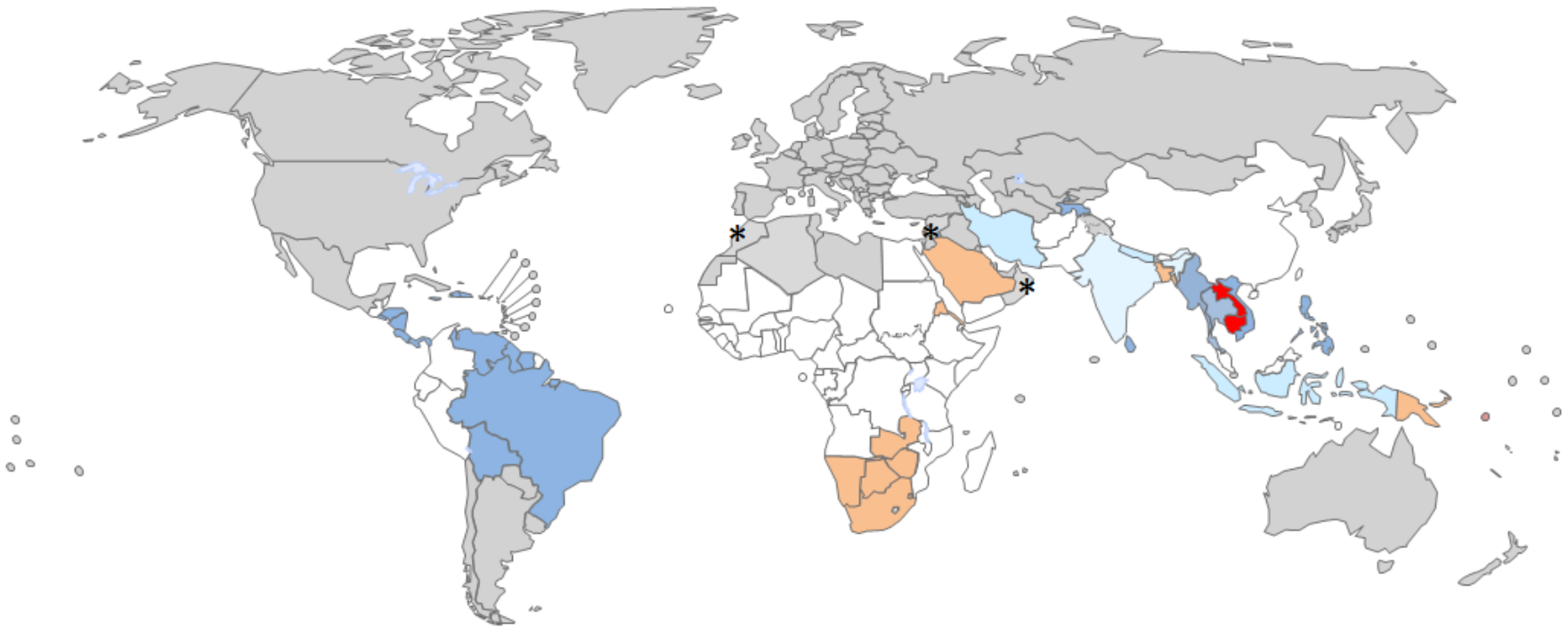
Dr Andrea BOSMAN

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

Cochrane Review

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

	Transmission intensity	Infectiousness Day 8	Potential infectiousness	
			% with gametocytes day 8	(log10 AUC)
ART partner	NA	NA	RR 0.15 (0.09 to 0.24) 4 studies N=1006 Moderate quality evidence	26-88% reduction (excluding one trial) 2 studies N=907 Moderate quality evidence
Non-ART partner	NA	RR 0.05 (0.0 to 0.8) 1 study N=184 low quality evidence	RR 0.62 (0.51 to 0.76) 4 studies, N=446 moderate quality evidence	24-27% reduction 1 study N=219 moderate quality evidence

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?

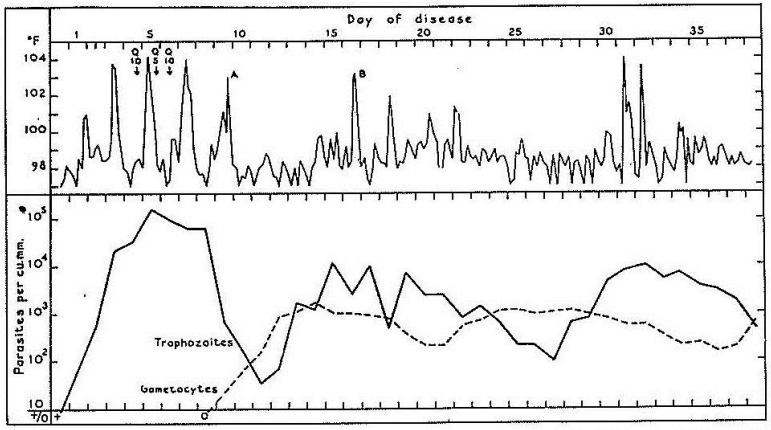
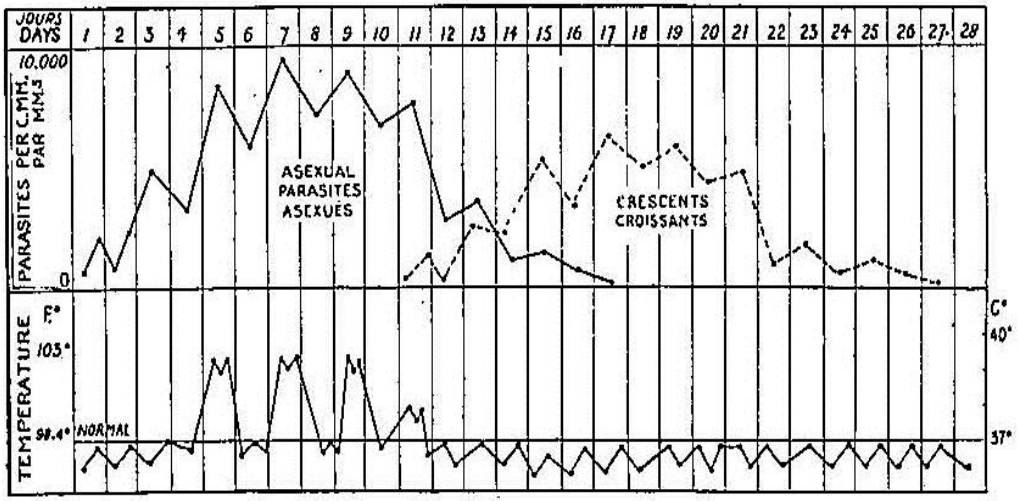
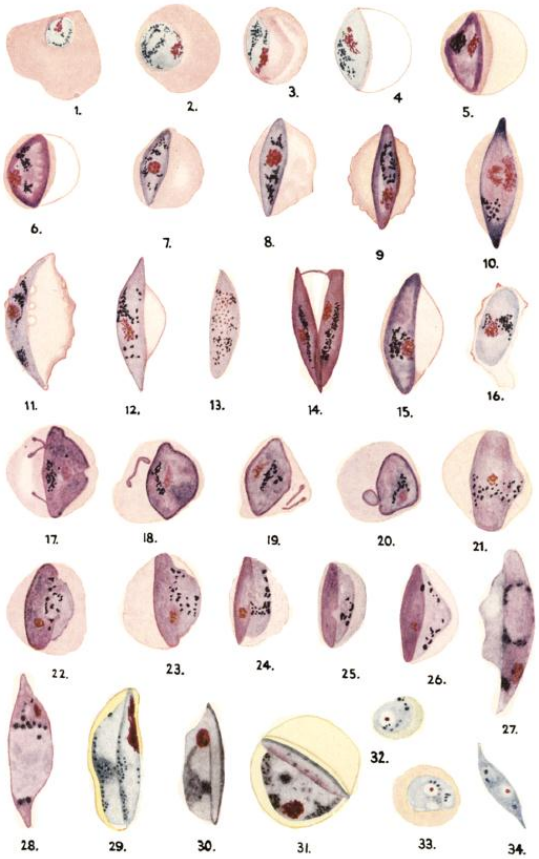
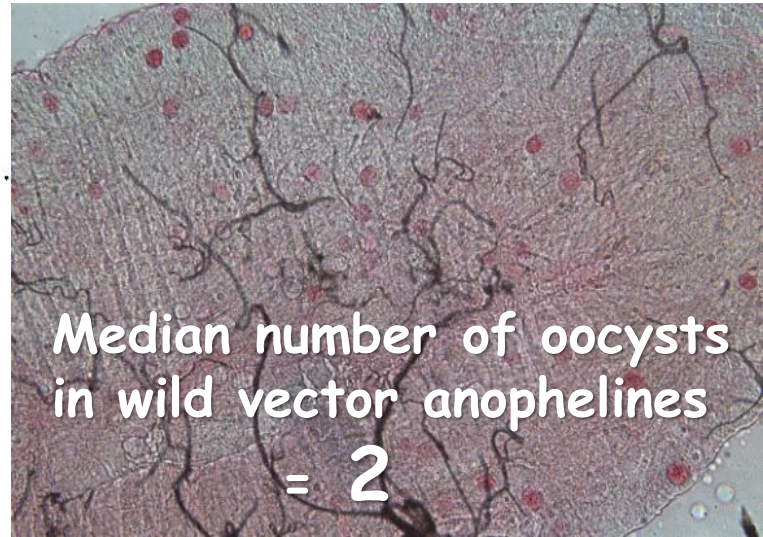


Fig. 10. TROPHOZOITE AND GAMETOCYTE WAVES IN A PRIMARY FALCIPARUM INFECTION WITH PROLONGED INITIAL ACTIVITY (after Kitchen, 1949).

The gametocyte "wave"

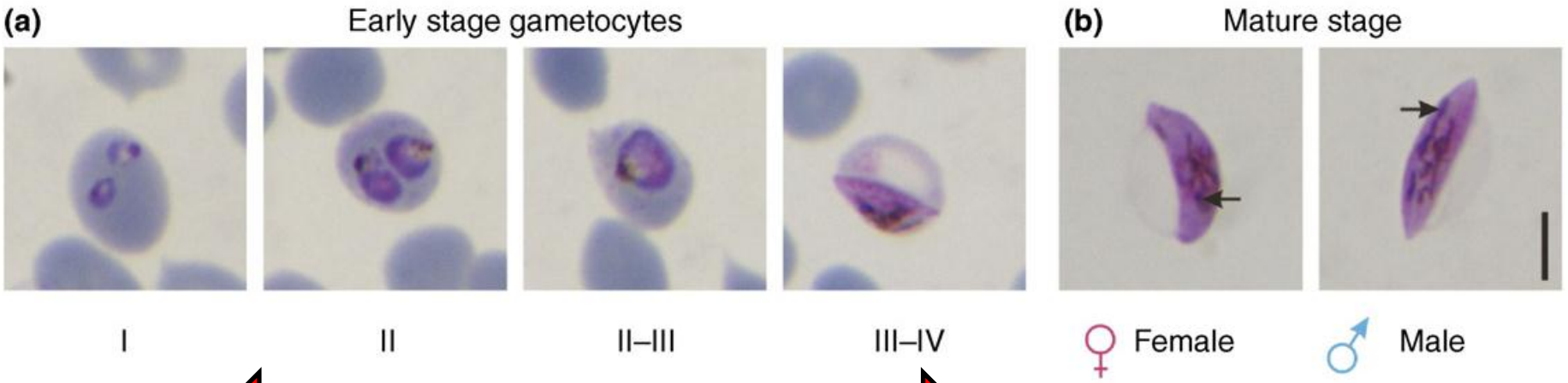






Median number of oocysts in wild vector anophelines = 2

Plasmodium falciparum gametocytes



Sequestered

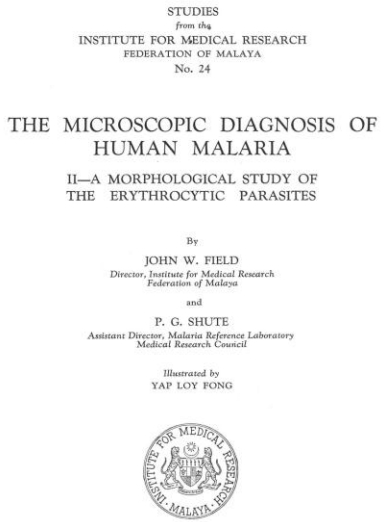
Sequestration time: 7.8 (7.5-8.2) days
Mean circulation time: 6.4 (5.2 – 10.6) days
Half-life: 4.4 (3.8 – 7.3) days
Asexual: sexual conversion rate: 1: 156 (7.4 to 3700)

Smalley ME, Sinden RE. Parasitology 1977;74:1–8
Diebner HH, et al. J Theor Biol. 2000 ;202: 113-27.
Eichner M, et al.Trans R Soc Trop Med Hyg. 2001; 95: 497-501.
Bousema et al. Malar J. 2010; 9: e136.

Who transmits?

TABLE 1. HIGHEST GAMETOCYTE COUNT RECORDED DURING ONE WEEK'S SCHIZONTOCIDAL TREATMENT IN 3,431 ACUTE FALCIPARUM INFECTIONS OBSERVED IN MALAYA.

	Highest gametocyte count per c.mm. peripheral blood				
	None	< 100	100-1000	1000-5000	> 5000*
Infections	1218	560	1180	390	83
Percentage	35	16	34	11	2


STUDIES
from the
INSTITUTE FOR MEDICAL RESEARCH
FEDERATION OF MALAYA
No. 24

THE MICROSCOPIC DIAGNOSIS OF HUMAN MALARIA

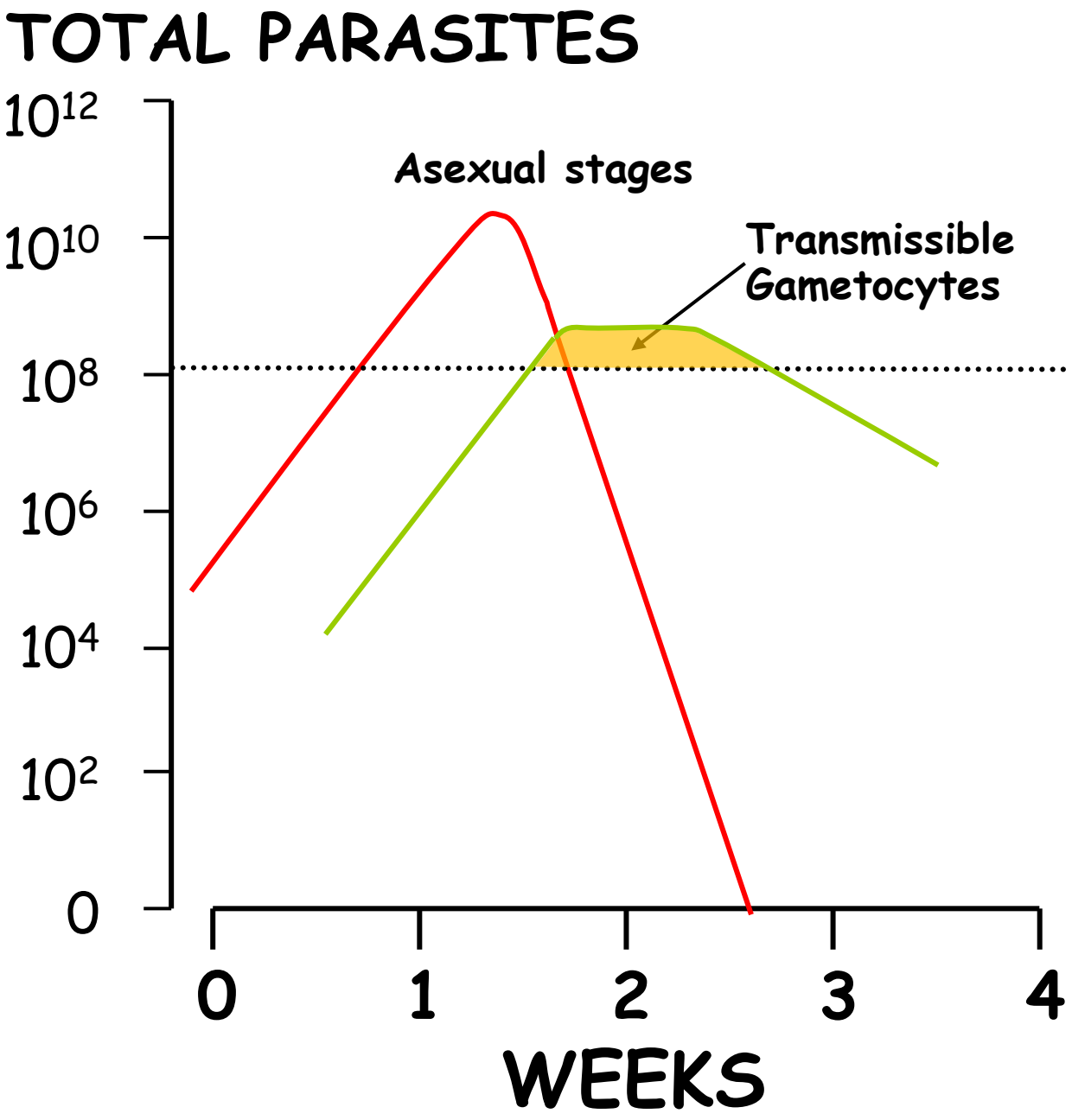
II—A MORPHOLOGICAL STUDY OF THE ERYTHROCYTIC PARASITES

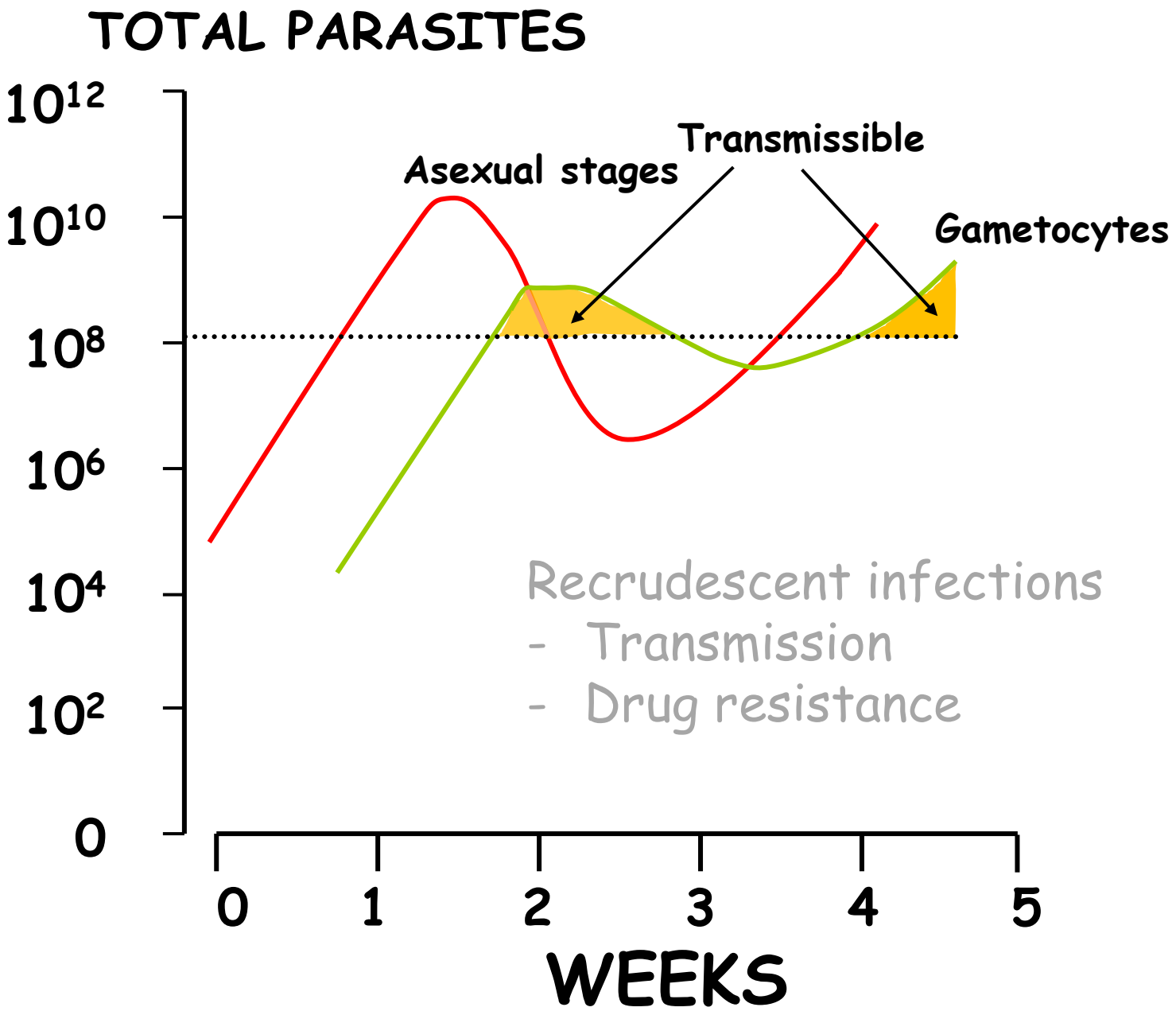
By
JOHN W. FIELD
Director, Institute for Medical Research
Federation of Malaya
and
P. G. SHUTE
Assistant Director, Malaria Reference Laboratory
Medical Research Council

