



Artemisinin-based suppositories

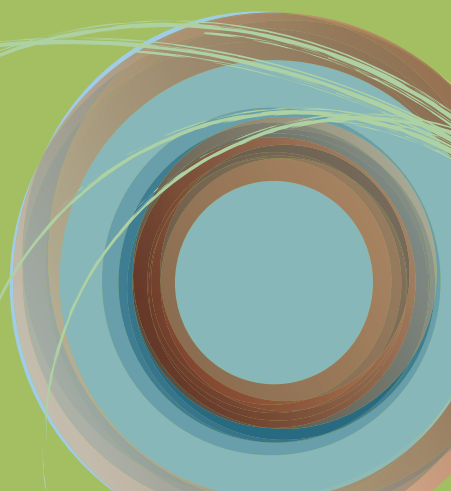
Use of rectal artemisinin-based suppositories
in the management of severe malaria



Report of a WHO Informal Consultation



World Health
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Global Malaria Programme

Artemisinin-based suppositories

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Report of a WHO Informal Consultation, 27–28 March 2006



**World Health
Organization**

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1. Background

Intrarectal administration represents a promising administration route of anti-malarial medicines in the field, and is especially convenient for patients unable to swallow and when parenteral formulations are unavailable or cannot be administered. *Plasmodium falciparum* malaria is associated with severe morbidity and, in the absence of early diagnosis and effective treatment, it may be fatal. The cumulative probability of death increases with each hour's delay in treating the disease (1).

The immediate objective of therapy in severe malaria is to save life and to reduce the risk of serious complications. This can be achieved by rapidly reducing the total parasite biomass, and the artemisinin derivatives are of special value as they achieve a faster reduction in parasitaemia by acting principally on young parasites, preventing their development into the more mature pathological stages which adhere to the vascular endothelium and in this way are sequestered in the microvasculature of vital organs (2).

The correct use of effective antimalarial medicines should not only shorten the duration of malaria illness and reduce the incidence of complications and the risk of death, but should also safeguard the medicine against development of resistance. The rectal administration of antimalarial medicines is simple and can easily be done by non-medical persons, especially in rural peripheral settings at different levels of health care (community or health facility). In addition, even when medicine can be given intravenously, patient discomfort and inconvenience, staff time, and risks such as overhydration and thrombophlebitis, may make parenteral administration less attractive than rectal administration.

In malaria-endemic countries, patients frequently present with severe malaria and require urgent therapy. However, at health institutions, particularly at the peripheral level, and even in some instances at the district level, facilities may not exist for parenteral administration, and yet oral dosing is precluded by the patient's altered level of consciousness or protracted vomiting. In these circumstances, emergency treatment with artemisinin-based suppositories can be instituted as pre-referral therapy while patients await transfer to a hospital, a process that may take many hours or even days (3). If referral to a higher level of care is not possible, this therapy may be the only alternative for severely ill malaria patients.

Results from a variety of clinical studies have indicated that artemisinin-based suppositories can be used for initial emergency and curative treatment in uncomplicated (4–6), moderate (7, 22), severe (9–17), and cerebral malaria (18–20). The compounds of therapeutic interest are artesunate, artemisinin and artemether, and their common metabolite, dihydroartemisinin. All reduce parasitaemia significantly faster than quinine or any other drug used for malaria in parenteral, oral and suppository formulations. Given the high level of malaria mortality, particularly in children in Africa, these compounds in suppository formulation may constitute a major advance when given as pre-referral therapy by preventing the evolution of the disease to its severe form and complications, thus saving the patient's life and making it possible for curative therapy to be instituted.

However, the World Health Organization (WHO) does not recommend the sole use of an artemisinin derivative except for the treatment of patients with severe falciparum malaria. The treatment guidelines drawn up by WHO emphasize the need for follow-up treatment of severe malaria with a complete course of an effective artemisinin-based combination therapy (ACT) in order to protect the therapeutic lifespan of the artemisinin derivatives. Measures should be taken to ensure follow-up treatment with an ACT in order to reduce the risk of shortening the lifespan of the artemisinin derivative if used as a monotherapy.