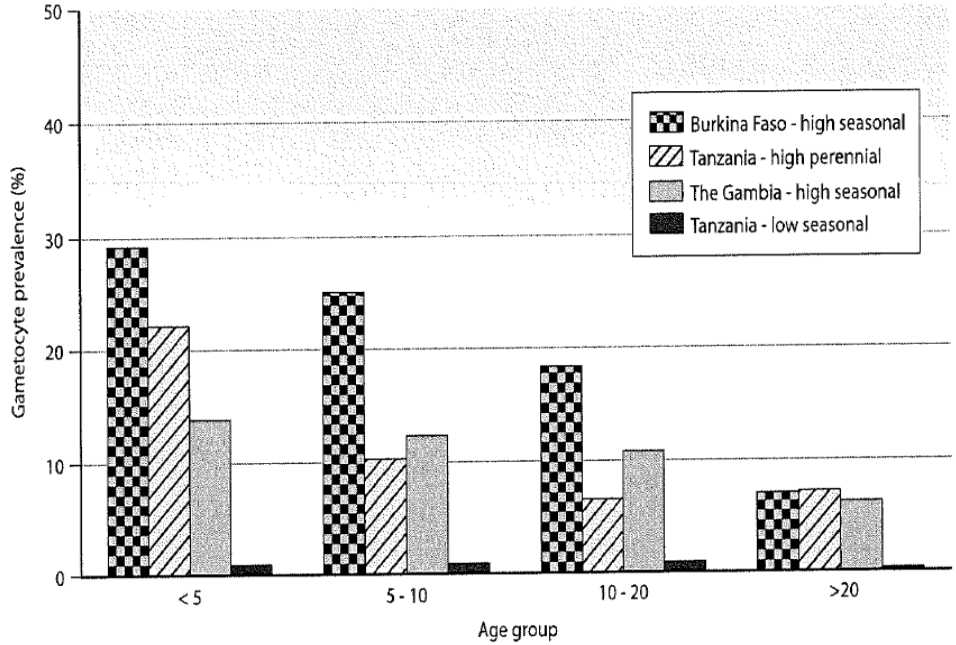
Illustrated by
YAP LOY FONG

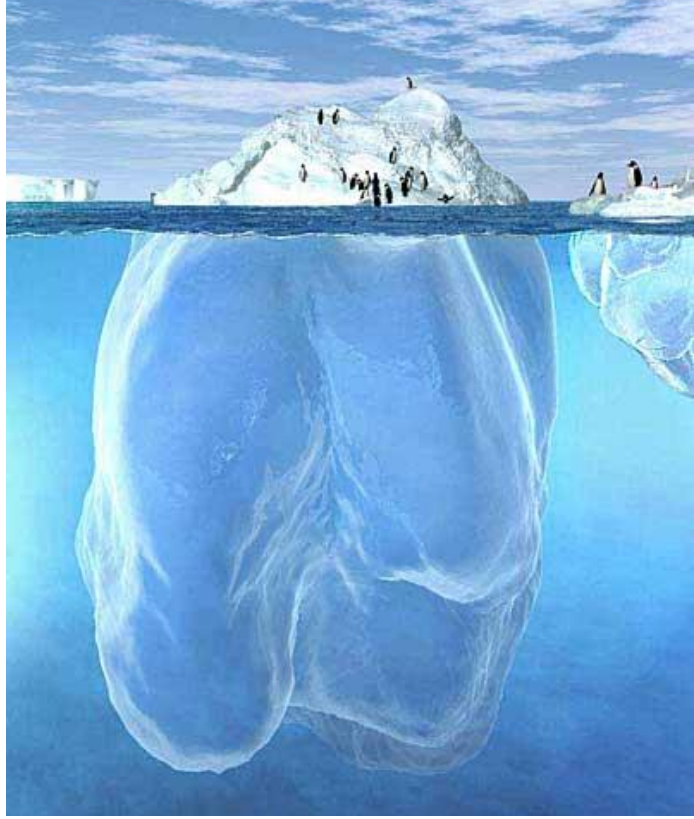
P.falciparum gametocyte prevalence and density *highly* dependent on

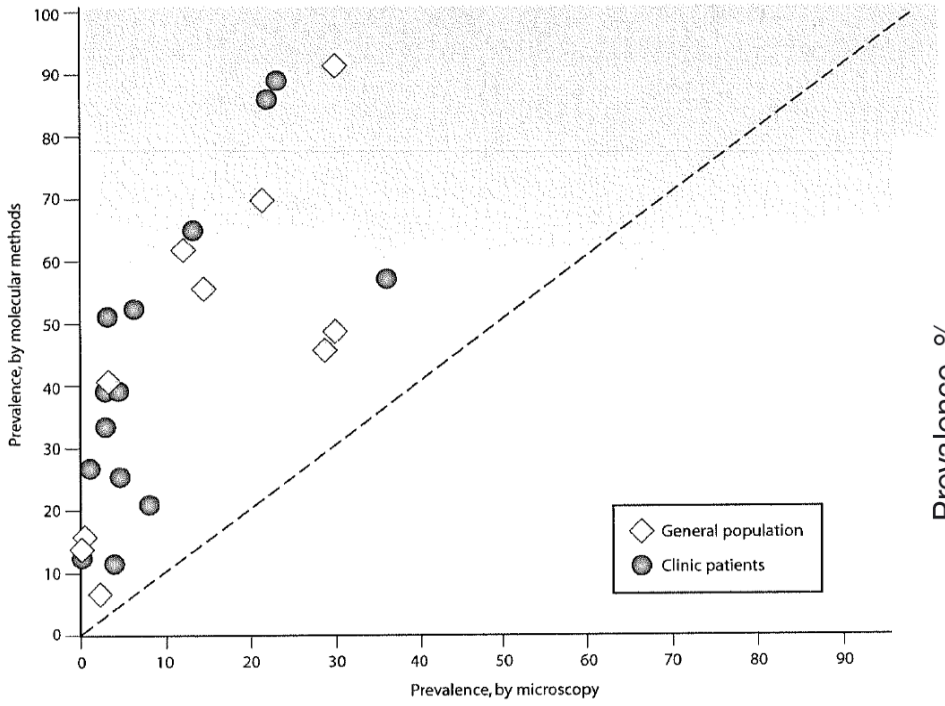
1. Transmission intensity – immunity
2. Treatment seeking and availability

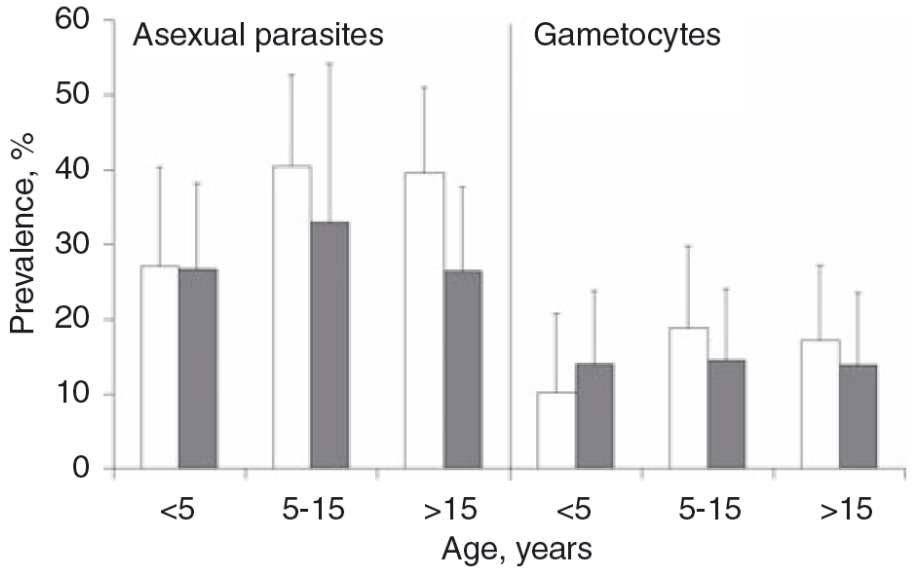

TOTAL PARASITES
10^{12}
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
0
Asexual stages
Transmissible
Gametocytes
0
1
2
3
4
WEEKS

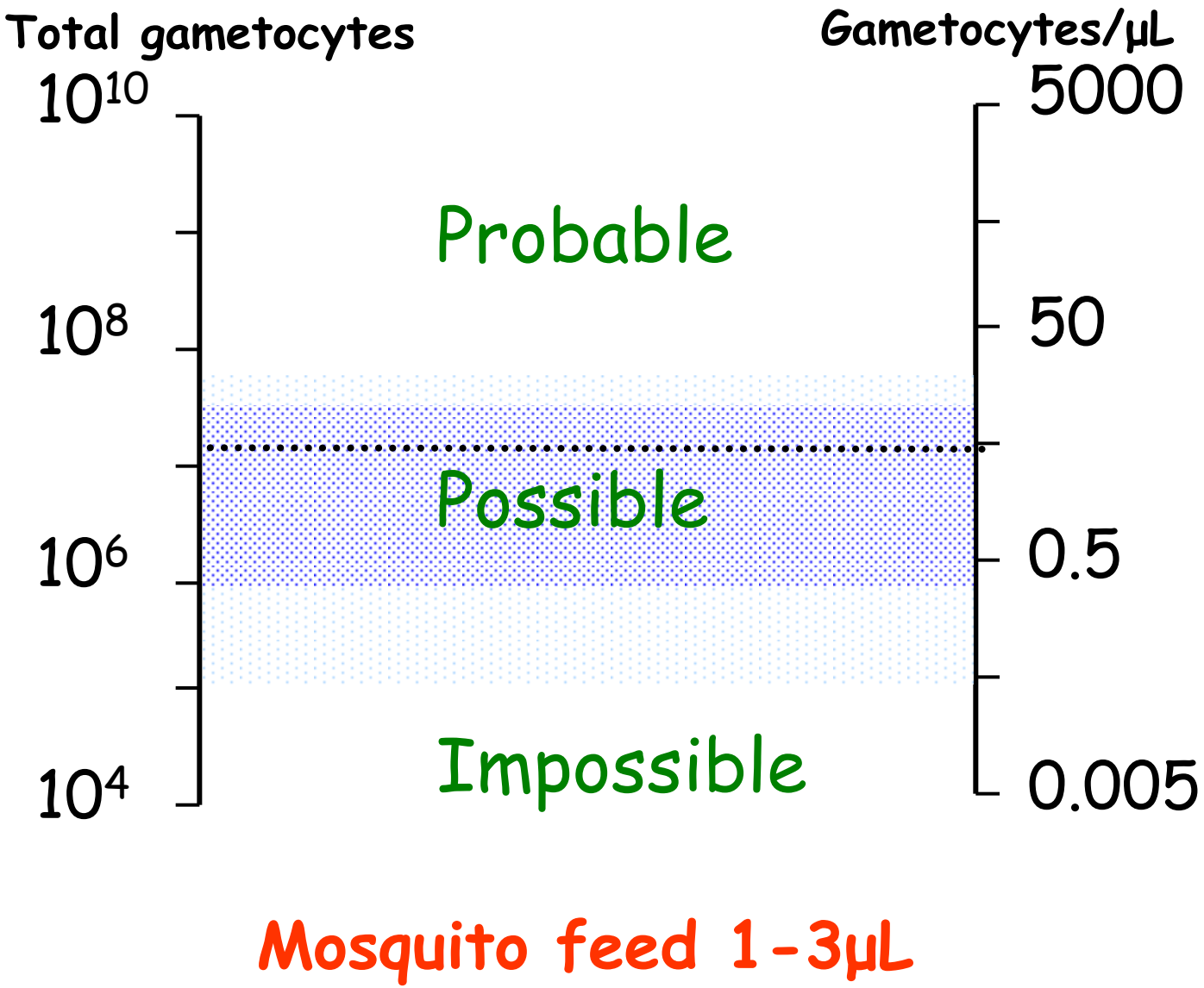

TOTAL PARASITES
10^{12}
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
0
Asexual stages
Transmissible
Gametocytes
Recrudescent infections
- Transmission
- Drug resistance
0
1
2
3
4
5
WEEKS

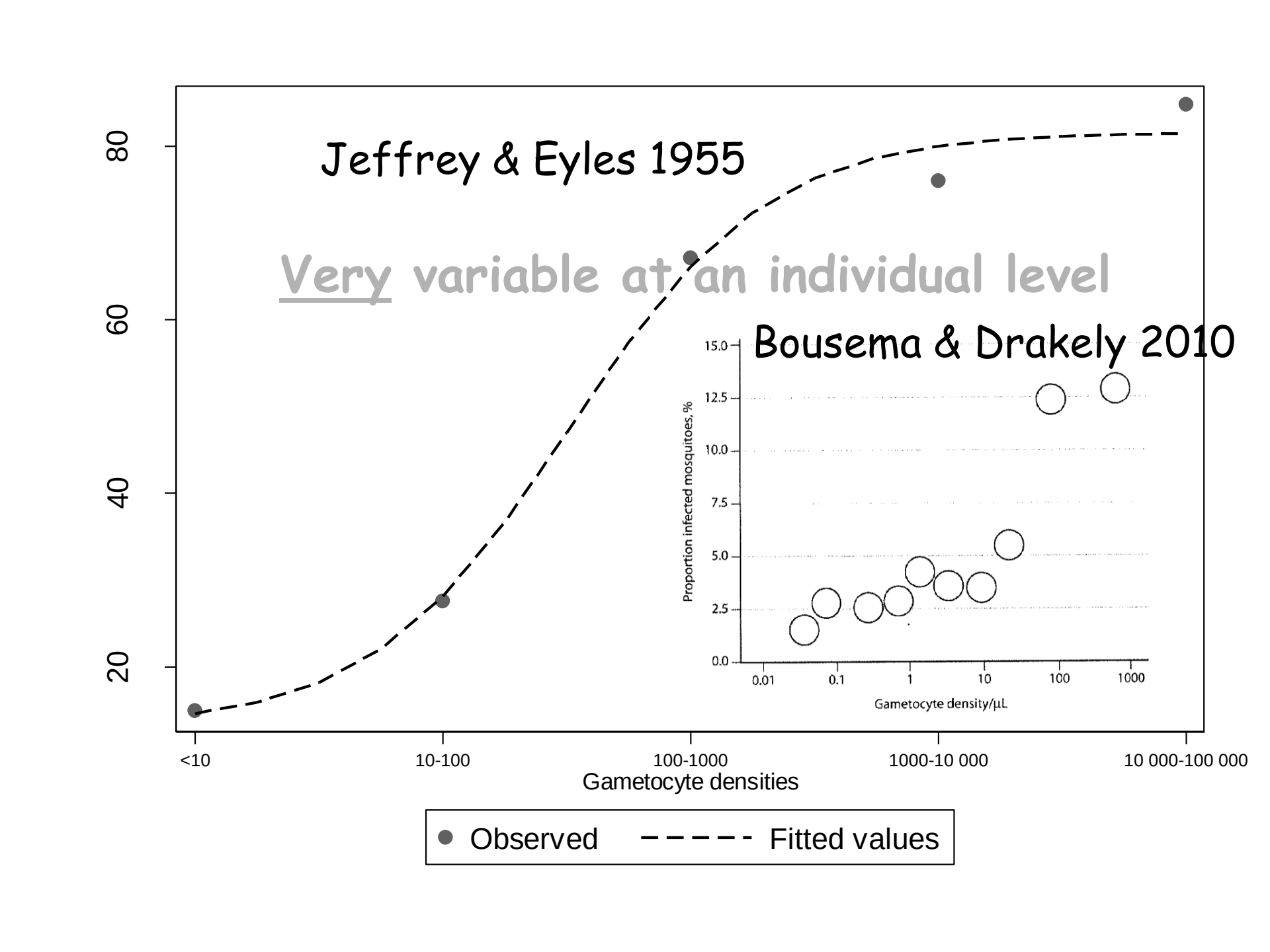

Gametocyte prevalence (%)
50
40
30
20
10
0
Burkina Faso - high seasonal
Tanzania - high perennial
The Gambia - high seasonal
Tanzania - low seasonal
< 5
5 - 10
10 - 20
>20
Age group



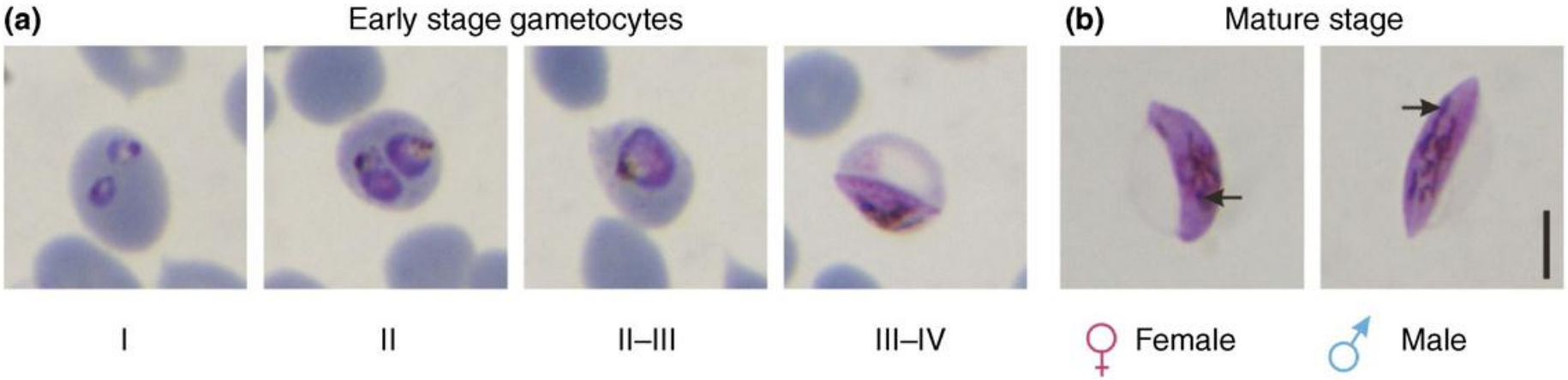

Prevalence, by molecular methods
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
Prevalence, by microscopy
General population
Clinic patients


Asexual parasites
Gametocytes
Prevalence, %
60
50
40
30
20
10
0
<5
5-15
>15
<5
5-15
>15
Age, years


Total gametocytes
Gametocytes/µL
10^10
10^8
10^6
10^4
5000
50
0.5
0.005
Probable
Possible
Impossible
Mosquito feed 1-3µL


Jeffrey & Eyles 1955
Very variable at an individual level
Bousema & Drakely 2010
Proportion infected mosquitoes, %
15.0
12.5
10.0
7.5
5.0
2.5
0.0
0.01
0.1
1
10
100
1000
Gametocyte density/µL
20
40
60
80
<10
10-100
100-1000
1000-10 000
10 000-100 000
Gametocyte densities
Observed
Fitted values