In the light of these considerations, WHO convened an informal consultation on the use of rectal suppositories of artemisinin derivatives in the management of severe malaria. The consultation was held at WHO headquarters in Geneva from 27 to 28 March 2006. The participants reflected a wide range of expertise and the meeting brought together experts in clinical pharmacology, including clinicians, pharmacists and field researchers. Its purpose was to enable a group of scientific and clinical experts to review all the evidence on the efficacy and safety of artemisinin-based suppositories, given in single and multiple doses, and to make recommendations on their clinical use for the treatment of severe malaria, bearing in mind concerns regarding the development of *P. falciparum* resistance to artemisinin when such medicines are used as a monotherapy. A list of the participants in the consultation appears in the Annex.

2. Review of the evidence

2.1 General findings

2.1.1 Artemisinin derivatives are effective against multidrug-resistant *P. falciparum* malaria, and, in the treatment of severe malaria, they have been shown to be either equivalent or superior to quinine when administered parenterally. It has also been shown that artemisinins administered by the rectal route are absorbed rapidly, and, despite considerable inter-individual pharmacokinetic variability, are effective in malaria (5, 15, 17, 21–24). Rectal artesunate has been used mostly in South-East Asia, especially China, Thailand and Viet Nam, but in recent years its use has been rapidly expanding in other regions, particularly in Africa (7, 15, 20, 22, 23, 28).

2.1.2 Rectal dihydroartemisinin, in combination with other antimalarials, has also been used to treat cases of severe malaria (25, 26). Rectal artemisinin and artemether have been proven to be safe and efficacious compared with parenteral quinine in the treatment of severe malaria in both children and adults (10, 11, 18–20, 26–28).

2.1.3 There are inherent difficulties in the clinical diagnosis of malaria, but information from the large-scale use of artemisinin-based suppositories in Africa, where practical clinical definitions of nil per os status – repeated vomiting, inability to eat/drink/suck, recurrent convulsions, obtunded response to painful stimuli, and coma or absent motor response – have been used in large-scale community-based trials, has shown that there is a high correlation (>75%) between *P. falciparum* malaria and these clinical signs.

2.1.4 Early treatment in high parasite biomass infections is likely to result in a survival benefit. Intervening rapidly in severe malaria changes the prognosis and the subsequent outcome. Artemisinin-based suppositories have been widely used in South-East Asia, notably in Viet Nam, for the reduction of malaria mortality, and a number of studies using artemisinin suppositories have been conducted over the years in most malaria-endemic regions. Published and unpublished individual patient data have been reviewed and analysed to provide scientific evidence for the clinical use of artemisinin-based suppositories (Figure 1).

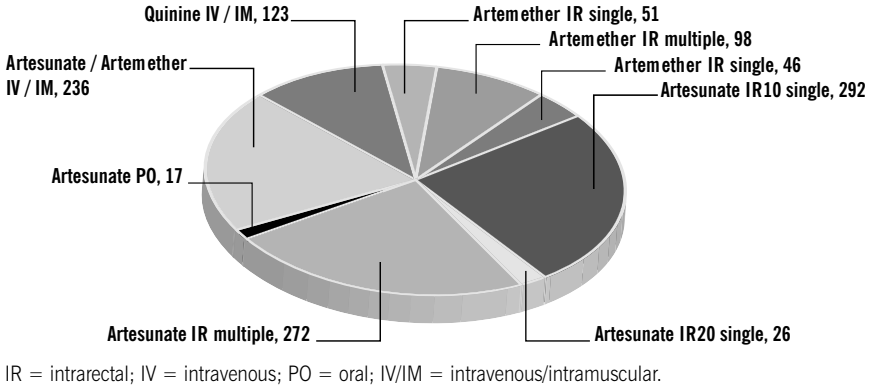


Figure 1. Individual patient data provided for analysis, by treatment group

2.2 Efficacy

2.2.1 The experts reviewed a large body of efficacy and safety data from clinical trials carried out in Asia and Africa (Figure 2). The integrated analysis demonstrated that artemisinin-based suppositories achieved a parasite response that was equivalent to parenterally administered artemisinins at 12 hours following