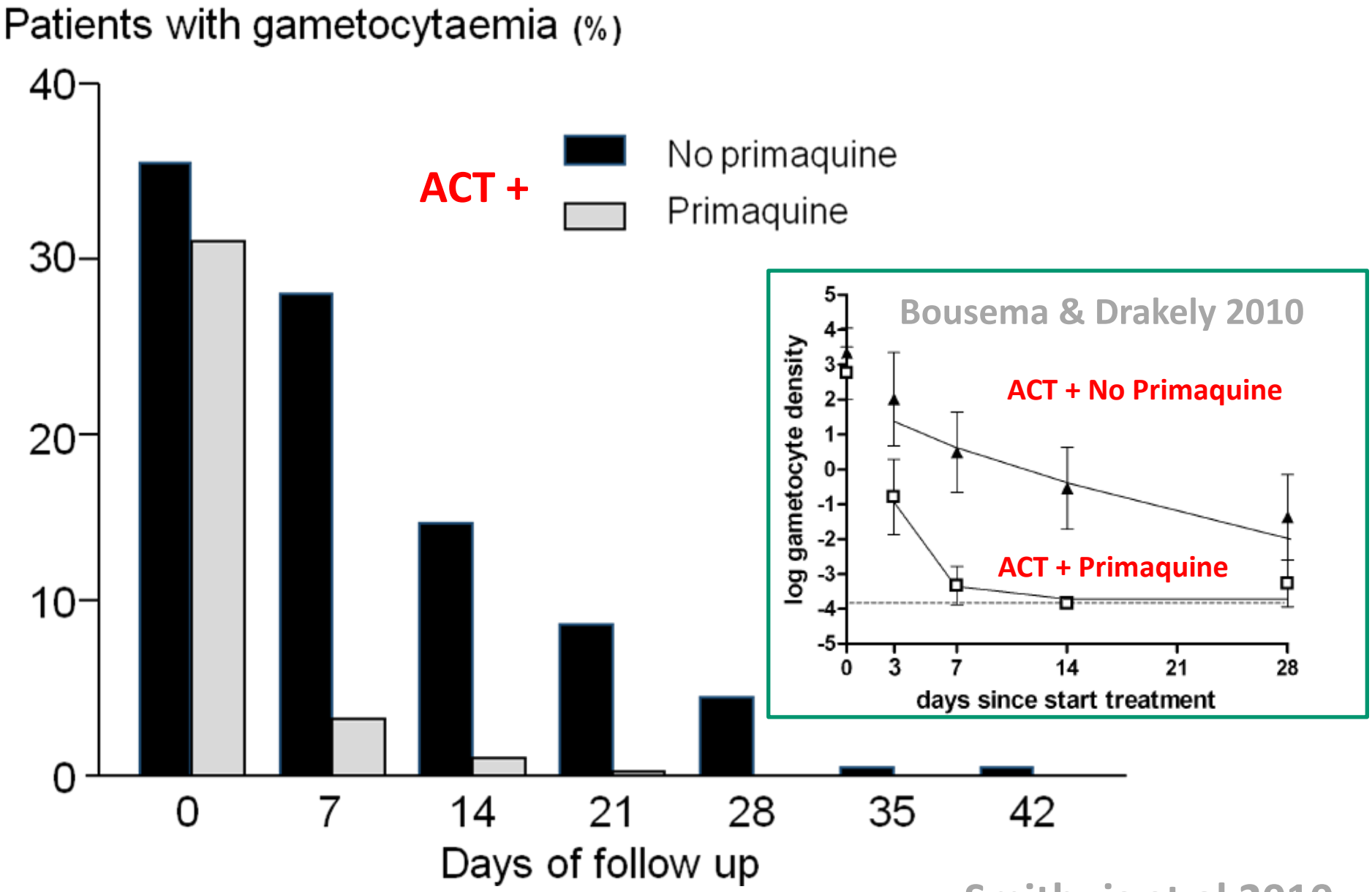
Plasmodium falciparum gametocytes



All effective drugs

Artemisinins

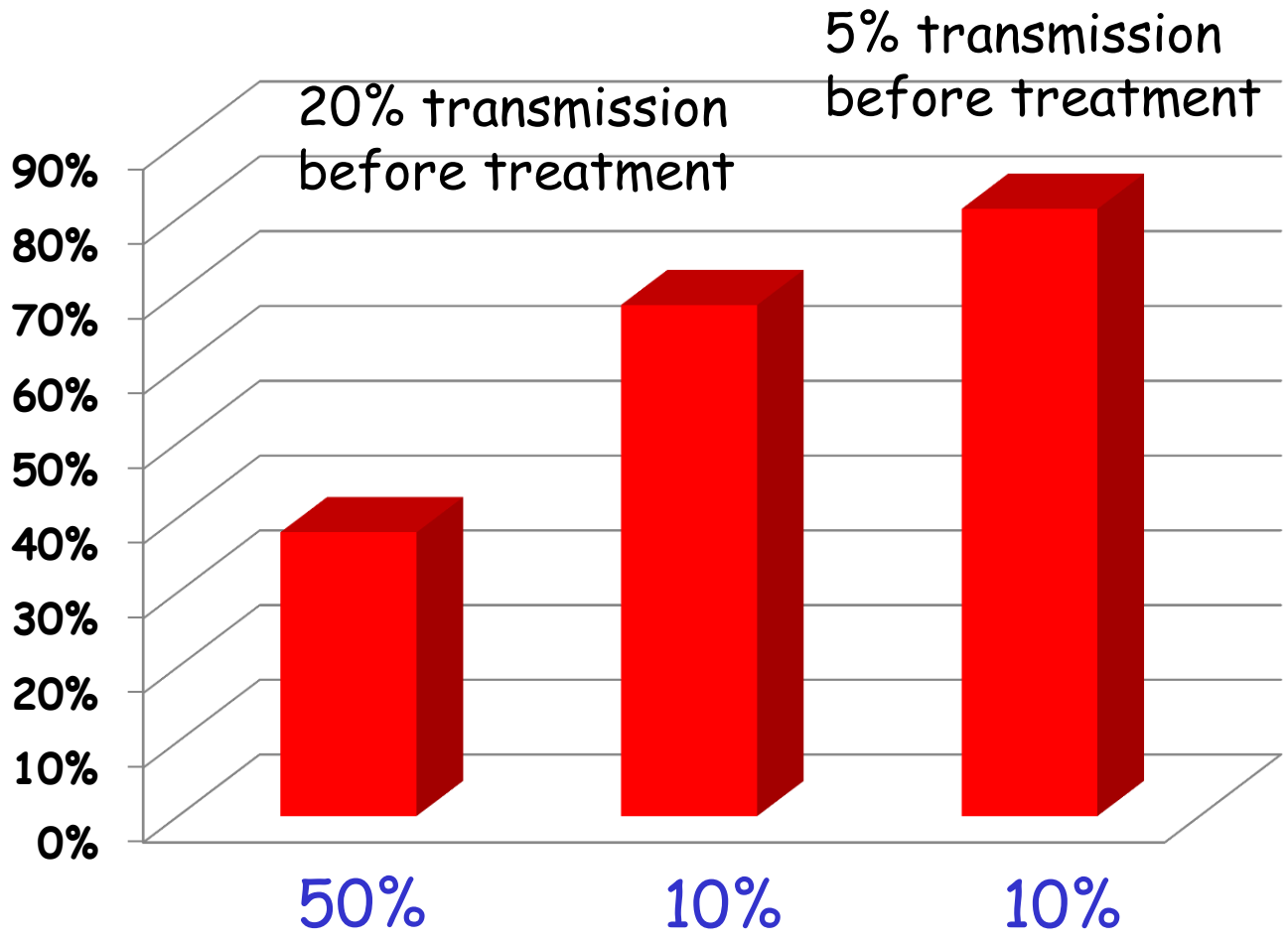
Primaquine



Smithuis et al 2010

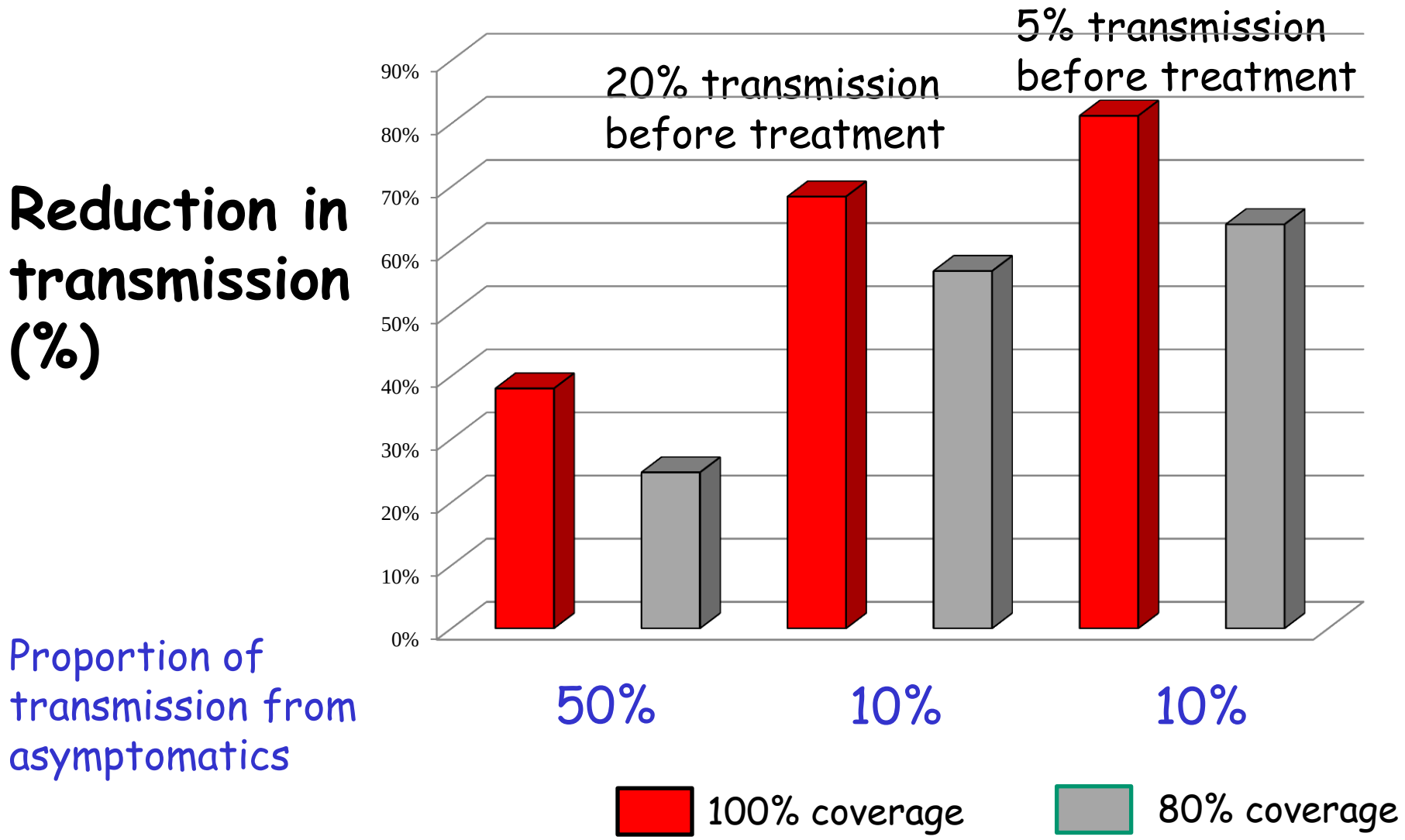
The effects of a gametocytocide on transmission depend on what proportion of all transmission occurs after its administration.

For example if primaquine reduces tranmissibility 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 (%)
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
20% transmission before treatment
5% transmission before treatment
Proportion of transmission from asymptomatics
50%
10%
10%
100% coverage
80% coverage

Schuleman et al 1926

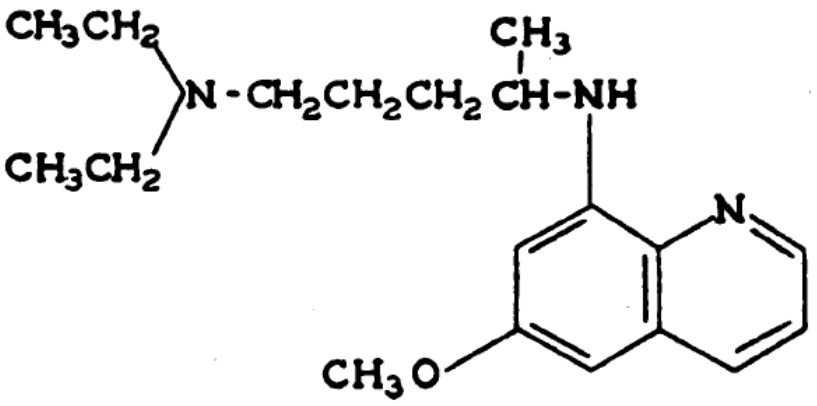
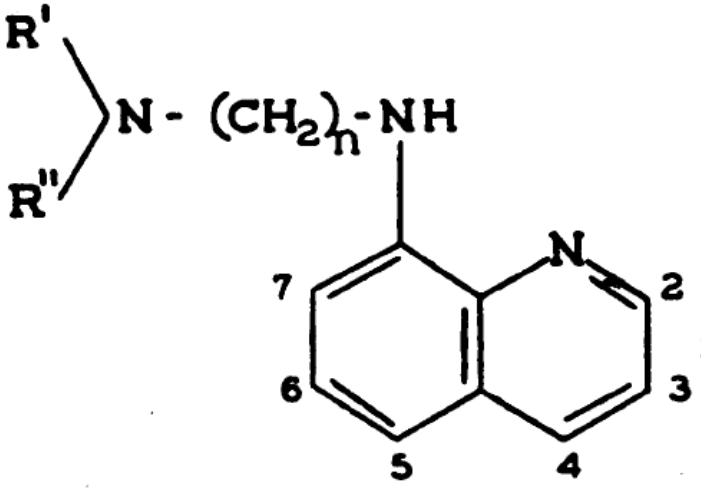


FIG. 1. STRUCTURAL FORMULA OF PAMAQUIN (PLASMOCHIN)

General formula of 8-(ω-aminoalkylamino) quinolines



Alving et al J Clin Invest 1948

PUBLIC HEALTH REPORTS

VOL. 44 JUNE 14, 1929 NO. 24

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: Malaquias 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.).

Date (1929)	Day	Treatment			Hour mosquitoes fed	Crescents per 1,000 leucocytes	Results of mosquito dissections			
		Plasmochin	Quinine sulphate	When given			Number dissected	Number positive	Per cent of mosquitoes infected	Average number of oöcysts per positive gut
Jan. 3	First	None	10 grains (65 cg.)							
Jan. 4	Second	None	30 grains (195 cg.)							
Jan. 5	Third	2 cg.	13¼ grains (86 cg.)	8.30 a. m.	10 a. m.	97	5	5	100.0	16
		2 cg.	8¼ grains (56 cg.)	5 p. m.						
Jan. 6	Fourth	None	10 grains (65 cg.)	8.30 a. m.	10.30 a. m.	100	17	0	0.0	0
			10 grains (65 cg.)	12 m.						
			10 grains (65 cg.)	5 p. m.						
Jan. 7	Fifth	None	10 grains (65 cg.)	8.30 a. m.	9 a. m.	51	16	0	0.0	0
			10 grains (65 cg.)	12 m.						
			10 grains (65 cg.)	5 p. m.						
Jan. 8	Sixth	None	10 grains (65 cg.)	8.30 a. m.	8.30 a. m.	11	13	0	0.0	0

NOTE 1.—The total amount of plasmochin, 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 plasmochin compound, No. II, b. i. d. for 12 days, a total of 48 cg. plasmochin 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 MISSIROLI (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).

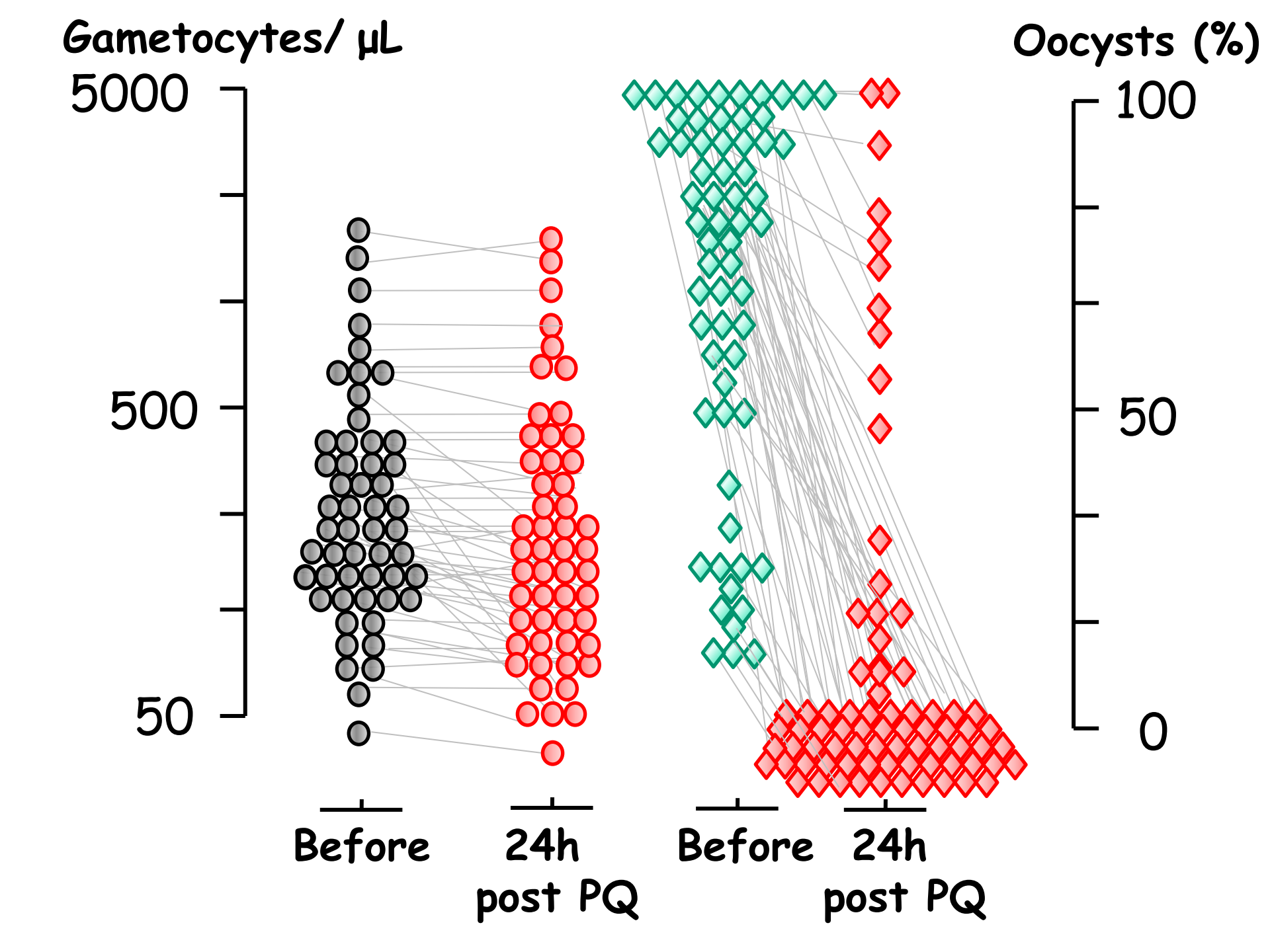
20mg

Health Organisation of the League of Nations; 1933

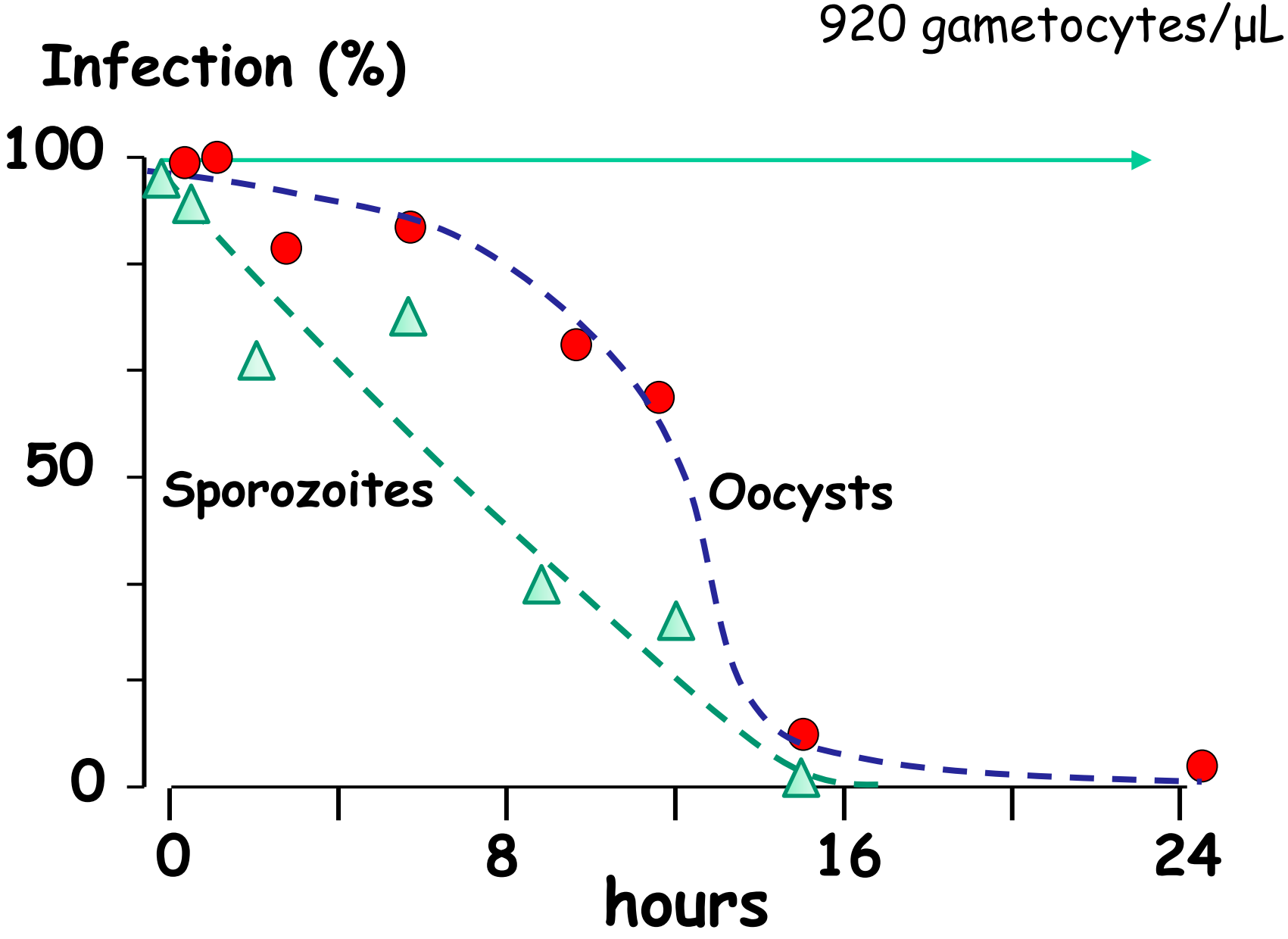
8-aminoquinolines

Transmission blocking in *P. falciparum* malaria

Reference	No subjects	Drug	Location	Patients	Malaria	mg base/kg	mosquitoes	oocysts	sporozoites	Infectivity †
Barber et al 1929[21]	4	Plmq	Panama	Natural	wild	0.2-1.4	A.albimanus	Y	N	N
Green 1929[23]		Plmq	Malaya	Natural	wild		A.maculatus	Y	Y	
Amies 1930[24]	8	Plmq	Malaya	Natural	wild	0.7-0.10	A.maculatus, A.philippinensis		Y	
Jerace & Giovannola 1933[25]	27	Plmq	Italy	Natural	wild	0.25-0.37	A. maculipennis	Y	N	
Chopra & Basu 1937[26]	2	Plmq	India	Natural	wild	0.3	A.stephensi	Y	Y	N
McErras & Ercole 1949[28]	2	Plmq	Cairns Australia	Military Volunteers	wild	0.15	A.punctalus	Y	Y	N
Jeffrey et al 1956[31]	12*	Prq	S.Carolina	Neurosyphilis	McLendon, SC, Panama	0.25-0.5	A. quadrimaculatus, A.albimanus	Y	Y	N
Young 1959[32]	8	Prq	S.Carolina	Neurosyphilis	Panama strain	0.05	A. quadrimaculatus, A.freeborni	Y	Y	N
Burgess & Bray 1961[33]	12	Prq	Liberia	Natural	wild	0.5	A.gambiae	Y	Y	N
Gunders 1961[34]	10	Prq	Liberia	Natural	wild	0.5-1.0	A.gambiae	Y	Y	N
Jeffrey et al 1963[35]	2	Prq	Thailand/USA	Natural	wild	0.5	A. quadrimaculatus, A.freeborni	Y	Y	
Rieckmann et al 1968[29]	2	Prq	Illinois	Prisoners	Camp	0.2-0.6	A.stephensi	Y	Y	Y
Rieckmann et al 1969[30]	16	Prq	Illinois	Prisoners	Camp, Uganda	0.2-0.6	A.stephensi	Y	Y	Y
Clyde et al 1970[36]	1	Prq	Maryland	Prisoners	Malayan	0.5-0.75	A.stephensi,	Y	N	N
Clyde et al 1971[37]	6	Prq	Maryland	Prisoners	Smith, Brai (VN)	0.5-0.75	A.stephensi, A.gambiae	Y	N	N
Chen et al 1994[38]	9	Prq	China, Hainan	patients	wild	0.75	A.dirus		Y	