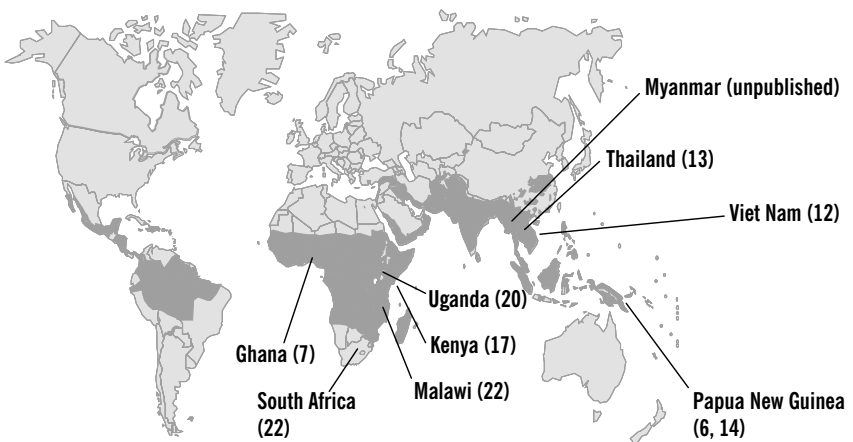


Figure 2. Studies included in the integrated analyses

initiation of treatment. The reduction in parasitaemia at 12 and 24 hours was consistently superior to that achieved by quinine, regardless of the route of administration or the number of doses of artemisinin derivative given.

2.2.2. The largest body of efficacy and safety evidence is related to artesunate suppositories (591 patients) and artemisinin suppositories (144 patients). The data analysed showed that multiple-dose schedules over a 24-hour period provided no added benefit over a single-dose treatment over the same period for either artesunate or artemisinin-based suppositories (Figure 3).