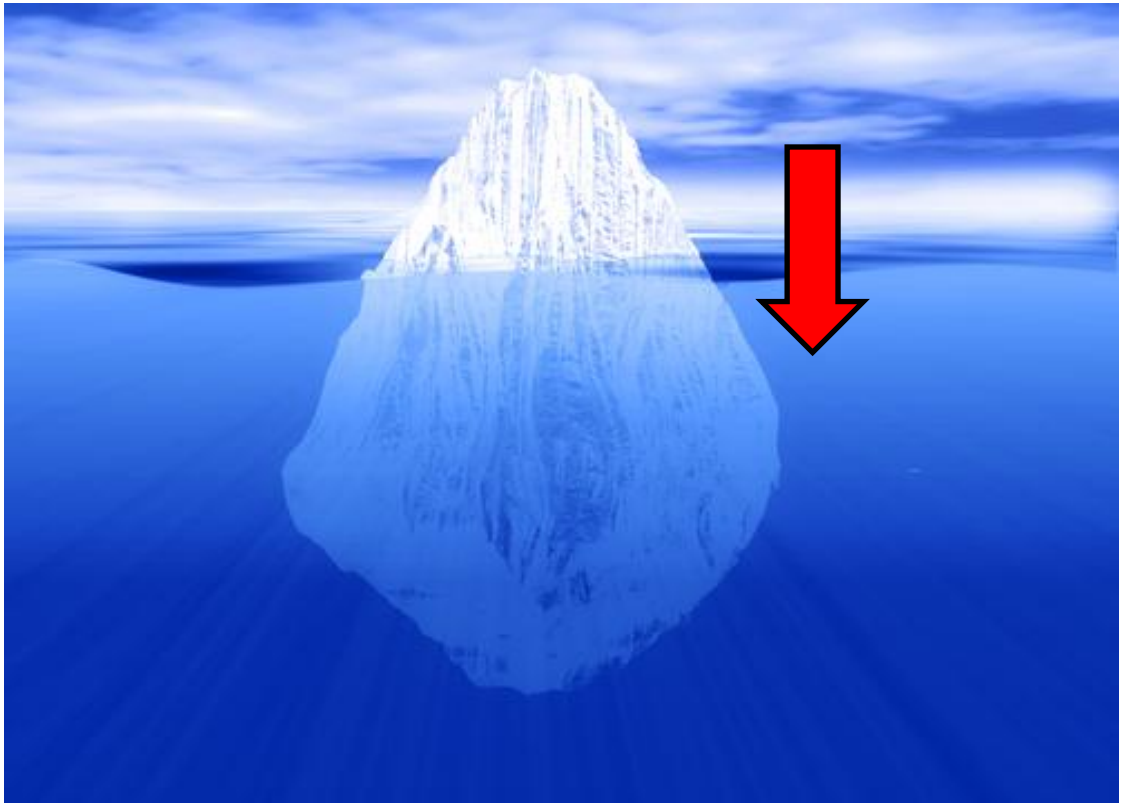

Gametocytes/ µL
5000
500
50
Oocysts (%)
100
50
0
Before
24h post PQ
Before
24h post PQ

Individual transmission blocking effects are **underestimated substantially** from assessments of gametocytaemia only



MacErras & Ercole 1947

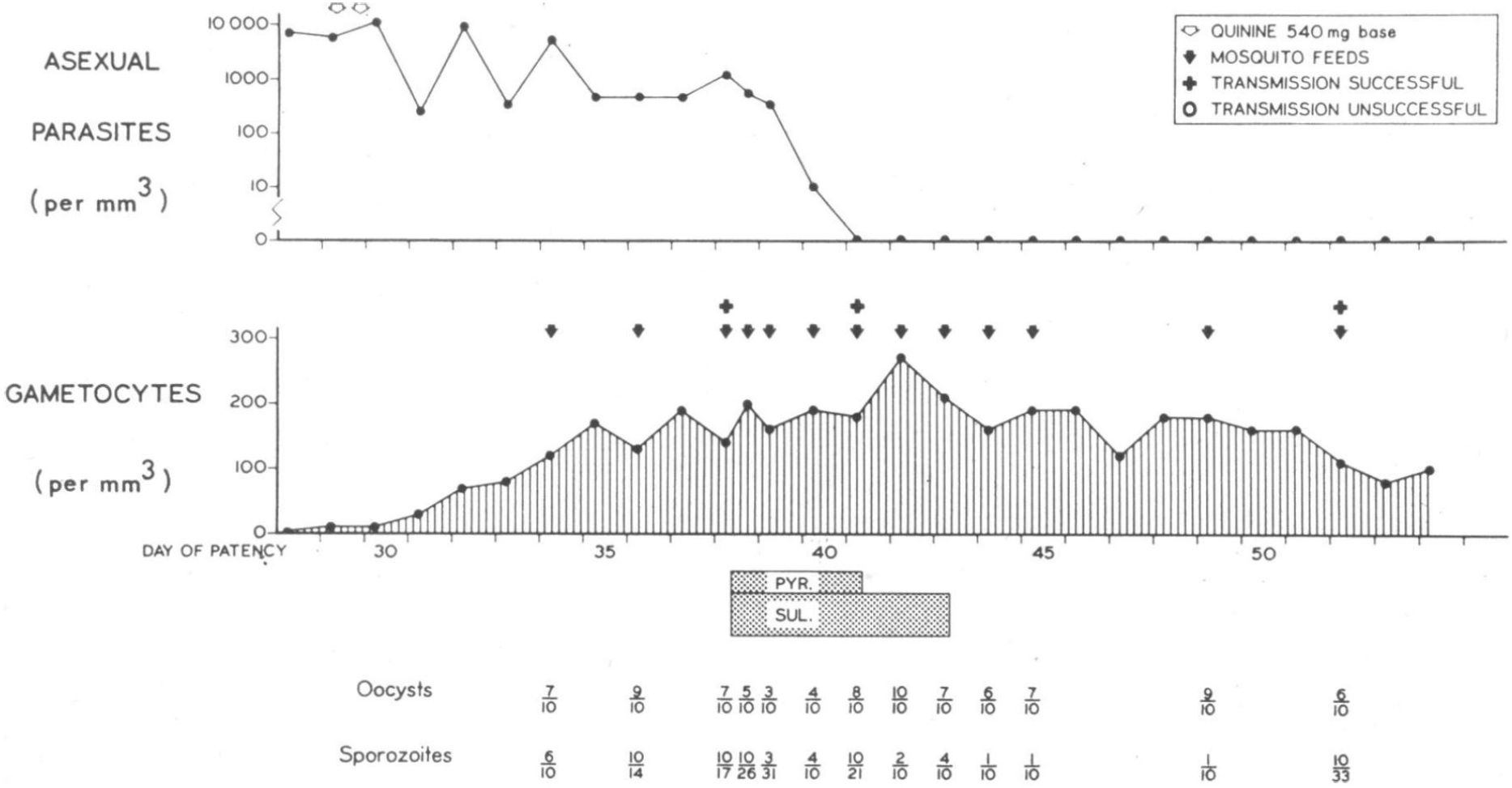
Dose-response



The effects of reducing gametocyte densities and viability on transmission from a population may be underestimated from studies of gametocytaemic individuals.

FIG. 1

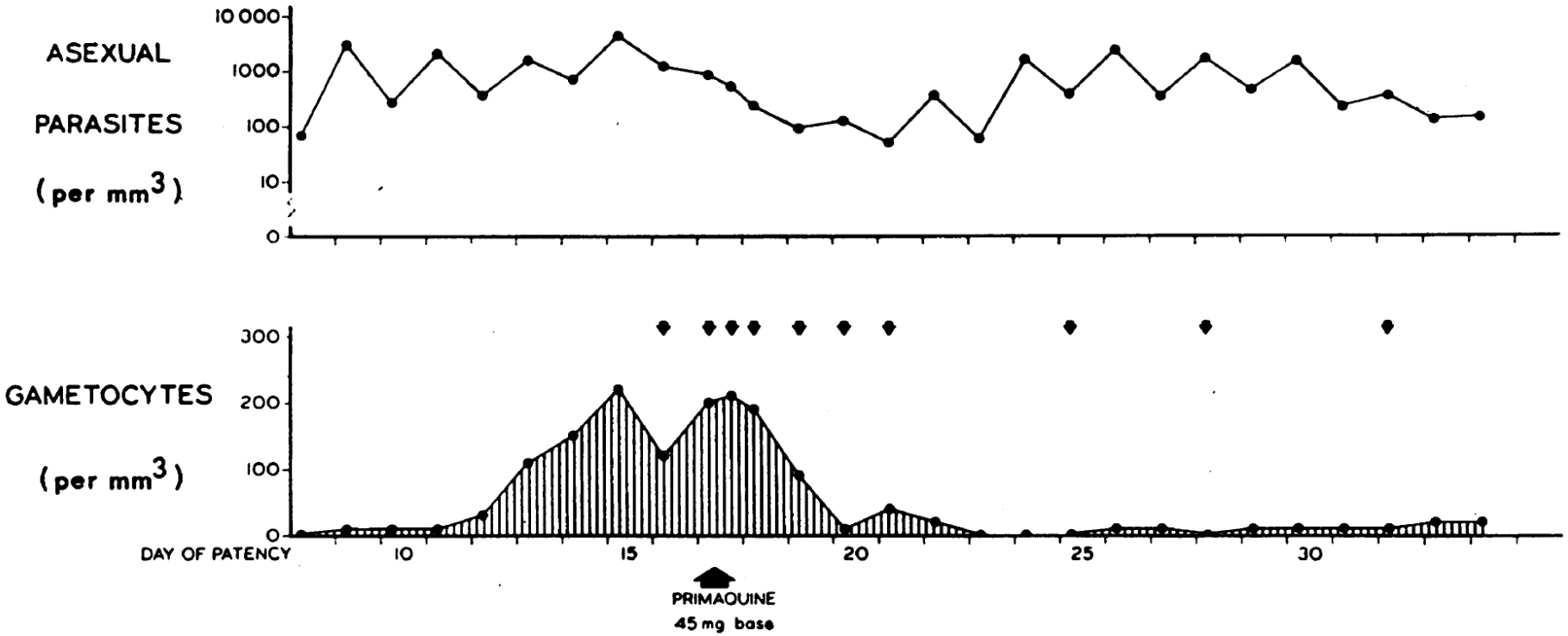
RESULTS OF STUDIES ON VOLUNTEER 1 [a]



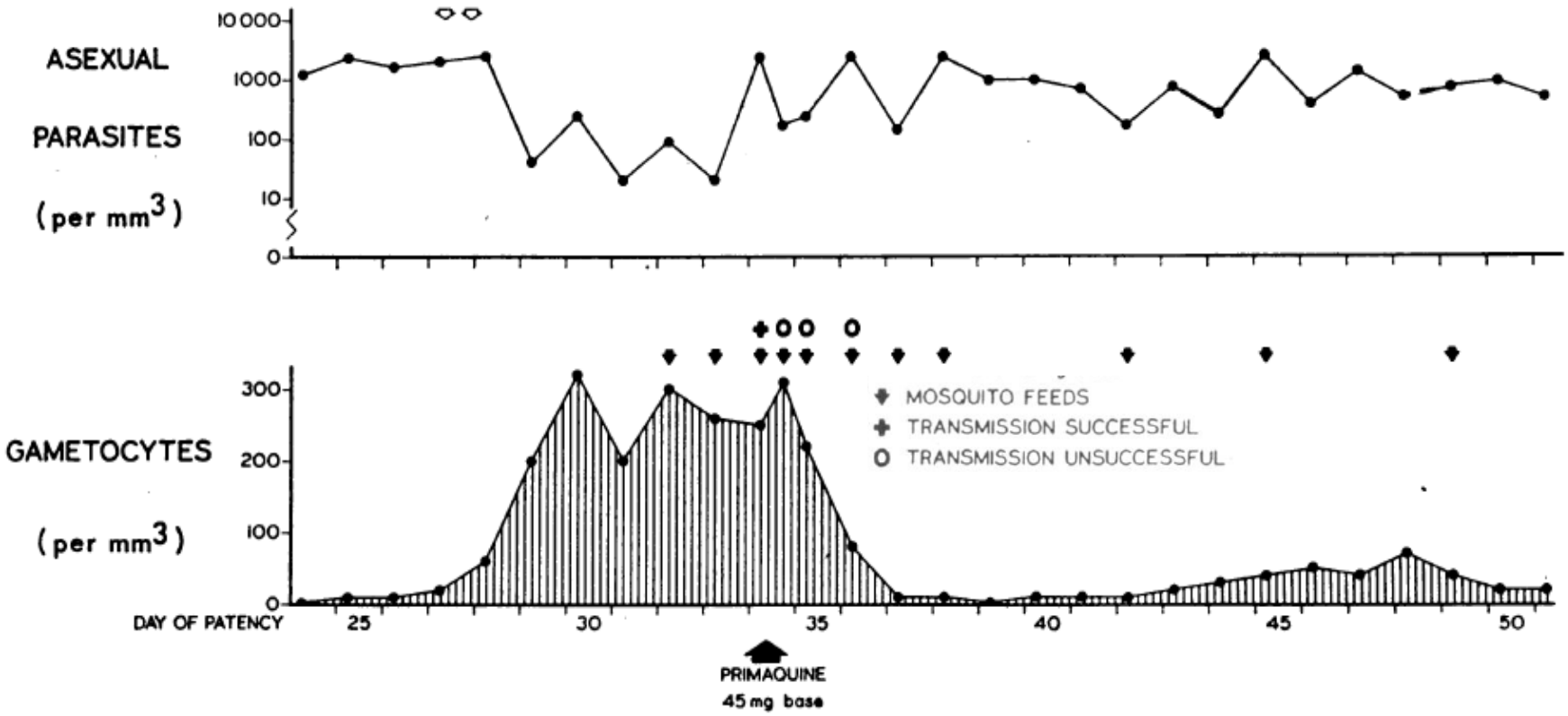
Rieckmann et al. Bull WHO 1968; 38: 625-632.

FIG. 2

RESULTS OF STUDIES ON VOLUNTEER 2[a]

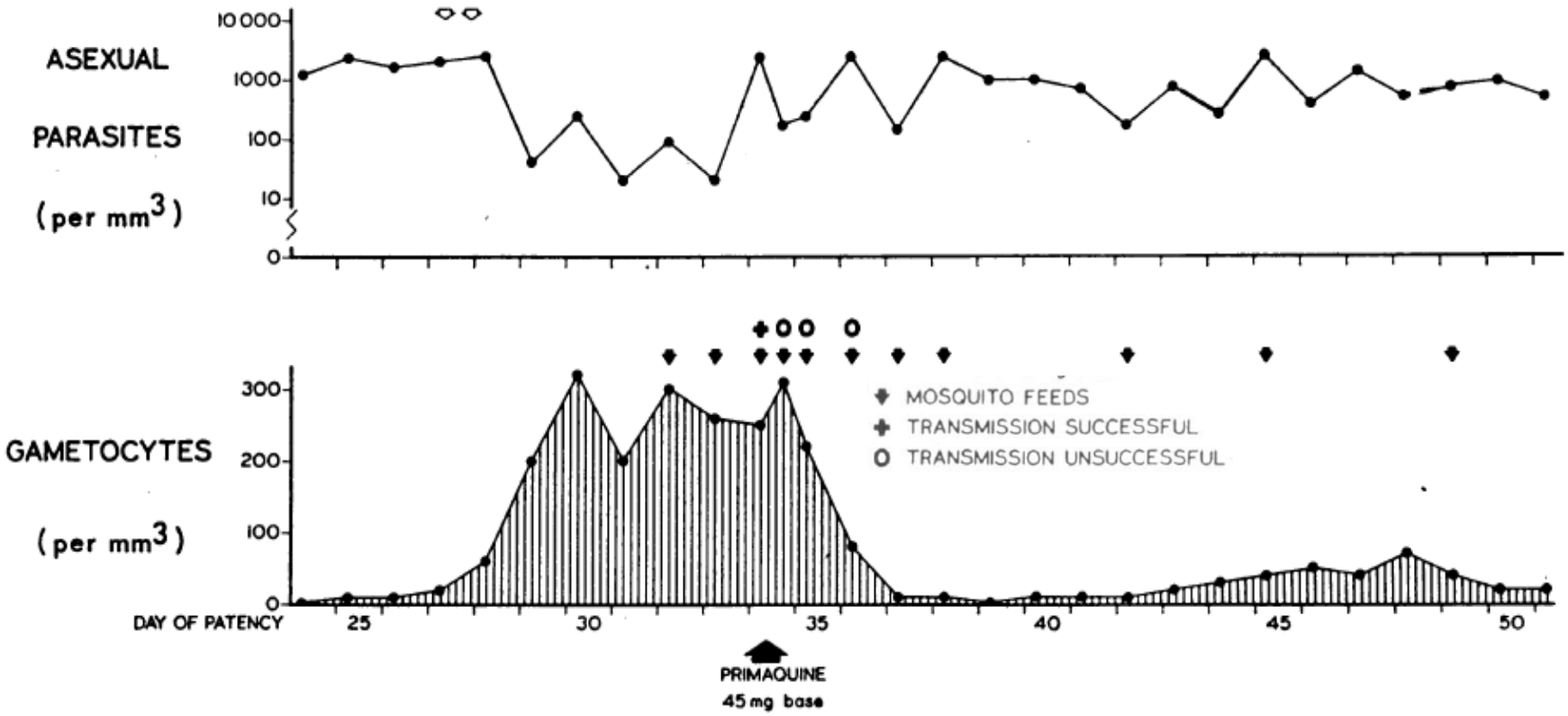


RESULTS OF STUDIES ON VOLUNTEER 3[a]



Oocysts	8/10	6/10	7/10	6/10	0/10	0/10	0/10	0/10		0/10	9/40	11/30
Sporozoites	3/10	2/10	35/85	11/85	9/85	2/85	0/10	0/10		0/60	5/60	15/52

RESULTS OF STUDIES ON VOLUNTEER 3[a]

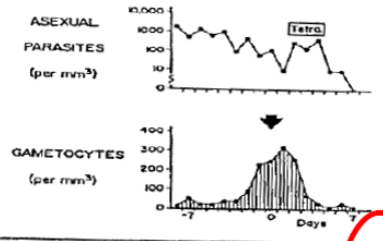


Oocysts	8/10	6/10	7/10	6/10	0/10	0/10	0/10	0/10		0/10	9/40	11/30
Sporozoites	3/10	2/10	35/85	11/85	9/85	2/85	0/10	0/10		0/60	5/60	15/52

PRIMAQUINE
(15 mg)

13.

MALAYAN STRAIN

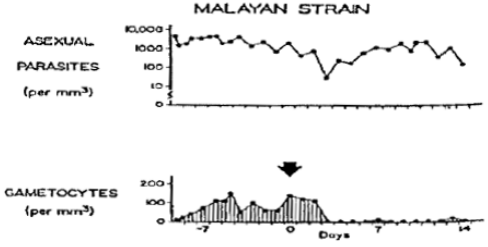


DAY	0		1	2	7
HOUR	0	12			
DRUG ADMINISTRATION	▼				
OOCYSTS					
No. mosq. positive / No. mosq. dissected	15/20	5/20	12/20	1/20	0/20
Total number of oocysts	1218	388	68	1	0
SPOROZOITES					
No. mosq. positive / No. mosq. dissected	17/20	3/22	3/23	1/38	0/25
Total infectivity	62	11	7	1	0

PRIMAQUINE
(15 mg)

14.

MALAYAN STRAIN

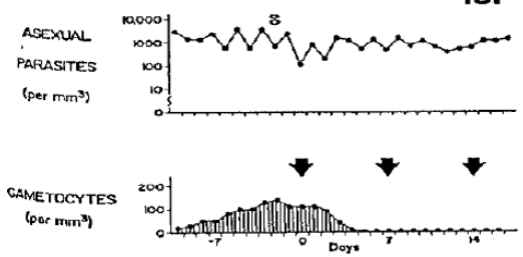


DAY	0		1	7	10	12	14
HOUR	0	12					
DRUG ADMINISTRATION	▼						
OOCYSTS							
No. mosq. positive / No. mosq. dissected	18/20	3/20	0/20	0/20	0/20	0/20	0/20
Total number of oocysts	189	5	0	0	0	0	0
SPOROZOITES							
No. mosq. positive / No. mosq. dissected	23/37	1/26	0/40	0/33	0/17	0/35	0/29
Total infectivity	81	3	0	0	0	0	0
TRANSMISSION	+	+					

PRIMAQUINE
(15 mg)

15.

MALAYAN STRAIN

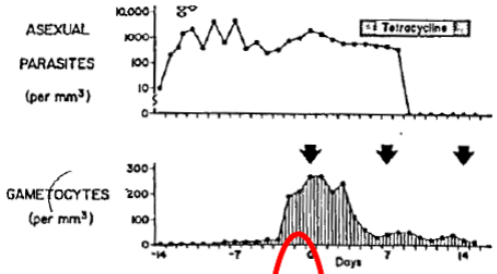


DAY	0	1	2	3	7
DRUG ADMINISTRATION	▼				▼
OOCYSTS					
No. mosq. positive / No. mosq. dissected	6/20	0/20	0/20	0/20	0/20
Total number of oocysts	7	0	0	0	0
SPOROZOITES					
No. mosq. positive / No. mosq. dissected	5/33	0/40	0/46	0/26	0/50
Total infectivity	13	0	0	0	0

PRIMAQUINE
(15 mg)

16.

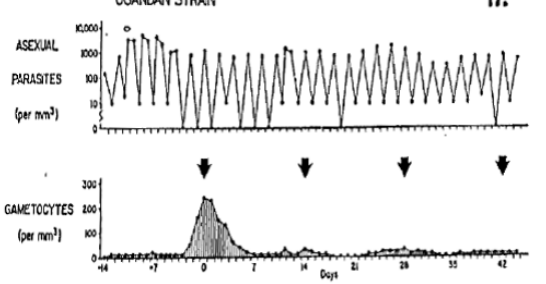
MALAYAN STRAIN



DAY	0	1	2	7	8	14	15
DRUG ADMINISTRATION	▼			▼		▼	
OOCYSTS							
No. mosq. positive / No. mosq. dissected	15/20	11/20	16/20	0/20	1/20	1/20	0/20
Total number of oocysts	564	161	406	0	1	1	0

17.

UGANDAN STRAIN

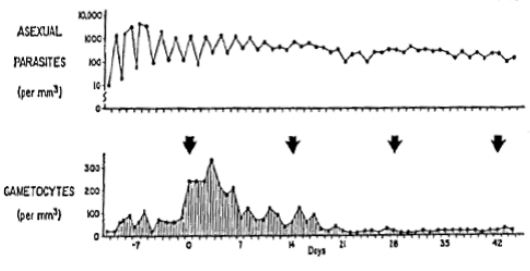


DAY	0	1	2	7	10	14	15	16	21	24	28	35	38	42	52
DRUG ADMINISTRATION	▼					▼					▼			▼	
OOCYSTS															
No. mosq. positive / No. mosq. dissected	13/20	9/20	0/20	0/20	0/20	0/20	0/20	0/20	0/20	2/20	5/20	0/20	0/20	0/20	0/20
Total number of oocysts	736	44	0	0	0	0	0	0	0	10	25	0	0	0	0

Fig. 13. Results of studies with Volunteer 17.

18.

UGANDAN STRAIN

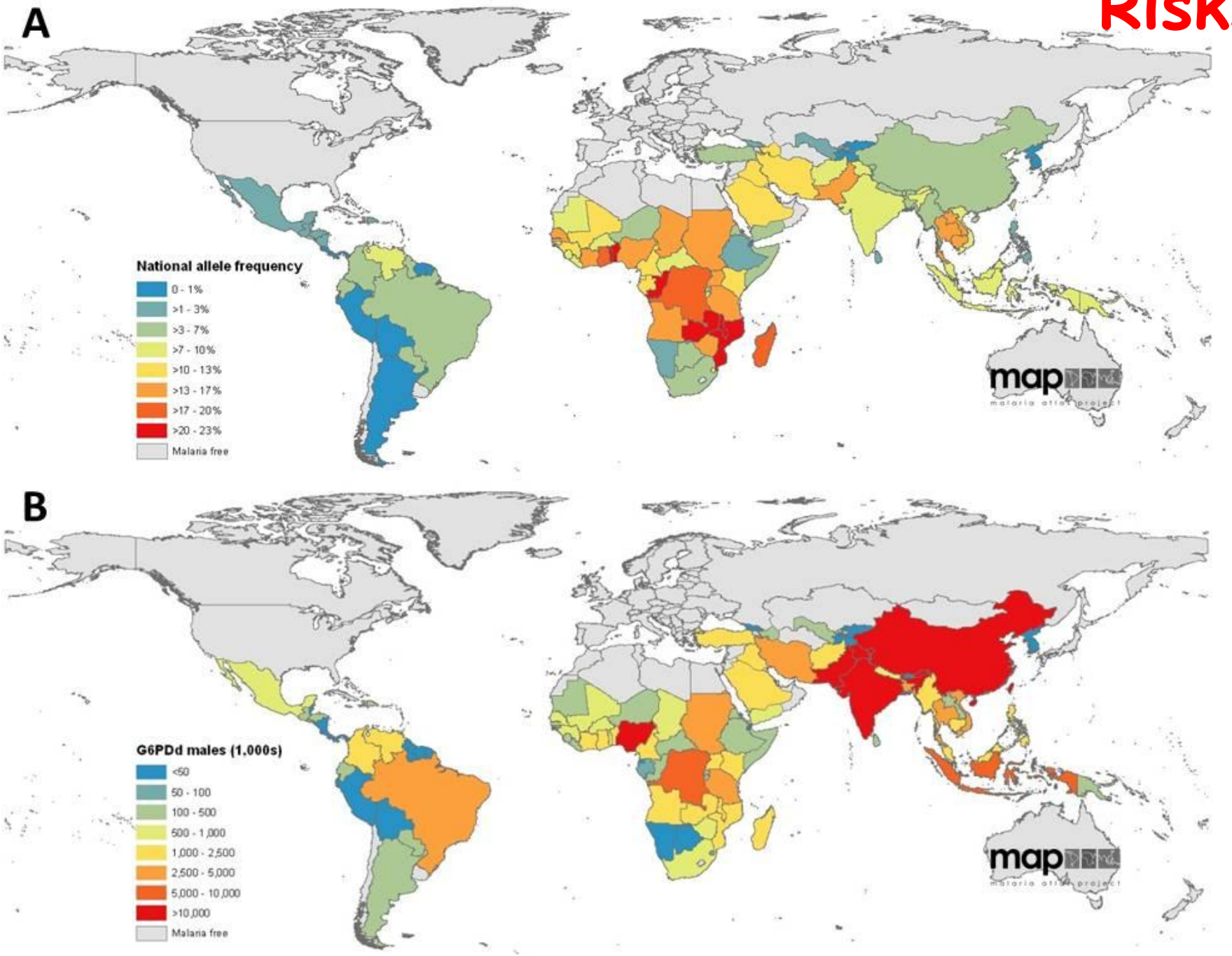


DAY	0	1	2	3	7	14	17	21	24	28	35	38	42	49	52	56
DRUG ADMINISTRATION	▼					▼				▼			▼			
OOCYSTS																
No. mosq. positive / No. mosq. dissected	11/20	6/20	0/17	6/20	3/20	3/20	2/20	0/20	0/18	0/20	0/20	0/20	0/20	0/20	0/20	0/20
Total number of oocysts	52	10	0	12	6	4	2	0	0	0	0	0	0	0	0	0
SPOROZOITES																
No. mosq. positive / No. mosq. dissected				8/22			0/7						0/34	0/19		0/13
Total infectivity				5			0						0	0		0
TRANSMISSION				+												

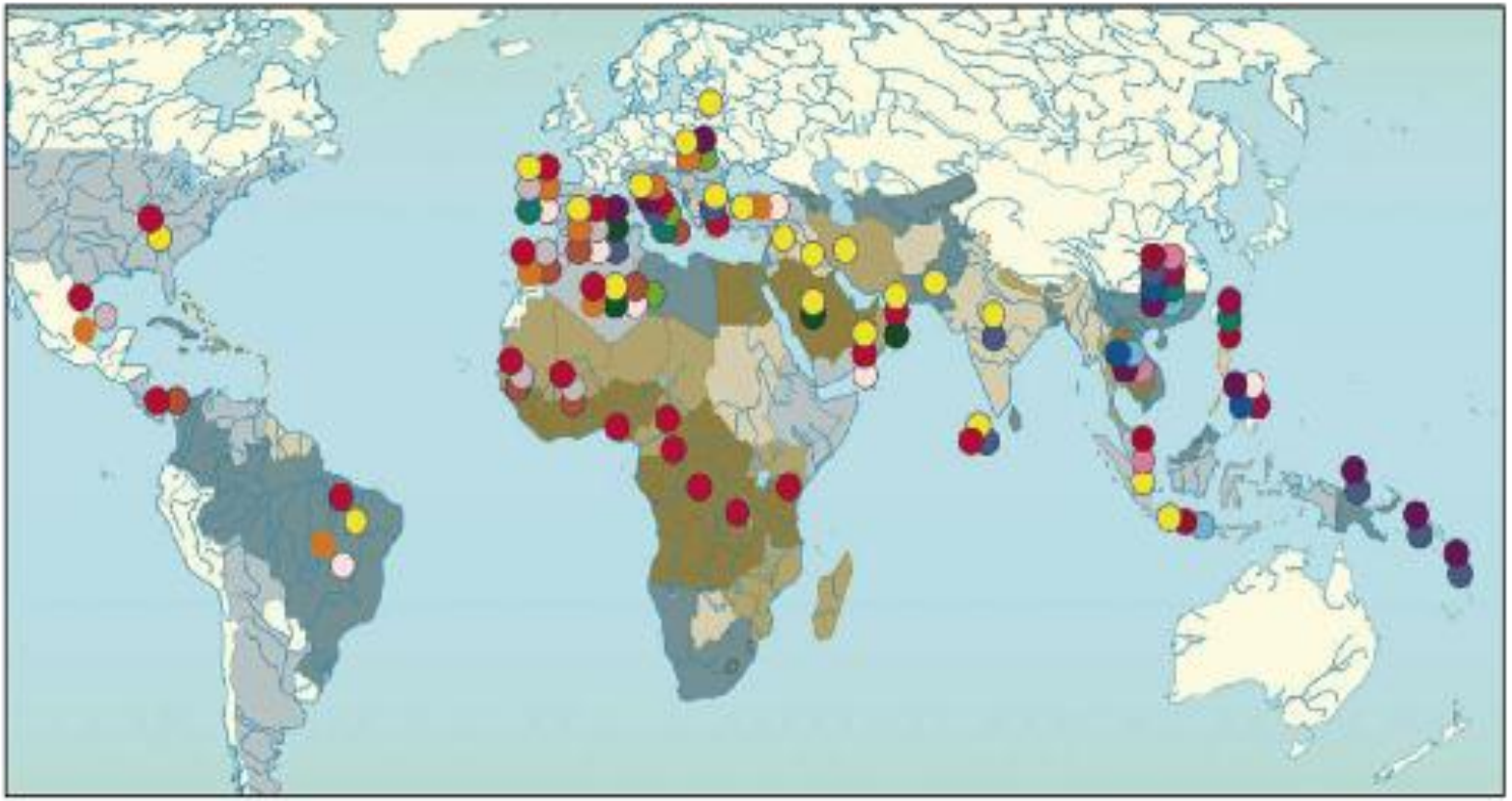
Fig. 14. Results of studies with Volunteer 18.

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
0 - 1%
>1 - 3%
>3 - 7%
>7 - 10%
>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

Risks

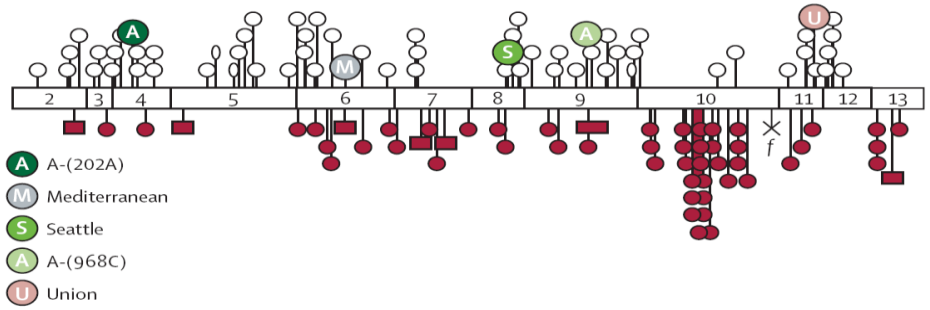


Frequency of G6PD deficient males

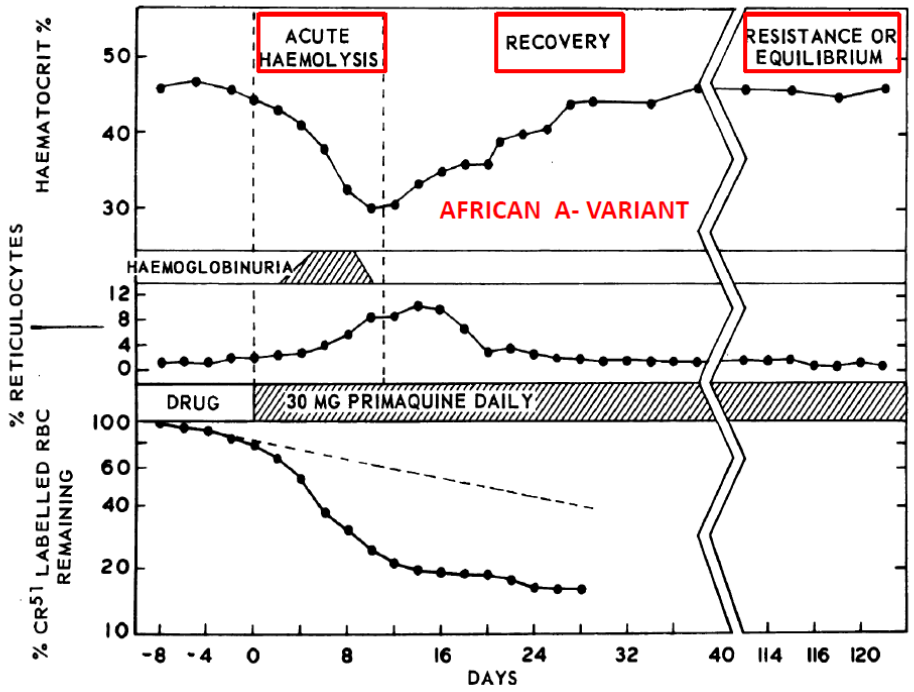
- <0.5%
- 0.5–2.9%%
- 3.0–6.9%%
- 7.0–9.9%%
- 10.0–14.9%%
- 15.0–126.0%%

Polymorphic G6PD variants

- A-(202A)
- A-(968C)
- Aures
- Canton
- Chatham
- Coimbra
- Cosenza
- Kaiping
- Mediterranean
- Mahidol
- Santamaria
- Seattle
- Taipei
- Union
- Viangchan
- Local variant



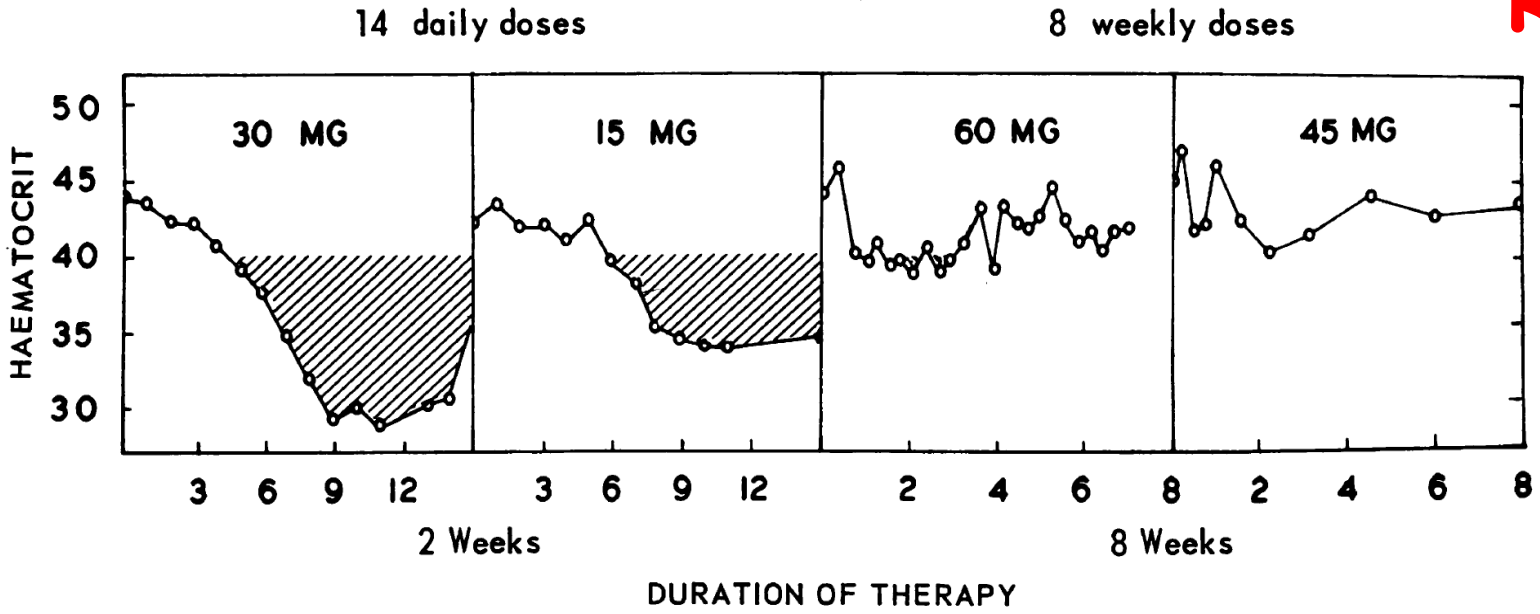
Risks



Primaquine causes haemolysis in <u>all</u> G6PD deficient individuals

Mortality
1in 692,307
(upper 95% CI: 1 in 448,500)

Risks



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

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.

ERG recommendations

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 *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.

	Indication
Thyroxine (1891)	Myxoedema
Insulin (1922)	Diabetic ketoacidosis
Vitamin B12 (1926)	Pernicious anaemia
Sulphonamides (1937)	Puerperal sepsis
Penicillin (1941)	Lobar pneumonia
Defibrillation (1948)	Ventricular fibrillation
Streptomycin (1948)	Tuberculous meningitis
Ganglion blockers (1959)	Malignant hypertension
Heimlich manoeuvre (1975)	Laryngeal obstruction by a foreign body
Cisplatin plus vinblastine and bleomycin (1977)	Disseminated testicular cancer
Acetylcysteine (1979)	Paracetamol poisoning
Ganciclovir (1986)	Cytomegalovirus retinitis
Laser treatment (2000)	Removal of port wine stains
Imatinib (2002)	Chronic myeloid leukaemia

***Table 3*: Some interventions with effectiveness established through historical controlled trials[3]**

World Health Organization

GLOBAL MALARIA PROGRAMME

Updated WHO Policy Recommendation (October 2012)

Single dose Primaquine as a gametocytocide in *Plasmodium falciparum* malaria

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Primaquine potentially has a major role in reducing malaria transmission, especially in efforts to eliminate *Plasmodium falciparum* malaria. The population benefits of reducing malaria transmission by gametocytocidal drugs require that a very high proportion of patients receive these medicines. WHO currently recommends the addition of a single dose of primaquine (0.75 mg base/kg) to artemisinin combination treatments (ACTs) for uncomplicated falciparum malaria as a gametocytocidal medicine, particularly as a component of pre-elimination or elimination programmes, "provided the risks of haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient patients are considered". However, G6PD testing currently is seldom available in the field, limiting the implementation of this recommendation. In areas threatened by *P. falciparum* resistance to artemisinins, all efforts should be made to contain its spread, and reducing transmission of parasites from treated individuals is imperative.

In light of these concerns, WHO has conducted a review of the evidence on the safety and effectiveness of primaquine as gametocytocide of *P. falciparum*, which indicates that a single 0.25mg base/kg is effective in blocking transmission and is unlikely to cause serious toxicity in subjects with any of the G6PD variants. Based on this review[1], the Malaria Policy Advisory Committee (MPAC) recommends the following:

In: (1) areas threatened by artemisinin resistance where single dose primaquine as a gametocytocide for *P. falciparum* malaria is not being implemented, and
(2) elimination areas which have not yet adopted primaquine as a gametocytocide for *P. falciparum* malaria:

A **single 0.25 mg base/kg primaquine dose** should be given to all patients with parasitologically-confirmed *P. falciparum* malaria on the first day of treatment in addition to an ACT, except for pregnant women and infants <1 year of age.

It is recognised that this recommendation may raise the issue of whether countries already using a single dose of 0.75 mg base/kg primaquine in the treatment of *P. falciparum* malaria should consider changing to the lower dose. WHO recommends that such countries continue with the current policy until more information on the efficacy of the lower dose is available, at which time WHO will review this recommendation.

[1] Report available on the WHO-GMP website at the following URL:
http://www.who.int/malaria/mpac/sep2012/primaquine_single_dose_pf_erg_meeting_report_aug2012.pdf

The malaria strategy mix for 2015-2025 – implications for other documents, including revision of the Global Malaria Action Plan (GMAP) and the development of a roadmap for malaria eradication

September 2012 – note for MPAC discussion

In 2008, the Roll Back malaria partnership launched the Global Malaria Action Plan (GMAP) following an extensive consultative process with a wide range of stakeholders. While the GMAP does not contain an end date (and in fact some of the projections, such as costs, go out for 20 years of more), there has been a request by some members of the RBM Board to consider a revision of the GMAP before the end of 2015. At its May 2012 meeting, the RBM Board requested the Bill & Melinda Gates Foundation, which had funded the initial development of the GMAP, to lead a task force that would explore options for revising the GMAP, and would report back to the Board at its December 2012 meeting.

During the discussion leading up to the May 2012 RBM Board meeting and at the meeting itself, GMP has repeatedly made the point that any revision of the GMAP should be based on the strategy mix as recommended by WHO-GMP under the guidance of the Malaria Policy Advisory Committee (MPAC). The RBM partnership should use the revision of the GMAP to reflect on the activities and actions required to advocate for the implementation of these WHO-recommended strategies, harmonize partners in support of National Malaria Control Programmes, and mobilize the needed resources. It is also an opportunity to reflect on the multi-sectoral requirements of an integrated and sustained response to malaria. However, it would not be appropriate for the revision of the GMAP to be seen as a means of obtaining consensus on the mix of technical strategies recommended for intervention over the next decade or more.

The question is whether the collection of WHO policy recommendations for malaria is sufficiently clear as they are now, or whether an over-arching review of the strategy mix, from 2015-2025, for example, should be commissioned by GMP under the oversight of the MPAC.

In addition, there has been a strong call from some in the malaria community, including senior leadership at the Gates Foundation and some MPAC members, for a detailed strategy (or roadmap) for eventual malaria eradication. This effort would need to bring together state-of-the-art modeling, costing, and existing roadmaps for new tool development that would chart the path for where we expect to be, perhaps in 5 year intervals, between now and ultimate malaria eradication. Such a document could: 1) provide a useful metric against which to score progress; 2) better refine the financial

requirements for malaria eradication; and 3) identify the likely "choke points" at which modeling suggests further progress may not be possible without new tools. Such a roadmap could be a powerful driver of investments both in scaling up today's interventions as well as research and development for tomorrow's tools.

Questions for MPAC:

1) Should the recommendation to RBM be that the technical basis of the next GMAP be the existing WHO recommended malaria control and elimination strategies, making it clear that this is not an area where consensus building is required?
2) Should there be a dedicated working group to develop a strategy mix for 2015-2025 as preparation for the development of the next iteration of the GMAP?
    a. If the MPAC recommends an actual strategy review process, how would the MPAC suggest that GMP commission this work, and how would MPAC like to oversee the process?
3) In the overall process of revision of the GMAP, are there particular issues that MPAC wishes to go on record as recommending for attention?
4) Should GMP, under the oversight of MPAC, develop a technical roadmap for eradication as described above?
    a. If so, should this process be separate from the process of developing the technical strategy mix and the GMAP?

Malaria Vector Control:
Proposed and Potential Advisory Mechanisms for Policy Setting

September 2012

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1. Background and Introduction

During the past decade, unprecedented progress has been achieved in controlling malaria, much of it attributable to successful vector control. However, reports of insecticide resistance in a number of countries especially from sub Saharan Africa, threaten these fragile gains. Long-lasting insecticidal nets (LLINs) and indoor residual spraying are the central pillars for malaria vector control; fortunately, they remain highly effective in most settings.

Urgent action to prevent resistance from emerging at new sites, and to maintain the effectiveness of vector control interventions in the short, medium and long-term have been clearly articulated out in the Global Plan for Insecticide Resistance Management in malaria vectors (GPIRM) – http://www.who.int/malaria/vector_control/ivm/gpirm/en/index.html – developed by the WHO Global Malaria Programme (GMP) in consultation with a wide range of Roll Back Malaria partners and other stakeholders.

The GPIRM consists of five major activities (pillars) which include the planning and implementation of insecticide resistance management in malaria endemic countries; ensuring proper, timely entomological monitoring and effective data management; developing new and innovative vector control tools; filling the gaps in knowledge on mechanisms of resistance and impact; and ensuring that enabling mechanisms (advocacy, human and financial resources) are in place.

Whereas the first two pillars are country-driven, the development of innovative vector control tools requires working closely with industry among other partners. This is not only key to finding alternative products to manage insecticide resistance but also to ensure that vector control interventions are scaled up and control gains are sustained.

2. Vector Control Advisory Group (VCAG) on new forms of vector control

The need for new forms and new tools for vector control broadly, and the lack of a comprehensive process to assess new tools, technologies and approaches for vector control, led WHO (GMP together with the Neglected Tropical Diseases department, where WHOPES is housed) to see the need to establish a Vector Control Advisory Group (VCAG) for new forms of vector control. To date, the process to generate public health norms, standards and policy recommendations has been primarily focused on new products within existing categories of technology (e.g. long-lasting insecticidal nets) – with no defined "entry point" or process for new forms or “paradigms” of vector control.