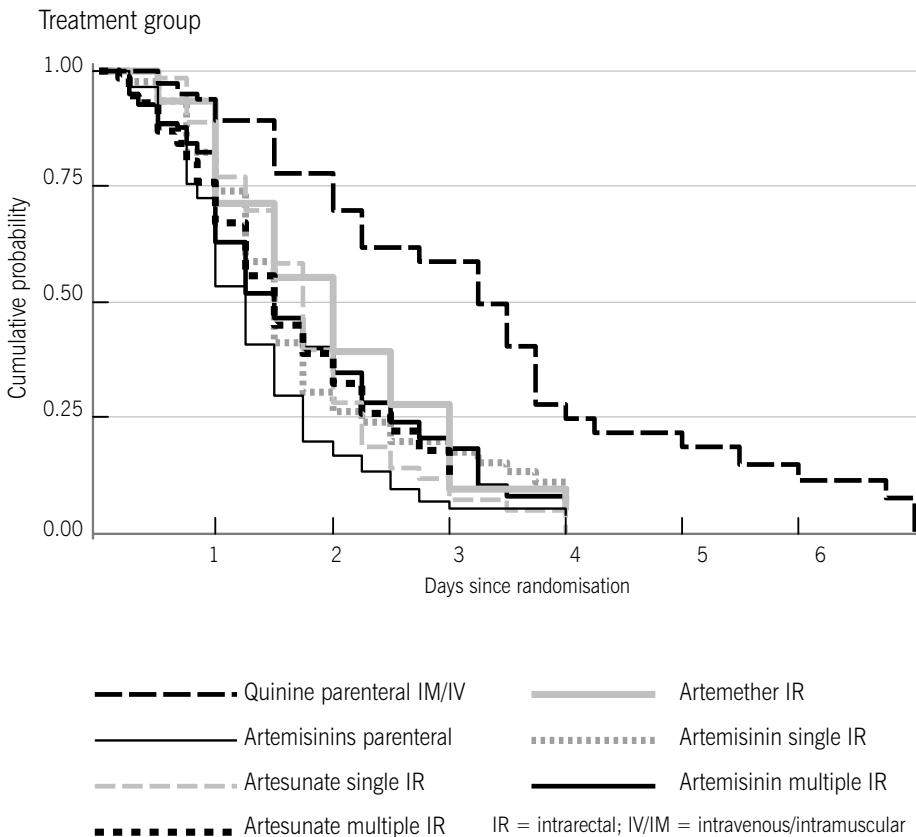


Figure 3. Cumulative probability of having parasitaemia Quinine vs. Artemisinins

2.2.3 In all multiple-dose studies conducted with artesunate suppositories, a mean total dose of 7.9 mg/kg over 12 hours was given, which is lower than the dose in the studies using a single dose of artesunate, where the mean dose was 8.5 mg/kg. The parasite reduction ratio over 12 hours was 32.7% with multiple dosing and 57.7% with a single, higher mean dose. An adjusted logistic regression model identified the total dose over 24 hours as a variable independently influencing the odds of achieving a 90% reduction in parasitaemia at 24 hours (odds ratio [OR] 1.14, $p = 0.000$) in a patient with moderately severe or severe falciparum malaria.

2.2.4 A single dose of rectal artesunate was superior in parasite response over 24 hours to parenteral quinine (hazard ratio [HR] 2.98, $p < 0.0001$; 95% confidence interval [CI] 1.79 – 4.95). These results were consistent irrespective of age, severity of disease, baseline parasitaemia and region of use. Equally, a single dose of rectal artemisinin was superior in parasite response over 24 hours to parenteral quinine (HR 2.96, $p = 0.005$; 95% CI 1.37 – 6.27).

2.2.5 There was no difference in clinical outcomes – time to regaining consciousness, time to return to per os status or to sit unaided – or in fever clearance time between treatment with an artemisinin-based suppository and parenteral treatment with quinine.

2.3 Safety

2.3.1 In the experts' review, the data provided on safety in relation to individual patients were primarily clinical. Where laboratory information was available, the schedules of evaluation were not consistent between the studies, making comparisons difficult. Because the methodology of trials included in the pooled analysis had not been prospectively standardized, there existed substantial inter-trial differences in defining, assessing, reporting and classifying adverse events. In addition, reliably distinguishing drug side-effects from manifestations of malarial infection (especially severe malaria) is often difficult and largely dependent on a subjective clinical assessment performed at the time of the event. These difficulties were partially addressed by contact with the principal investigators and reassessments of the individual patient data from the case record forms, where archived data were accessible. Each reported event was thus reclassified by the clinical investigator as being unlikely, possibly, probably or definitely due to the treatment. Those events considered possibly, probably or definitely drug-related were then all reclassified as "potentially drug-related" for the purposes of the pooled analysis.

2.3.2 A total of 306 adverse events were reported in 194 patients (16.7%) out of 1162 adults, adolescents and children exposed to the different drugs in the pooled analyses. Excluding the 5 patients who received rectal artesunate and quinine simultaneously and the 253 patients who received parenteral or oral artemisinins, there were 196 adverse events in 140 out of 786 patients exposed to the rectal artemisinin suppositories and 67 adverse events in 30 out of 123 patients treated with parenteral quinine.

2.3.3 Of the 196 adverse events reported in patients treated with artemisinin-based suppositories, 37 events in 21 patients were considered to be potentially drug-related, 105 events in 69 patients were not considered drug-related, and 54 events in 50 patients could not be assigned cause or were not assigned causality. Therefore, 2.7% (21/786) of all rectally artemisinin-treated patients were thought to have had a potentially drug-related adverse event, 8.8% (69/786) had a non-drug-related adverse event and an additional 6.4% (50/786) of rectally artemisinin-treated patients had an adverse event of uncertain causality. By comparison, 27 adverse events occurring in 11 patients of the 123 quinine-treated patients were considered drug-related, which means that 8.9% (11/123) of quinine-treated patients experienced an adverse event that was considered potentially drug-related.

2.3.4 For the rectally administered artemisinins, approximately 29.7% (11/37) of adverse events considered drug-related were defined as affecting the body as a whole (including fever, headache and unspecified pain), 2.7% (1/37) were related to the nervous system (dizziness), 8.1% (3/37) were related to the special senses (hearing impairment) and 48.6% (18/37) related to the gastrointestinal system (vomiting, nausea, diarrhoea, constipation, abdominal pain). For quinine, 25.9% (7/27) of adverse events were considered to be related to the nervous system, 29.6% related to the digestive system, 18.5% (5/27) were defined as affecting the special senses/hearing, and 14.8% (4/27) related to the haemopoietic system.

2.3.5 A meaningful comparison of safety profiles between the different artemisinin products was beyond the scope of this analysis. It should be noted that most of the safety data presented were derived from patients treated with either rectal artesunate (591) or artemisinin suppositories (144) and extrapolation from these safety data should be made with caution.

2.3.6 Despite the methodological limitations of this analysis, overall, the safety profile of artemisinin-based suppositories in the studies analysed appeared to be benign. The total incidence of adverse events considered by clinicians to be possibly drug-related was estimated at between 2.7% and 9.0% of

all rectal artemisinin-treated patients, compared with 8.9% of quinine-treated patients. The majority of possibly drug-related adverse events in rectal artemisinin-treated patients either involved the gastrointestinal system or were generalized and non-specific in nature and were not severe. In general, the safety profile of the artemisinin drugs (when given by other routes of administration) appears to be excellent (30, 31). The data from this analysis therefore do not suggest that there are any additional concerns related specifically to the rectal route of administration (Table 1)

Table 1. Adverse events noted in patients treated with suppositories and parenterally, by treatment group

	Rectal artemisinin	Non-rectal artemisinin comparator	Non- artemisinin comparator (quinine)	TOTAL
Total no. of patients included in analysis	786	253	123	1162
Total no. (%) of patients in whom one or more adverse event reported	140 (18)	24 (9)	30 (24)	194
Total no. of adverse events	196	43	67	306
Classification (aetiology)				
Possibly drug-related	37	14	27	78
Not likely to be drug-related	105	28	40	173
Unable to be classified	54	1	0	55
Classification of possibly drug-related events according to body system				
Generalized	11	1	0	12
Neurological	1	1	7	9
Digestive	18	10	8	36
Urogenital	1	1	0	2
Haemopoietic	3	1	4	8
Special senses (hearing)	3	0	5	8
Other	0	0	3	3

3. Conclusions

3.1 Artemisinin-based suppositories, particularly artesunate and artemisinin suppositories, are safe and efficacious for pre-referral treatment of severe malaria. The clinical evidence provided by the data analysed is overwhelmingly in favour of their use because they rapidly eliminate parasites and are safe, although there is not yet proof that such an intervention reduces mortality. Most of the clinical data are derived from studies conducted using artemisinin and artesunate suppositories. This safety and efficacy information cannot, therefore, yet be extrapolated to suppositories containing other artemisinin derivatives and those of different formulations.

3.2 Substantially less information exists on artemisinin suppository bioavailability than on artesunate suppository bioavailability; more information on artemether and dihydroartemisinin suppositories is required before any conclusions can be drawn about these or any other formulation of artemisinin suppositories. Moreover, no study has been carried out that provides a direct assessment of bioavailability between the different rectal artemisinin-based derivatives.