Stakeholders have indicated that the absence of a defined process has, in the past, delayed the adoption and implementation of new forms of vector control. VCAG is intended to fill this gap, and to provide a predictable and clear process by which new forms of vector control can gain an initial "proof of principle" recommendation. The process of developing the VCAG was begun approximately 2 years ago; funding for the process was secured in August 2012, and the VCAG is now in the process of being constituted.

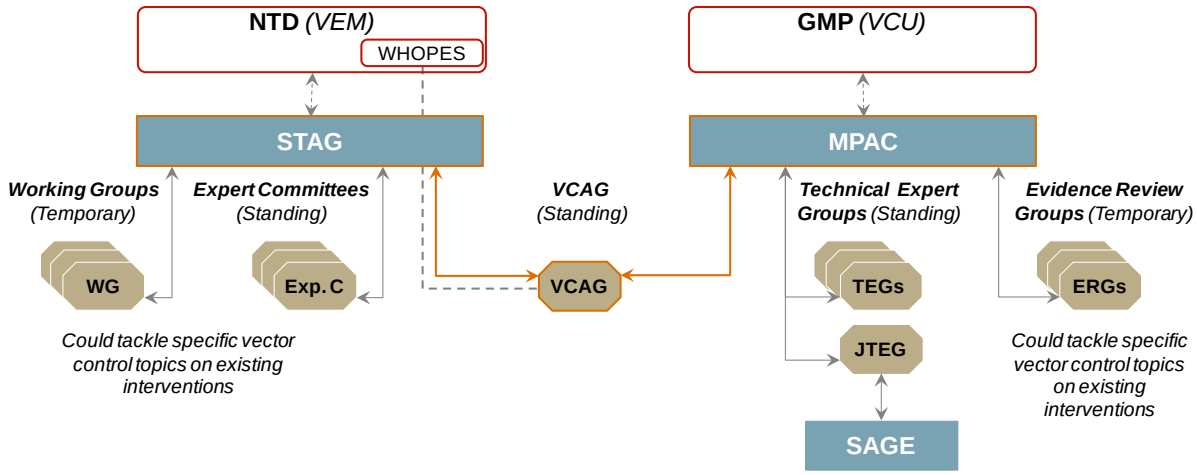
In summary, VCAG has the potential to benefit to vector-borne disease control by:

- Providing a predictable and defined process by which new forms of vector control can be introduced into public health practice
- Reducing uncertainty for innovators through this clarification
- Accelerating the process of public health implementation of new forms of vector control
- Providing a forum for dialogue and guidance to innovators on evidence requirements early in the process to reduce risks; and
- Providing WHO GMP and NTD departments, with evidence-based advice on the epidemiological mode of action[1] and the public health value of new forms of vector control, and, through the NTD STAG and the GMP Malaria Policy Advisory Committee, provide such advice to national vector-borne disease control programmes and other stakeholders.

VCAG will act as a standing group with dual reporting to MPAC and STAG (see Figure 1). For vector control topics outside of VCAG's scope (e.g. recommendations on the appropriate mix of existing vector control interventions in different settings), temporary Evidence Review Groups, Expert Committee Meetings or Working Groups may be convened by MPAC or STAG as appropriate.

[1] The Epidemiological Mode of Action of an intervention describes how the effect of the intervention on mosquitoes and mosquito populations lead to epidemiological benefits for populations at risk, e.g. in the case of ITNs, the relative importance of personal protection and the "mass effect" (see Lengeler et al: "Net Gain: A New Method for Preventing Malaria Deaths", Chapter 2)

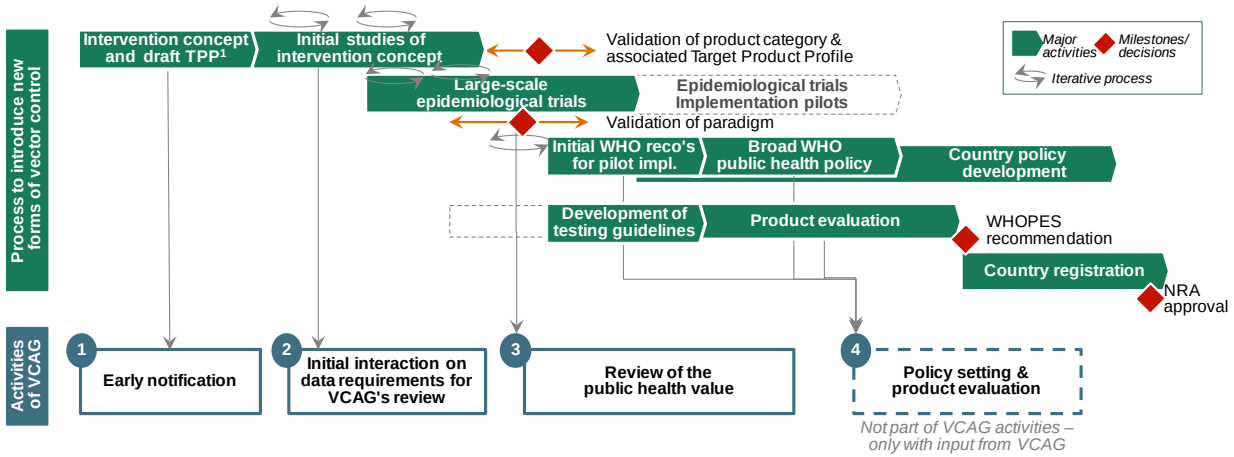
Figure 1: Organogram



3. Detailed VCAG activities in relation to MPAC

In order to illustrate the gap that VCAG is intended to fill, it is helpful to consider the process of introducing a new form of vector control. For candidate new vector control technologies, the process of obtaining a recommendation from WHO will in most cases begin with an assessment by VCAG of "proof of principle", in other words, whether the evidence about the intervention is sufficient to justify its potential application for some public health purpose in one or more specific settings. The assessment will ensure that the evidence generated is relevant for obtaining a public health policy recommendation. The activities performed by VCAG depend on where the proposed new form of vector control stands in the innovation process. There are three major steps of the innovation process in which VCAG can play an essential role, and a fourth step in which its input would be required (see Figure 2).

Figure 2: Three major steps where VCAG has a role to play



Step 1: Early notification:

At the very early stages of innovation, product developers can notify new ideas (and interventions concepts being drafted) to VCAG. The secretariat will log these notifications in a confidential list which will be regularly shared with VCAG members, so that VCAG can comprehend future requirements (e.g. expertise needed for future assessments and potential issues to consider). The VCAG secretariat will also be available to respond to any general inquiries about the review process (e.g. nature of assessment and timelines)

Output(s) of this step: VCAG secretariat runs a list of projects notified by product developers and communicates it on a regular basis to VCAG members.

Step 2: Initial interaction on data needs:

If the product developers wish, VCAG can provide advice on the type and depth of evidence that will likely be used for the assessment, providing an opportunity for product developers to align with VCAG on overall evidence requirements before the launch of resource-intensive activities such as large-scale epidemiological trials.

The advice will be provided in individual discussions between the product developers and the Group at the VCAG meeting. It may cover, for instance, the needs concerning evidence of epidemiological and entomological outcomes, epidemiological mode of action, economic feasibility or user acceptability. To support its deliberations, VCAG may consider the initial results of tests and studies carried out by the product developers.

Output(s) of this step: VCAG provides advice to innovators on the type of evidence that will likely be used in the review in step 3 to help them strengthen their dossier. VCAG reports to

MPAC and STAG on the advice provided to the innovator to see if there are additional elements relevant in the broader context of the targeted diseases

Step 3: Review and assessment of public health value:

Once a relevant body of evidence has been presented to VCAG, which contains at least some indication of the epidemiological outcome of the new form of vector control, VCAG will review all available evidence (which may include other available sources than the data presented by the product developers).

Based on this review, VCAG evaluates the public health value of the new intervention, by answering a question of this form: "*Is this new intervention efficacious, for some defined public health purpose and in some defined circumstances, and will it be useful to and feasible for its intended users?*". The answer might in some instances request additional evidence.

As soon as VCAG decides that the answer to this question is "yes", and that proof of principle has indeed been established for the new form of vector control, responsibility within WHO for further assessment will pass: (a) to the advisory bodies (MPAC and STAG) of the technical department(s) (WHO GMP and NTD) responsible for the particular vector-borne disease(s) against which the new intervention is considered likely to be useful; and (b) to WHOPES.

Hence, after validating the value of the new form of vector control, VCAG will present its results to MPAC and STAG in their respective meetings, expressing its opinion on the usefulness of the new intervention. In particular, VCAG will detail the epidemiological mode of action and value of the new paradigm in a given setting.

In the case of establishment of a proof of principle, VCAG may submit a technical data package to MPAC, STAG and WHOPES for further use in policy and product standard setting. In parallel, product developers are informed of VCAG's opinion of the technology reviewed.

Output(s) of this step: VCAG prepares a report including its assessment of the public health value of the new form of vector control. It may advise product developers on need for additional evidence in some instances. VCAG presents to MPAC and STAG its findings, through the expression of its recommendation ("yes", "no", "yes but" and describing the specific considerations to take into account). A technical data package is also transmitted to MPAC, STAG and WHOPES if relevant.

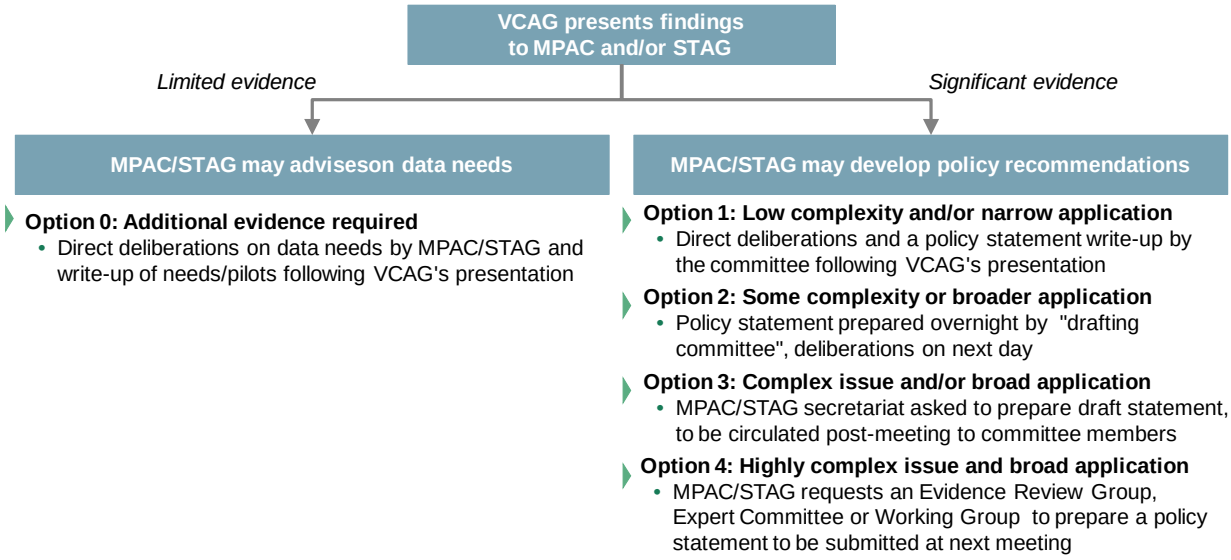
Step 4: Policy development and product evaluation: *[In this step, VCAG mainly provides input]*

Once VCAG has presented its findings at the MPAC and STAG meetings, the task of defining what public health roles and functions are appropriate for the new form of vector control in the context of the disease will devolve to these committees. In particular, they will establish the role of the new intervention for a specific disease and eco-epidemiological setting,

and in relation to other disease control interventions. While VCAG will concentrate on the characteristics of the intervention itself and whether it is technically efficacious, MPAC and STAG work at a higher strategic level on the role of the intervention vis-à-vis other interventions within specific disease control programmes, i.e. when, where and how the intervention should be deployed.

Figure 3: Illustrative options of how the articulation between VCAG and MPAC/STAG could work

[Initial propositions for consideration by MPAC and STAG; may require adaptation]



In parallel to the VCAG review, WHOPES will need to develop standard definitions, testing/assessment methods (efficacy and safety) and quality control criteria adapted to the pesticide product, so that other commercial products using the same technology can be assessed using a common set of criteria, and appropriate recommendations can be given to prospective purchasers.

In order to minimize the time of developing these guidelines, WHOPES will be in close contact with the VCAG secretariat and participate in VCAG meetings/communications throughout the VCAG process. This will enable WHOPES to develop draft guidelines (with relevant experts) in parallel with the VCAG review, using VCAG's on-going assessment as primary input for defining relevant indicators and guidelines. Once the VCAG review is finalized establishing public health value of a new tool, technology or approach, WHOPES will then proceed to a larger consultation of the draft guidelines for finalization and publication.

Although VCAG reviews classes of technology, some evidence considered by VCAG may refer to a "first-in-class" commercial product. If this product is also submitted to WHOPES, WHOPES will build on VCAG's work, taking all the already existing evidence fully into account to avoid duplication of efforts.

Output(s) of this step: GMP and NTD publish policy recommendations, based on the advice of their respective policy committees MPAC and STAG. WHOPES publishes product category testing/assessment guidelines and product recommendations for specific products.

4. Membership of VCAG

Members of VCAG will be expected to provide GMP and NTD with high quality, well considered advice on matters related to new methods of vector control and the factors that determine their efficacy, and to contribute to the role and reputation of VCAG as a useful and internationally-recognized advisory group in the field of vector control. The provisional plan is that VCAG will comprise up to 11 members, who will serve in their personal capacity and will represent a wide range of expertise relevant to practical vector control, including vector biology, ecology and management, insecticides and insecticide resistance, epidemiology of vector-borne diseases, study design and statistics as well as operational research. The panel will include a broad range of opinion, with the capacity to challenge assumptions, as well as direct experience in the design and management of vector control programmes. As far as possible, members will be selected on the basis of the principles of equitable geographical representation from developed and developing countries and gender balance.

An open call for inviting submissions and/or nomination of experts to serve on VCAG will be posted on WHO web site and sent out through other appropriate channels. VCAG members, including the Chairperson, will be appointed by a panel composed of the Directors of NTD and GMP, a regional WHO vector advisor and the STAG and MPAC Chairpersons, upon the proposal of the Coordinators of VCU and VEM. The panel may also consult with other relevant WHO departments. Members of VCAG, including the Chairperson, will be appointed to serve for an initial term of two years. The two-year terms can be renewed, but as a general rule, members, including the chairperson, will be expected to serve for no more than four years out of any six, although exceptions may be made at the discretion of the appointment panel. The Chairperson of VCAG will be invited as a resource person to all MPAC and STAG meetings at which vector control issues are being discussed.

Membership of VCAG may be terminated for any of the following reasons:

- failure to attend two consecutive VCAG meetings;
- change in affiliation resulting in a conflict of interest; and
- lack of professionalism involving, for example, a breach of confidentiality.

WHO Regional Offices and other WHO departments, including Special Programme for Training and Research in Tropical Diseases (TDR), will be invited as members of the Secretariat to participate in VCAG meetings and deliberations.

Additional experts will be invited to participate in meetings, as appropriate, to ensure that a sufficiently broad base of expertise is available for the specific agenda items at each meeting.

5. VCAG Operating Procedures

VCAG will meet at least once a year in open and closed meetings. For the four year period of the project, five meetings are planned, including four yearly meetings and one addition ad hoc meeting that could be set up if needed depending on the number of new vector control tools that are submitted for review. Open meetings can be attended by anyone interested in vector-borne diseases and are intended for discussion of new tools, technologies and approaches and issues related to the agenda item(s) of the closed meeting. Closed meetings will follow the open meetings and will be restricted to VCAG members and the other independent experts to be invited by GMP and NTD. Depending on the needs and requests received to assess new products, additional ad-hoc VCAG meetings could be proposed by GMP and NTD.

A web page will be established for VCAG. Initially, draft procedural guidelines for VCAG will be published on the website, and comments and suggestions will be invited on VCAG working procedures through the website and by direct contact with a selected set of stakeholders. Later, the website will be used to allow access to supporting documentation and the agenda of VCAG, to solicit further items for the agenda, and to disseminate the recommendations and meeting reports of VCAG.

6. Malaria vector control policy setting beyond the VCAG

The relevant issues in malaria vector control that may require WHO to provide policy recommendations are summarized in Table 1. These issues appear to fall into three classes, needing potentially different skill sets: new vector control technologies, insecticide resistance management, and implementation of malaria vector control programmes. Of these, the functions needed for new technologies and insecticide resistance have already been given some attention through previous discussions about VCAG and through the recommendations articulated in the Global Plan for Insecticide Resistance Management; hence, the issues of general programme management are listed in more detail. It may be noted that, according to the RBM Harmonisation Working Group, the issues that are most likely to cause failure of Global Fund proposals are related to this latter category: stratification, quantification, cost-effectiveness, IEC, monitoring and evaluation.

In recent years, the RBM Vector Control Working Group (VCWG) has become a vibrant and active forum for global discussion around issues related to malaria vector control. The group, which generally meets annually, has often attracted more than 100 participants from the global malaria community for its meetings. There has been some degree of confusion around the role of this group, with some members appearing to view the VCWG as a policy setting body. This is not the case, as RBM's core roles are advocacy, partner harmonization, and resource mobilization. The RBM partnership secretariat and its mechanisms do not have a policy setting mandate. This is particularly important given that groups such as the VCWG are self-selected, and include partners with a financial stake in the interventions being discussed.

In part, the current situation has arisen because of the absence of a clear policy setting mechanism at WHO with regard to malaria generally, and malaria vector control more specifically. The creation and implementation of the MPAC offers an opportunity to rectify this situation.

It is not possible to merge the issues related to practical malaria vector control implementation with the role of the VCAG (or vice versa). One reason is that the VCAG is not a malaria-specific body: it deals with all forms of vector control, e.g. for leishmaniasis, trypanosomiasis, dengue, tick-borne diseases, etc. The main point, however, is that different skills are needed.. The VCAG will mainly assess whether new technologies do or do not have the desired effect on the vectors, and for this upstream proof-of-principle decision-making, deep expertise in public health management is not needed, while knowledge of technology, chemistry, biology, and product development is essential. The downstream issues are malaria-specific, and directly connected to practical programme management at country-level, e.g.: the role of IRS in malaria epidemics; how to combine alternative LLIN distribution systems; and LLIN procurement quantification that takes into account expected lifespan of LLINs. For these decisions, it is critical to have specialised malariologists with public health training and experience.

Thus, there is a need for the MPAC to decide how it wishes to address malaria vector control issues that are not covered under the VCAG. Broadly, there are two options.

The first is for the MPAC to create a Technical Expert Group (TEG) for malaria vector control. This TEG could include task forces on issues of perennial importance, such as insecticide resistance. The potential advantages of convening such a group are: 1) there would be a standing group that could respond quickly to the needs of the MPAC as new issues arise that require policy recommendations; 2) an overarching group such as a TEG would allow for a synthetic view of the vector control issues requiring policy recommendations. The potential disadvantages are: 1) the original conception of the MPAC was to largely rely on time-limited

ERGs and to avoid the creation of too many standing TEGs; 2) the malaria vector control issues that require policy recommendations are highly heterogeneous, and may require highly specialized experts. Given this, a standing TEG on malaria vector control might still need to convene ERGs to review specific issues, adding a third layer into the policy setting process, which would not be desirable from a perspective of efficiency or timeliness.

The second is for the MPAC to convene time-limited ERGs to address specific malaria vector control issues as the need arises. The potential advantages of such a system are: 1) being nimbly responsive to policy requirements without creating further fixed architectural components for malaria policy setting; 2) being able to convene highly specialized groups of experts capable of making recommendations directly to the MPAC. Potential disadvantages include: 1) The ERGs might consider a single vector control policy recommendation without taking other vector control issues into context (although presumably the MPAC would be charged with that synthetic function); 2) there are so many vector control issues pending that there will be a continuous convening and disbanding of ERGs that could be time consuming and inefficient.

In either case, the VCAG would remain a distinct and smaller entity, convened jointly by GMP and NTD, focussed on upstream decisions about candidate technologies and reporting to the MPAC either directly or through a malaria vector control TEG if the MPAC were to convene such a group.

The MPAC is asked to consider the needs of the global malaria community with regard to policy advice on vector control, and recommend to WHO whether to establish a standing TEG for malaria vector control, or whether to convene time-limited ERGs on particular malaria vector control issues as the need for policy decisions or recommendations arises.