An assessment of the pharmacokinetic information (for all the routes of administration) needs to be undertaken in order to identify the minimum inhibitory drug concentrations that should be achieved in order to allow the comparison of different artemisinin suppository formulations. The assessment will require guidance on the minimum standards for all the other artemisinin derivative and artesunate-based suppositories.

3.3 The clinical indications for the use of rectal artemisinin-based suppositories as pre-referral treatment should be limited to acute, suspected life-threatening malaria, where patients cannot take medicines by mouth and where patients cannot access injectable treatment. There is, at present, insufficient evidence to demonstrate that rectal artesunate/artemisinin is as good as intravenous or intramuscular options in the complete treatment of severe malaria.

3.4 An analysis of the integrated data indicates that multiple dosing schedules show no superiority over a single-dose treatment for either artesunate or other artemisinin-based suppositories. A single dose of treatment should, therefore, be sufficient, prior to the patient's immediate referral to a hospital or health facility as soon as possible for definitive therapy. If the patient responds and referral is not possible, rectal treatment should be continued once daily until the

patient can tolerate oral medication, at which point a full course of the nationally recommended artemisinin-based combination therapy for uncomplicated malaria should be administered.

3.5 Data available from Viet Nam, Bangladesh, Tanzania and Ghana show that deployment of rectal suppositories is feasible at the community level. In Viet Nam, the drugs were provided following a rapid diagnostic test; in different resource-poor settings in Africa, they have been provided on the basis of clinical diagnosis of the danger signs (see paragraph 2.1.3 above), which correlates highly with laboratory diagnosis of *P. falciparum* malaria in children. It has therefore been recognized that deployment of rectal suppositories as pre-referral treatment in the community is feasible and can be successful. It is not dependent upon the literacy of the population.

However, the experiences of Viet Nam, Cambodia, Tanzania and Bangladesh in deploying suppositories at the community level have shown that the implementation of artemisinin-based suppository treatment should be accompanied by a minimum package of activities that should include:

- engaging communities and raising the awareness not only of community-based health providers and medical personnel but also of communities;
- training community-based health providers in the clinical recognition, diagnosis and treatment of malaria;
- establishing a system of continuous supervision and monitoring of community-based health providers;
- providing supportive job aides; and
- establishing a clear link between communities and health facilities.

3.6 WHO should engage with the national regulatory authorities that have registered artemisinin-based suppositories and with pharmaceutical manufacturers to ensure that artemisinin-based suppository treatment is used and marketed specifically as pre-referral treatment, followed by a course of ACT, and that the use and registration of such suppositories as stand-alone monotherapy is discouraged and disallowed. Such use could contribute to the development of artemisinin resistance, and it is therefore essential that artemisinin-based suppositories are used in conjunction with an artemisinin-based combination treatment designed to maximize cure rates and minimize the selection of artemisinin-resistant parasites (32).

4. Policy recommendations

- 4.1 Artesunate or artemisinin-based suppositories are recommended for use as pre-referral treatment for severe malaria combined with either (i) referral of the patient to a facility where parenteral treatment with artesunate, quinine or artemether can be instituted; or (ii) follow-up treatment with a full course of ACT.
- 4.2 Artesunate or artemisinin-based suppositories should be both packaged for marketing and used for pre-referral treatment of severe malaria as a single dose (or, in the event that referral is not possible, as a single daily dose) until parenteral treatment or oral ACT treatment is instituted.
- 4.3 Artesunate or artemisinin-based suppositories used as pre-referral treatment for severe malaria should be deployed where parenteral pre-referral treatment is difficult or not possible at peripheral health institutions, and at the community level in the context of home management of malaria.