Table 1: A summary of issues in malaria vector control and proposed mechanisms for policy decisions

GMP and NTD		**GMP: Management of Malaria Vector Control in Public Health**	
Mechanisms	**VCAG (not only malaria)**	**TBD**	**TBD**
Approximate size	11	TBD	TBD
Skills	**Technological**: vector control engineers: entomology, biology, basic epidemiology, insecticides, product development, testing methods etc. Note the need for broad skills across all vectors (not just malaria).	**Insecticides and insecticide resistance:** genetics and population genetics (including '80s modelling work), operational vector control, malaria programme planning and management.	**Technical implementation of malaria vector control programmes (entomologists)**, including logistics and operational planning, public health epidemiology, and economics including cost-effectiveness, social science
Potential Questions	New methods of vector control (not only malaria): (a) proof of principle (not only malaria) (b) epidemiological mode of action i.e. the causal chain from the intervention's direct entomological effects on insects, through to epidemiological benefits for people – e.g. repellency vs killing; mass effect vs personal protection. (This is needed in order to develop standard tests and to generalise from trial data to a wide range of other settings).	Managing insecticide resistance: 1) Regular (at least annual) reviews of new data, and at sub-regional level: a) interpretation of those data, b) making recommendations on technical developments, tactics and trends e.g. "spraying programmes in the east of the region should be preparing for a switch away from insecticide x and towards either insecticide y or z. LLIN programmes should be closely monitoring insecticide z." 2) Strategic support for the decision-matrix initially presented in the GPIRM: a) Technical guidance on implementation b) Keep the matrix up-to-date and be responsive to the rapid appearance of new data on the evolution of resistance, its impact on control, and methods for resistance management.	1) Stratification for choice of vector control methods: a) Where to use LLINs alone b) Use of IRS as i) Sole method of VC ii) supplement to LLINs iii) epidemic prevention and control – highland, arid iv) urban fringe v) diverse settings in Asia and Latin America vi) cordon sanitaire (barrier spraying) c) Where and when to use a niche-specific form of vector control: i) Environmental engineering for source reduction ii) Larviciding iii) Outdoor transmission iv) Housing modifications etc. d) Where, when and how to use new forms of vector control (following Proof of Principle from VCAG): which applications are so far justified, given existing evidence from trials and pilot projects, and reasonable extrapolation to other vector species and eco-epidemiological settings e) Role of VC for elimination of residual foci of transmission and prevention of re-invasion f) VC post-elimination: assessment and suppression of receptivity 2) Management of IRS vs LLINs: Where and when to choose one or the other or some combination of both? How to manage the delivery of both (logistics, training, capacity, procurement etc). 3) Managing LLIN delivery systems so as to sustain universal coverage efficiently, especially: a) combining routine continuous distribution with campaigns: e.g.

			we tell programmes to "regard the campaign as day 1 of the routine service, plan for both together!" but there is no-one to tell them how to do this, e.g. the practicalities of procurement and quantification for the combination b) proposed "push-pull" systems c) the HWG's 8:20:50 rule for allowing for existing nets d) what to do when there is enough donor funding for some nets but not for all (Free Universal Coverage is not affordable) e) is the WHO's "1 for 1.8" rule working? f) manage end-of-life of nets g) define the mechanism by which donors can allow countries to procure the locally-most-durable brand of LLIN h) manage pressures from donors for increased standardisation in net size…and the contrary pressures from social scientists and local activists for less standardisation in net size and shape, more adjustment to local user-preferences i) role of social marketing (for some donors this is still an attractive option) j) net usage: some promotion of usage is needed, but how much is too much? Need rules of thumb for what is cost-effective, and what is not? 4) General vector control capacity building: i) by defining a core curriculum which builds on Garett-Jones course from the 60's ii) especially capacity on entomological monitoring – is this not collected because no-one has the skill (or field allowances) to collect good data? Or because no-one has the skill to use the data well for programme management? iii) linking entomological monitoring with all the "which VC where" questions listed above
Potential Outputs	1) Proof of Principle recommendations (not just malaria) 2) Interim findings on 'epidemiological mode of action'	Annual report on new developments in: • Spread of resistance • New understanding of resistance and its mechanisms • Management strategies by sub-region	Occasional papers on specific policy issues – e.g. "maintaining universal coverage with LLINs that wear out gradually over a long period" (i.e. how to combine campaigns with routine LLIN delivery systems)

Policy Setting Landscape for Malaria Vector Control

Meeting of the Malaria Policy Advisory Committee
Geneva, 11-13 September, 2012

Abraham Mnzava: BSc, MSc, PhD
Coordinator, Vector Control
Global Malaria Programme

World Health Organization

GLOBAL MALARIA PROGRAMME

Outline

- Progress and challenges in malaria vector control
- Potential threats and the need for new tools/technologies
- Establishment of a vector control advisory group (VCAG)
- Other proposed advisory mechanisms beyond VCAG
- Request to MPAC for action/recommendation

Malaria control and elimination – a decade of progress

- Unprecedented progress in malaria control over past decade, with increased funding leading to major scale-up of vector control interventions, diagnostic testing, and effective treatment
- Estimates suggest more than one million lives saved over 10 years
  - Primarily attributed to increased coverage with indoor residual spraying (IRS) and long-lasting insecticidal nets (LLINs)
  - Vector control will always remain a central pillar in the control and elimination of malaria

Insecticide resistance: we are ahead of the curve but need to act now

- Mosquito resistance to at least one class of insecticides reported from, or confirmed through independent studies in 64 countries with on-going malaria transmission
- Existing prevention tools (LLINs and IRS) remain highly effective in all endemic countries

  - Urgent action needed to prevent further development of insecticide resistance, and to preserve effectiveness of vector control interventions and remarkable recent gains in malaria control

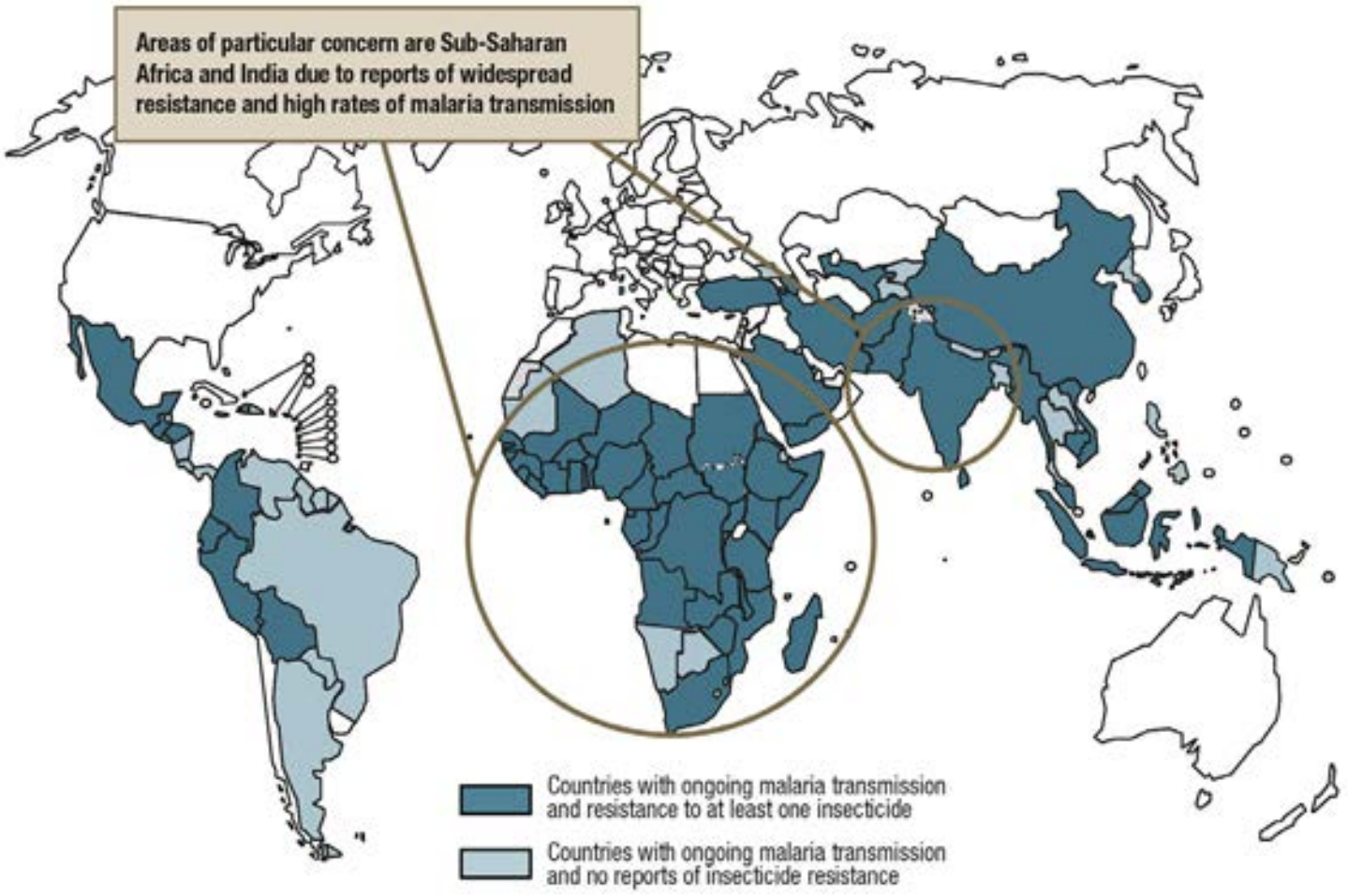
Some of the challenges/threats include

- Insecticide resistance management
- Lack of adequate new products and technologies
- Inability to take into account expected life span of products on procurement decisions (e.g. LLINs)
- Weak systems to deliver and manage vector control interventions i.e.
  - Optimize resources by maintaining coverage in financial hard times
  - Capacity for entomological monitoring and vector control
- Lack of clear policy advisory mechanisms for malaria vector control

Capacity for entomological monitoring and vector control

Collection

Insecticide resistance: 64 countries to date, and mostly to pyrethroids



From WHO regional entomologists in WHO Regional Offices, completed by literature review by the Global Malaria Programme.
IR, insecticide resistance
1 Includes countries with confirmed susceptibility to all insecticides used and countries where susceptibility testing is not currently conducted or results are not available.
2 The map provides no indication of how widespread resistance is within a country; therefore, a single report of resistance would be sufficient to mark a country as having resistance.

GPIRM strategy: a window of opportunity to improve sustainability and impact of vector control

Five pillars of strategy

I. Plan and implement insecticide resistance management strategies in malaria-endemic countries.

II. Ensure proper, timely entomological and resistance monitoring and effective data management.

III. Develop new, innovative vector control tools.

IV. Fill gaps in knowledge on mechanisms of insecticide resistance and the impact of current insecticide resistance management approaches.

V. Ensure that enabling mechanisms (advocacy, human and financial resources) are in place.

Innovative new vector control tools are urgently needed

- Current pipeline for reformulations of existing insecticides and new active ingredients is promising but more investment is required to speed up the research and development process
- The Innovative Vector Control Consortium (IVCC) is a product development partnership playing a key role in bringing together public and private sectors to accelerate the development of new vector control tools

Innovation on Vector Control – Challenges and Areas for Improvement

Needs	Issues faced today
Viable & predictable market	• Small public health vector control market with unpredictable size and growth
Facilitation of "breakthrough innovation"	• No formal process to generate evidence for new paradigms, recognize their public health interest and develop recommendations (done ad hoc) • **VCAG – to facilitate breakthrough innovation**
Protection of investments while allowing competition	• Data protection viewed as limited since trial results of products evaluated by WHO are fully published for transparency • Indirect use of trial data generated for original product in evaluation of "me too" products accelerates access to market for new entrants & fosters competition, but seen as creating a disadvantage for product developers • Limited "recognition" of added value of innovative products within established product categories • Value for money
Recognition of innovation	

Needs	Issues faced today
Cheap process and short time-to-market	• Limited capacity at WHOPES (secretariat, collaborating centers, working group meetings etc.); limited capacity within national authorities for assessment and evaluation of pesticides • Country regulatory processes not harmonized
High quality products	• Limited capacity and policy for quality control of procured PHPs
Products that respond to end user needs	• Feedback loop from users / procurers limited • Visibility on innovation pipeline limited for countries and procurers (restricting their possibility to plan ahead in procurement)
Strong collaboration between groups	• Local researchers request more information on how to get support to develop ideas to products and bring to market • Frequent communication between groups to align on objectives and outcomes before launching resource intensive phases required

The need for a Vector Control Advisory Group to facilitate innovation

High level proposal for creation of the Vector Control Advisory Group

The Vector Control Advisory Group could validate paradigm

The Vector Control Advisory Group could validate the epidemiological impact of a new paradigm, as well as promote coordination and dialogue of all stakeholders

- VCAG will answer the question: ***"Is this new intervention efficacious, for some defined public health purpose and in some defined circumstances, and will it be useful to and feasible for its intended users?"***

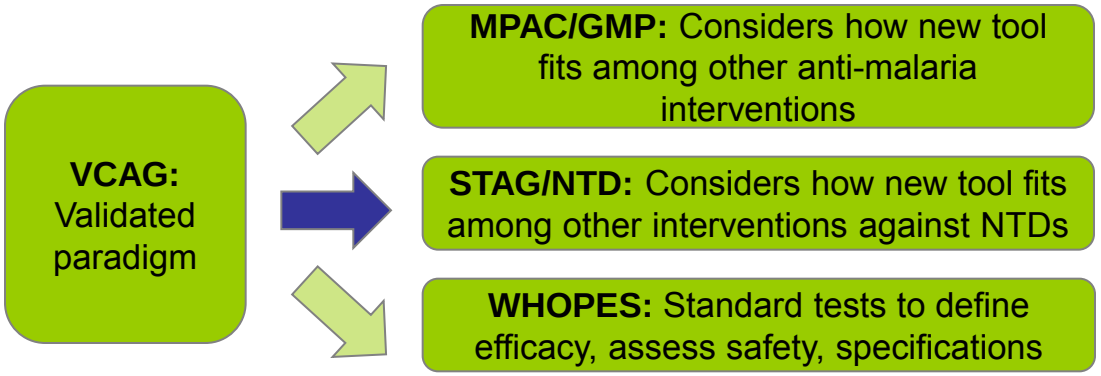
The VCAG assessment would then feed into the work of WHOPES and GMP/NTD

After VCAG validation, responsibility for policy recommendation is passed to MPAC/GMP and STAG/NTD...

- Will establish role of new vector control tool specifically for one disease, and in relation to other interventions, answering the question: *In which circumstances would this new intervention be implemented for a specific disease?*

...and creation of testing guidelines will be passed to WHOPES

- Will establish relevant testing guidelines for safety and efficacy and specifications for quality control



Source: Interviews; BCG analysis

Vector Control Advisory Group (VCAG) on new forms of vector control

- GMP and NTD identified a need to establish a Vector Control Advisory Group (VCAG) for new forms of vector control
- Lack of a comprehensive process to assess new tools, technologies and approaches for vector control
- Standards…..focused on new products i.e. LLINs with no defined "entry point" or process for new forms or “paradigms” of vector control

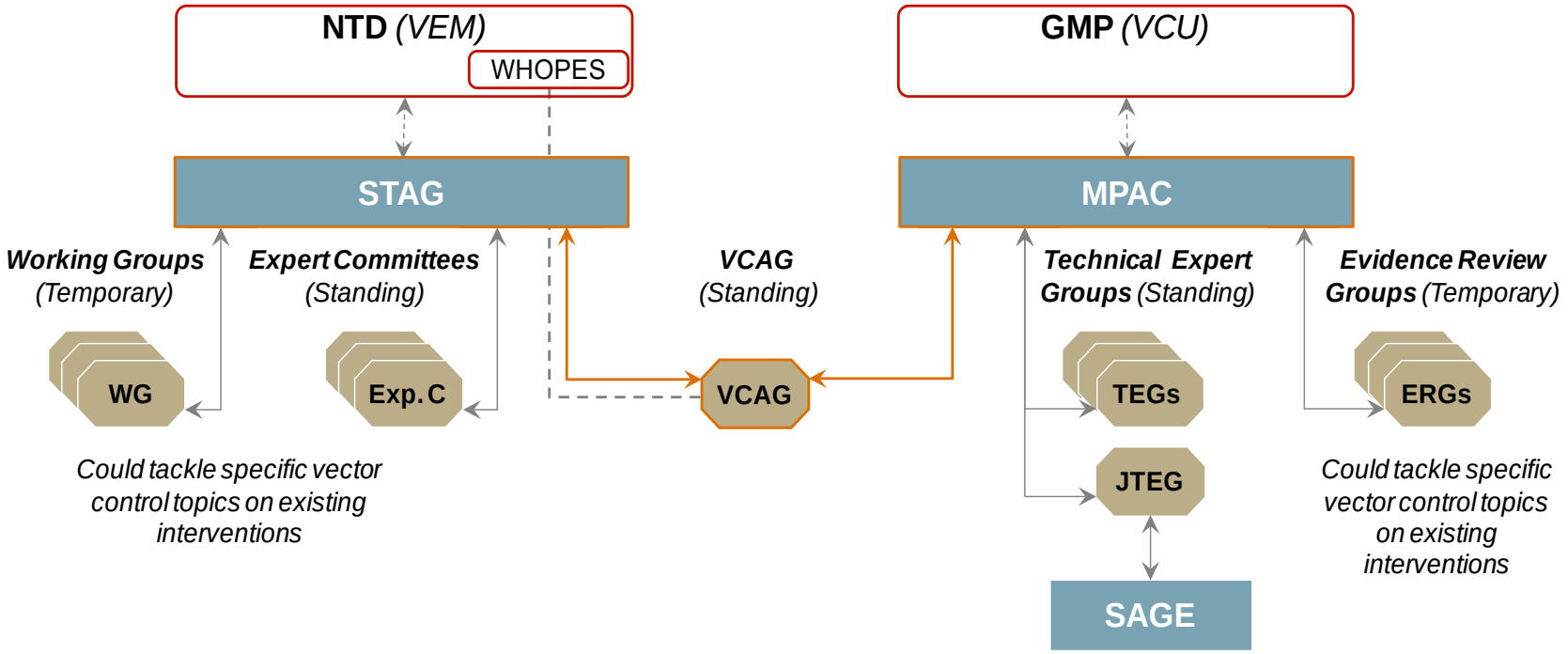
VCAG, continued

- Delayed the adoption and implementation of new forms of vector control
- VCAG is intended to fill this gap, and provide a clear process for "proof of principle"
- Way in which new forms of vector control can gain an initial recommendation
  - Process of VCAG started 2 years ago
  - Funding for process secured in August 2012
  - Now being constituted

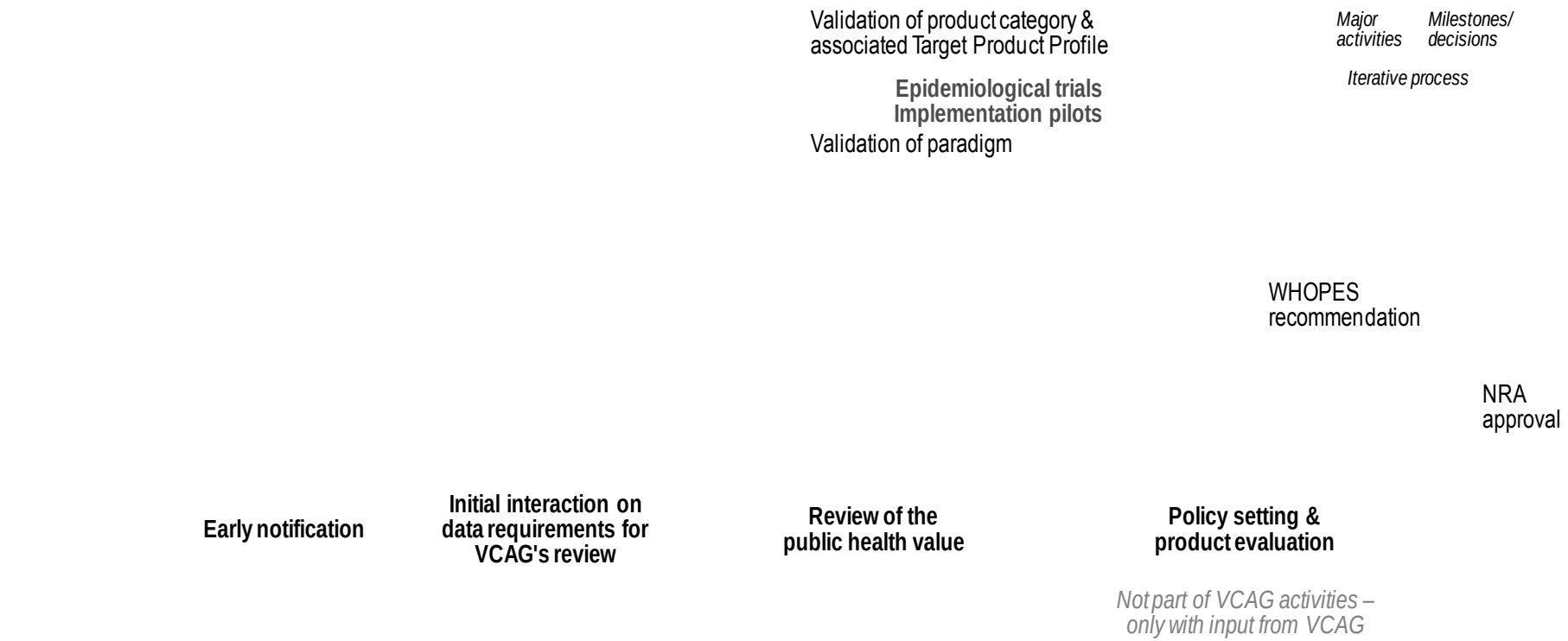
Potential benefit of VCAG to vector control

- Process to introduce new forms of vector control into public health practice
- Reduce uncertainty for innovators through this clarification
- Accelerate the process of public health implementation of new forms of vector control
- A forum for dialogue and guidance to innovators
- Evidence-based advice on epidemiological mode of action and public health value of new forms of vector control

VCAG - Dual reporting



Three VCAG major activities in the innovation process



VCAG input for policy development by MPAC

Limited evidence *Significant evidence*

Option 0: Additional evidence required
- Direct deliberations on data needs by MPAC/STAG and write-up of needs/pilots following VCAG's presentation

Option 1: Low complexity and/or narrow application
- Direct deliberations and a policy statement write-up by the committee following VCAG's presentation

Option 2: Some complexity or broader application
- Policy statement prepared overnight by "drafting committee", deliberations on next day

Option 3: Complex issue and/or broad application
- MPAC/STAG secretariat asked to prepare draft statement, to be circulated post-meeting to committee members

Option 4: Highly complex issue and broad application
- MPAC/STAG requests an Evidence Review Group, Expert Committee or Working Group to prepare a policy statement to be submitted at next meeting

Product evaluation by WHOPES in relation to VCAG

- WHOPES will develop standard definitions, testing/assessment methods (efficacy and safety) and quality control criteria of product
- WHOPES will be in close contact with the VCAG secretariat and participate in VCAG meetings/communications
- WHOPES will proceed to a larger consultation of the draft guidelines for finalization and publication
- WHOPES will build on VCAG's work, for a "first-in-class" commercial product

Membership of VCAG

- Provide high quality and well considered advice – an internationally recognized group (geography & gender balance to extent possible)
- Comprised of 11 members representing
  - Practical vector control skills
  - Vector biology
  - Ecology and management
  - Insecticides (product development) and insecticide resistance
  - Epidemiology of vector-borne diseases (malaria) – including statistics and study design
- Secretariat (GMP, NTD, other WHO departments, Regional Offices, and TDR) plus additional experts as needed

Selection of Members

- Open call – posted on WHO web site
- Members and Chairperson appointed by a panel
- Serve for 2 years - could be renewed but not more than 4 years out of every 6 years
- Chairperson invited to MPAC meetings as a resource person

VCAG working procedure

- Meet once a year (open and closed meetings)
- Possibility of *ad hoc* meetings depending on needs
- Open to observers – depending on agenda
- Closed – VCAG members and independent experts as needed
- Establishment of a web page
  - Draft procedural guidelines
  - Solicit for suggestions and comments – broader stakeholder
  - Disseminate recommendations and VCAG reports

Malaria Vector Control Beyond VCAG

Current malaria vector control policy environment

- Need potentially different skill sets
  - New vector control technologies (VCAG)
  - Insecticide resistance management (GPIRM)
  - Implementation of malaria vector control programmes
- According to RBM/HWG, failure of GFATM proposals are often related to last category
- RBM has a vector control working group (VCWG); active, vibrant but self-selected group, including partners with a financial stake
  - Although no mandate for policy setting, has at times attempted to do so
- Creation and implementation of MPAC rectifies existing confusion

VCAG not designed to address full range of malaria vector control policy issues

- VCAG:
  - Not a malaria-specific body; deals with all forms of vector control
  - Upstream proof-of-principle decision-making for new technologies
  - Members need knowledge of technology, chemistry, biology, and product development, not deep expertise in public health management
- Many other issues are malaria-specific and more downstream - connected to practical programme management at country level
  - Examples of topics include:
    - role of IRS in malaria epidemics
    - combining alternative LLIN distribution systems
    - LLIN procurement quantification in relation to lifespan of LLINs
  - Members need to be malaria experts with public health training and experience

Two options for MPAC decision: Option 1 - TEG

- Create a TEG for malaria vector control with “task forces” on perennial issues (e.g. insecticide resistance)
- Advantages:
  - Respond quickly to issues needing policy recommendations
  - Allow a synthetic view of issues for policy recommendations
- Disadvantages:
  - Goes against original concept of MPAC to rely more on ERGs
  - Since vector control issues are heterogeneous – requiring highly specialized skills – TEG may still need to convene an ERG – adding a third layer

Two options for MPAC decision: Option 2 - ERGs

- Convene time-limited ERGs as required
- Potential advantages:
  - Nimbly responsive without creating further architectural components
  - Convene highly specialized experts making recommendations directly to MPAC
- Disadvantages:
  - ERG might consider a single vector control policy recommendation without the broader context of vector control
  - With so many pending issues of vector control – means continuous convening and disbanding of ERGs – time consuming and not efficient

Request to MPAC

- In either case – VCAG would remain a distinct and smaller entity for upstream technologies – reporting directly to MPAC
- Request MPAC to consider carefully the needs of the global community for policy advice on vector control
- Recommend to WHO:
  - whether to establish a standing TEG for malaria vector control
  - or to convene time-limited ERGs as the need for policy decisions arises

I thank you for your attention

Plasmodium vivax Control & Elimination: Development of Global Strategy and Investment Case

September 2012

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1. Background

While *Plasmodium falciparum* is responsible for the vast majority of cases and deaths from malaria worldwide, *P. vivax*, the most geographically widespread species, is responsible for a large number of cases; it is increasingly recognized as a cause of severe malaria and even death. There are an estimated 2.6 billion people at risk of *P. vivax*; and the *World Malaria Report 2011* estimated 19.4 million *P. vivax* cases (range 13.4 to 24.6 million) in 2010, with the greatest number in Asia and Latin America. A number of countries have exclusively *P. vivax* transmission.

There are abundant data showing that transmission of *P. falciparum* is actually more responsive to malaria control measures. As a result, in areas where the two species co-exist, the scale up of integrated malaria control measures generally results in a shift in the balance between the two species such that *P. vivax* becomes the dominant species. This phenomenon can be attributed in part to a number of factors, including: 1) that *P. vivax* has a dormant liver stage (hyponozoite) that is not killed by any currently used antimalarial other than primaquine; 2) the earlier appearance of gametocytes during infection (even prior to the appearance of clinical symptoms); 3) the tolerance of its sporogonic cycle to lower temperatures; and 4) the vectors of *P. vivax* are exophilic and/or exophagic in some areas. Therefore, transmission control measures such as LLIN and IRS that were successfully implemented for *P. falciparum* may have less impact on reducing the *P. vivax* burden. Therefore more robust efforts are required for reduction and elimination of *P. vivax* transmission

There are numerous strains of *P. vivax* that are broadly grouped into temperate and tropical strains. *P. vivax* is increasingly becoming resistant to chloroquine, the primary drug used for treatment. To date, *P. vivax* has often been considered benign, with country and global policy and programming priority given to the prevention and control of *P. falciparum,* especially in Africa.

The prevention of *P. vivax,* especially in settings where vectors are exophilic and/or exophagic, has received inadequate attention. Although control strategies such as mass treatment with primaquine have been used successfully in some settings in Central Europe and Asia, inadequate documentation of safety and efficacy has prevented the wider uptake of such interventions. Parasitological diagnosis of *P. vivax* has been hampered by late development and slow roll out of highly sensitive and specific bivalent Rapid Diagnostic Tests (RDTs). WHO recommends standard treatment regimens for *P. vivax* based on available evidence, but radical

treatment of confirmed *P. vivax* infection with primaquine is not a policy recommendation in some transmission areas; where it is a policy, it is sometimes not prescribed by health workers due to fears of primaquine-induced haemolytic anaemia among patients with G6PD deficiency, for which reliable field tests are still not available.
Where primaquine is recommended, there is often confusion and disagreement over dosages and duration of treatment as well as approaches for ensuring full compliance -- which is required for complete cure (thereby preventing relapses). Overall, the long treatment duration is a barrier to uptake of primaquine.

There have been many technical guidance documents on malaria control in recent years, including updated guidelines for the Treatment of Malaria (WHO 2010), the operational manual on Universal Access to Diagnostic Testing (WHO 2011); Community-based Reduction of Malaria Transmission (WHO 2012); and an updated version of the Handbook for the Management of Severe Malaria (WHO 2012, in development). In addition, a global strategy -- the Global Malaria Action Plan -- was developed by the Roll Back Malaria partnership in order to harmonize partner efforts with regard to malaria control and elimination (RBM 2008). While each of these technical and strategy documents makes reference to *P. vivax*, there has never been a global strategy developed that articulates how to approach the problem of *P. vivax* at a global, regional and country levels, and that proposes time-bound objectives for these efforts.

Researchers and academics continue to call for more support for basic and operational research in diagnostic testing and treatment. There are on-going research consortia focused on *P. vivax*, including the i-VAX research Consortium, and PregVax- *Plasmodium vivax* Malaria in Pregnancy Project, both of which are coordinated by the Barcelona Centre for International Health Research (CRESIB). There is focus on *P. vivax* elimination by the Asia Pacific Elimination Network. The evidence and experience generated from these groups will support the development of a global strategy for prevention and control of *P. vivax* in the short to medium term, and the identification of research gaps.

There is now a growing need and demand for a comprehensive global strategy and plan with operational guidance to support containment and elimination of P. *vivax* and acceleration of research and development of new tools. This global strategy would be based on: 1) a review of the most recent evidence on programmatic effectiveness of different prevention, control and surveillance interventions of vivax malaria; 2) a review of the current policy and practice on *P. vivax* service delivery at country and regional level; 3) a review of *P. vivax*-specific recommendations that are dispersed across various WHO guidance documents and 4) an analysis of on-going research with regard to *P. vivax*, and how results emerging from such work are likely to influence control and elimination strategies over the next decade, and what research gaps remain; and 5) an economic analysis of the requirements for *P. vivax* control and elimination.

2. Goal

To develop a global strategy and investment case for *P. vivax* control and elimination

3. Specific Objectives

1) Conduct country case studies and document regional overviews
2) Review the current global epidemiology of *P. vivax*
3) Review the diagnostic techniques for *P. vivax*
4) Review the drugs and treatment regimens for radical cure of *P. vivax*
5) Review the mass treatment and chemoprophylaxis options for the control of *P. vivax*
6) Review the malaria vector control interventions that are cost-effective to reduce *P. vivax* transmission
7) Review the cost of *P. vivax* control and the potential economic benefits of control in affected countries
8) identify gaps between expert opinion/treatment recommendation and knowledge/attitudes and behavior of prescribers and develop strategies to close these gaps
9) Identify the evidence gaps and define research priorities and programs on *P. vivax*
10) Prepare a Global Strategy and investment case for *P. vivax* Control and Elimination

4. Method of work

1) Establish a small steering committee to develop a more detailed plan of work and identify topics and countries for the reviews
2) Establish an evidence review group (ERG) reporting to the Malaria Policy Advisory Committee (MPAC)
3) Recruit consultant to WHO secretariat in preparatory work for the ERG
4) Support WHO regions and countries to prepare country case studies and regional overviews
5) Provide APWs for the conduct reviews in different thematic areas for *P. vivax* control & elimination
6) Conduct a wider stakeholder and partner consultation to get input on the Strategy and Investment Case
7) Present Strategy, Investment Case to the Malaria Policy Advisory Committee (MPAC) for review and endorsement
8) Design and implement knowledge management and launch strategies for the above-mentioned documents

5. Outputs/ Products

1) Regional overviews with Country case studies on *P. vivax*
2) Thematic peer reviews of key areas of *P. vivax* management and containment
3) Global Strategy for *P. vivax* Control and Elimination
4) Costed business plan / investment case for the control and elimination of *P. vivax*

5) Provide specific recommendations on the target audience, key contents, core interventions which will lead to the later development of a WHO Operational manual on the control and elimination of *P. vivax*.

Other
Chapter on *P. vivax* in World Malaria Report 2013
Web page on the WHO site http://www.who.int/malaria/en/

6. Collaborating alliance on *P. vivax* control and elimination

- **Proposed Key regions and countries (final list subject to confirmation):** PAHO: Brazil, Peru, Guatemala, Venezuela; SEARO: India, Indonesia, DPRK, Sri Lanka and Myanmar; EURO: Azerbaijan and Tajikistan; EMRO: Afghanistan and Pakistan; AFRO Ethiopia and Eritrea; WPRO: China and Papua New Guinea.
- **Proposed Steering Group:** Barcelona Centre for International Health Research-Spain; Medicines for Malaria Venture (MMV); Centres for Disease Control and Prevention (CDC-USA); Eijkman-Oxford Clinical Research Unit –Jakarta
- **Other Key Technical Partners:** National Institute for Research and Indian Council for Medical Research - India; Martinowsky Institute - Russia; Centres for Disease Control (CDC) - Shanghai; Eijkman-Oxford Clinical Research Unit –Jakarta; Mahidol-Oxford University - Thailand; Tropical Medicine Foundation of Amazonas – Brazil; University of Cali
- **Key Development Partners:** AusAID; China; DFID; Gates Foundation; Global Fund; Russian Federation; USAID; and others.
- **Key Private Sector Partners**: (SANOFI, IPCA, GSK and others)

7. Time line 2012 and 2013 and estimated budget

Vivax strategy development: Time lines 2012 and 2013 and estimated budget

Activities 2012	July	Aug	Sept	Oct	Nov	Dec	Units	Unit cost (USD)	Total cost (USD)
WHO working group & global network	X	X	X	X	X	X	6	1000	6,000
Secretarial Support	X	X	X	X	X	X	6	3000	18,000
Regional overviews and country case studies (SEARO, PAHO, WPRO, EMRO, EURO, AFRO)*				X	X	X	6	25,000	150,000
Thematic Reviews	X	XX	X	X			5	25,000	125,000
Total									**$299,000**

*Possible countries include: Brazil, Venezuela, Guatemela, Peru, India, Indonesia, DPRK, Myanmar, Sri Lanka, Azerbaijan, Tajikistan, Afghanistan, Pakistan, Ethiopia, Eriteria, China, PNG

Activities 2013	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sept	Units	Unit Cost (USD)	Total cost (USD)
WHO working group & global network	X	X	X	X	X	X	X	X	X	9	1,000	9,000
Secretarial Support	X	X	X	X	X	X	X	X	X	9	3000	27,000
Draft global malaria strategy and plan	X	X	X							1	50,000	50,000
Working group meeting			X							1	75,000	75,000
Stakeholders & Partners meeting						X				1	75,000	75,000
Publication, Knowledge Management and Launch									X	1	100,000	100,000
Total												**$336,000**
Grand total												**$635,000**

Technical Expert Group on Malaria Chemotherapy

Terms of Reference

I. Background and rationale

The Malaria Policy Advisory Committee (MPAC) has been constituted to provide independent advice to the Global Malaria Programme (GMP) of the World Health Organization (WHO) for the development of policy recommendations for the control and elimination of malaria. The mandate of MPAC is to provide strategic advice and technical input aligned with the Global Technical Strategy for Malaria 2016-2030 as part of a transparent, responsive and credible policy setting process, and extends to all aspects of malaria control and elimination. In addition to the MPAC, standing Technical Expert Groups (TEGs) have been established to provide WHO/GMP with advice within specific technical areas. WHO/GMP recognises that a standing TEG on malaria chemotherapy is needed to review new evidence on malaria chemotherapy, draft recommendations on necessary policy, and set research priorities.

II. Role and functions of the TEG on malaria chemotherapy

The TEG is constituted by and provides advice to WHO/GMP. The TEG on malaria chemotherapy is tasked with reviewing evidence, providing guidance and making draft recommendations on issues of malaria diagnosis and use of antimalarial medicines both for treatment and prevention. The TEG on malaria chemotherapy will function in close collaboration with the TEG on antimalarial drug efficacy and response because the use of antimalarial medicines is inextricably linked with the development of resistance and the appropriate response.

The responsibilities of the TEG on malaria chemotherapy will be to:

i. review new evidence on malaria case management and define the implications for strategy, policy and planning; specific areas include:
   - Policies on malaria diagnostic testing
   - Review of evidence on safety and efficacy of antimalarial medicines and their use, defining their role in the treatment and/or prevention of malaria within the context of public health;

ii. formulate technically sound and feasible policy on the therapeutic use of antimalarial medicines based on evidence generated through research and experiences from field operations;

iii. when requested by WHO/GMP, may also review evidence and formulate policy on preventive uses of antimalarial medicines;

iv. propose to WHO/GMP norms and standards in malaria chemotherapy, and develop guidelines which provide simple and straightforward treatment recommendations based on sound evidence that can be applied even in severely resource-constrained settings;

v. identify gaps in evidence and suggest specific priority areas of research and development in the field of malaria chemotherapy.

III. Membership and structure of the TEG

The TEG will comprise 10 core members, and up to 5 co-opted members to meet the requirements for expertise depending on the specific issues which need to be addressed. They shall serve in their personal capacity and represent the range of disciplines relevant to the area of work. The membership of the TEG should include acknowledged experts on malaria chemotherapy and public health from

around the world, and policy makers and implementers from endemic countries. The TEG composition should also strive for appropriate geographical representation and gender balance. In addition, the TEG should include members who have worked or are currently working as national malaria control programme managers with specific expertise in development of policies in malaria case management.

Members of the TEG must have excellent technical knowledge of malaria, scientific publications in peer-reviewed journals and more than 10 years of experience in at least one of the areas listed below.

The following areas of expertise should be represented in the TEG:

- Epidemiology and public health
- Clinical management - Paediatrician /adult physician
- Clinical trials of antimalarial medicines
- Pharmacology and therapeutics
- Pharmacokinetics of antimalarial drugs
- Pathology and pathophysiology of malaria
- Guidelines development methodology

Following an open invitation to submit nominations, the TEG members will be selected by a nomination panel appointed by WHO/GMP. Members of the TEG shall be appointed to serve for an initial term of up to three years, renewable once, for a period of up to an additional three years.

Membership in the TEG may be terminated by WHO/GMP, including for any of the following reasons:

- failure to attend two consecutive TEG meetings;
- change in affiliation resulting in a conflict of interest;
- a lack of professionalism involving, for example, a breach of confidentiality.

Prior to being appointed as a TEG member and prior to renewal of term, and prior to each meeting, nominees shall be subject to a conflict of interest assessment by WHO, based on information that they disclose on the WHO Declaration of Interest (DOI) form. In addition, TEG members have an on-going obligation throughout their tenure to inform WHO/GMP of any changes to the information that they have disclosed on the DOI form. Summaries of relevant disclosed interests that may be perceived to give rise to real or apparent conflicts of interest will be noted during the meeting and posted on the WHO/GMP website.

In addition, prior to confirmation by WHO of their appointment as TEG members, TEG nominees shall be required to sign a WHO confidentiality agreement. Although all papers presented at the TEG may be made publicly available on the WHO/GMP website, pre-publication manuscripts or confidential documents will be clearly labelled as such and will only be provided to TEG members for discussion.

IV. Responsibilities of TEG members

Members of TEG have a responsibility to provide WHO/GMP with high quality, well considered, evidence-informed advice and recommendations on matters described in these ToR. The TEG has no executive or regulatory function. Its role is to work with the WHO/GMP Secretariat to provide draft recommendations to WHO/GMP.

TEG members may be approached by non-WHO sources for their views, comments and statements on particular matters with regard to antimalarial chemotherapy and asked to state the views of TEG or details related to TEG discussions. TEG members should refer all such enquiries to WHO/GMP.

V. Structure

The TEG will have a chairperson who will be selected from among the appointed TEG members. Each chairperson will serve for 3 years, renewable once. Rapporteurs will be elected at each meeting as required. The Prevention, Diagnosis and Treatment (PDT) unit, WHO/GMP will serve as secretariat for the TEG on malaria chemotherapy.

VI. Working Procedures

The TEG will be convened ideally once per year by WHO/GMP and have additional meetings and/or teleconferences as needed to ensure timely review of new evidence. WHO/GMP will provide support for travel and accommodation for the members of the TEG to participate in TEG meetings. Staff from WHO Regional Offices and other WHO departments may be invited as members of the Secretariat to participate in TEG meetings and deliberations as appropriate. Additional experts may be invited to participate in meetings, also as appropriate, to ensure that a sufficiently broad base of expertise is available for the specific agenda items at each meeting. Key partner organizations can be invited as observers at their own expense. However, only TEG members can participate in formulation of recommendations by consensus. Observers shall not take the floor unless requested to do so by the chairperson.

Decisions on TEG recommendations to WHO/GMP will, as a rule, be taken by consensus. In the exceptional situation that consensus cannot be reached the chairperson shall report the majority and minority views. It is also the chairperson's responsibility to ensure there is clarity for TEG members on what exactly is being decided.

In addition to attendance at TEG meetings, active participation will be expected from all TEG members throughout the year, potentially including participation in Evidence Review Groups, video and teleconferences, as well as interactions via e-mail. Review of documents may also be solicited. TEG members may be requested to participate as observers in other important WHO departmental or cross-departmental meetings. It is estimated that the time commitment required from TEG members is up to a total of three weeks over the course of a year.

Recommendations from the TEG will be referred to WHO/GMP for consideration. The Chairperson of TEG may be invited as a resource person to MPAC meetings at which chemotherapy or diagnosis issues are being discussed.

VII. Dissolution of TEG

The relevance and terms of reference of the TEG will be assessed regularly by WHO/GMP.

Chemotherapy Technical Expert Group – Draft Terms of Reference

Meeting of the Malaria Policy Advisory Committee
Geneva, 11-13 September, 2012

Dr. Peter Olumese
WHO / GMP

World Health Organization

GLOBAL MALARIA PROGRAMME

Background and rationale

- The MPAC at it's inaugural meeting* recognised and recommended that the standing TEG on malaria chemotherapy, be maintained as there is now - and will be in the future - a continual need to review new evidence on malaria chemotherapy
- The TEG on malaria chemotherapy
  - is constituted by and reports to the MPAC
  - will function in close collaboration with the TEG on antimalarial drug resistance and containment, as the use of antimalarial medicines is inextricably linked with the development of resistance and its containment.

*_WHO Malaria Policy Advisory Committee and Secretariat: Inaugural meeting of the malaria policy advisory committee to the WHO: conclusions and recommendations._

Malaria Journal 2012, 11:137.

Role and functions

The responsibilities of the TEG:

- based on evidence generated through research and experiences from field operations
  - formulate technically sound and feasible policy on the therapeutic and preventive use of antimalarial medicines;
  - propose norms and standards in malaria chemotherapy, and develop guidelines which provide simple and straightforward treatment recommendations that can be applied even in severely resource-constrained settings;
- review new evidence on malaria case management and define their implications for strategy, policy and planning;
- identify gaps in evidence and suggest specific priority areas of research and development in the field of malaria chemotherapy.

Membership and structure of the TEG

- The TEG will comprise 10 core members and up to 5 co-opted members, serving in their personal capacity
- The membership will include experts on malaria chemotherapy, public health, policy makers and implementers from endemic countries.
- The following areas of expertise should be represented:
  - Epidemiology and public health
  - Clinical management - Paediatrician /adult physician
  - Clinical trials of antimalarial medicines
  - Pharmacology and therapeutics
  - Pharmacokinetics of antimalarial drugs
  - Pathology and pathophysiology of malaria
  - Guidelines development methodology

Membership and structure of the TEG

- The TEG members
  - will be selected by a nomination panel appointed by MPAC and GMP.
  - shall be appointed to serve for an initial term of up to three years, renewable once, for a period of up to an additional three years.
  - appointment may be terminated by WHO, including for any of the following reasons:
    - failure to attend two consecutive TEG meetings;
    - change in affiliation resulting in a conflict of interest;
    - a lack of professionalism involving, for example, a breach of confidentiality
  - prior to being appointed or renewed, shall be subject to a conflict of interest assessment by WHO, based on the WHO Declaration of Interest procedure,
  - shall also be required to sign and abide to the WHO confidentiality agreement

Structure

- The TEG will have 2 co-chairpersons selected from among the appointed members.
- Each chairperson will serve for 3 years, renewable once.
- At least one member of MPAC should serve as a member of the TEG.
- Rapporteurs will be elected at each meeting as required.
- Diagnosis, Treatment and Vaccines unit (DTV), will serve as secretariat
- GMP with approval of the chairpersons, may invite
  - observers to the TEG meetings, including representatives from non-governmental organization, international professional organizations, technical agencies, and donor organizations.
  - additional experts, and Technical Resource persons, as appropriate, to contribute to specific agenda items
- Relevant staff from WHO Headquarters (other departments), and Regional Offices will attend as members of the Secretariat

Working Procedures

- The technical focal point in the DTV unit will work with the chairpersons to develop a plan for routine operations of the TEG.
- The TEG will meet and/or conduct teleconferences as needed to ensure timely review of new evidence.
- When practicable, the TEG meetings will be scheduled in association with the TEG on drug resistance and containment and will have a joint session when indicated.
- Specific topics may be addressed by ad-hoc Evidence Review Groups (ERG), and the TEG will take note of ERG report and recommendation in their reviews of the evidence and further deliberations.
- Decisions on TEG recommendations will, as a rule, be taken by consensus. In the exceptional situation that consensus cannot be reached the chairperson shall report the majority and minority views.

Dissolution of TEG

- The relevance of the TEG will be assessed regularly by the MPAC.
- The terms of reference will also be reviewed once a year by the TEG.
  - Any proposed changes in the ToR must be submitted to and approved by the MPAC