5. Identified research gaps

A number of research gaps were identified during the informal consultation, and the lack of sufficient data in several key areas prevented conclusions from being drawn for the deployment of artemisinin-based suppositories. Some of these areas are:

- 5.1 The impact of deploying artemisinin-based suppositories for pre-referral treatment of severe malaria on the overall strategy of home management of malaria.
- 5.2 The comparative efficacy, safety and bioavailability of different artemisinin-based suppositories.
- 5.3 Basic community-level research into such aspects as acceptability, the best dispensers, and community health education to ensure effective deployment of artemisinin-based suppositories within communities.

5.4 Development of a combination suppository.

5.5 Demonstration of the efficacy and safety of an artemisinin-based suppository in the full treatment of severe malaria at the health facility as an alternative to parenteral treatment.

5.6 Establishing the dosing regimen where referral is not possible.

5.7 Post-marketing surveillance – includes monitoring of efficacy, safety and resistance.

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Annex – List of participants

WHO Informal Consultation on the Use of Rectal Artemisinin-based Suppositories in the Management of Severe Malaria

WHO headquarters, Geneva, Switzerland, 27–28 March 2006

• **Technical advisers**

Dr Jane Aceng, Department of Paediatrics and Child Health, Makerere Medical School, P. O Box 7072, Kampala, Uganda; e-mail: janeaceng@yahoo.com

Dr Tsiri Agbenyega, Kwame Nkrumah University of Science and Technology, School of Medical Sciences, Kumasi, Ghana; e-mail: tsiri@ghana.com

Mr Marlon Banda, UNICEF Supply Division, HIV/AIDS & Health Centre, Copenhagen, Denmark; e-mail: mabanda@unicef.org

Professor Abul Faiz, Department of Medicine, Dhaka Medical College, Dhaka 1000, Bangladesh; e-mail: mrg@spnetctg.com

Professor Peter Folb (Chair), Medical Research Council, P.O Box 19070, Tyberg 7505, Cape Town, South Africa; e-mail: peter.folb@mrc.ac.za

Dr Tran Tinh Hien, Centre for Tropical Diseases, 190 Ben Ham Tu, Ho Chi Minh City, Viet Nam; e-mail: tthien@hcm.vnn.vn

Dr Harin Karunajeewa, University of Western Australia, Stirling Hw, Nedlands, Western Australia 6009, Australia; e-mail: harin@cyllene.uwa.edu.au

Professor Sanjeev Krishna, Department of Cellular and Molecular Medicine, St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, United Kingdom; e-mail: s.krishna@sghms.ac.uk

Dr Stephen Oguche, Department of Paediatrics, College of Medical Sciences, University of Maiduguri, Maiduguri, Borno State, Nigeria; e-mail: soguche2001@yahoo.com

Dr Isabella Ribeiro, Rua Verdes Matas 90, Barra da Tijuca - 22793-410, Rio de Janeiro - RJ, Brazil; e-mail: isabela.q.ribeiro@terra.com.br

Dr Marian Warsame, National Institute of Medical Research, P.O. Box 38594 Upanga, Dar es Salaam, United Republic of Tanzania; e-mail: rectocap-kilosa@kicheko.com

Professor Nick White, Faculty of Tropical Medicine, Wellcome Trust Research Laboratories, Mahidol University, 420/6 Rajvithi Road, 10400- Bangkok, Thailand; e-mail: nickw@tropmedres.ac

WHO Secretariat

- **Regional advisers**

Dr Eva Christophel, Medical Officer, WHO Regional Office for the Western Pacific, Manila, Philippines; e-mail: christophele@wpro.who.int

Dr Jackson Sillah, Medical Officer, WHO Regional Office for Africa, Ouagadougou, Burkina Faso; e-mail: sillahj@tg.afro.who.int

WHO headquarters, Geneva, Switzerland

Dr Andrea Bosman, Medical Officer, Global Malaria Programme; e-mail: bosmana@who.int

Dr Melba Filimina Gomes, Scientist, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases; e-mail: gomesm@who.int

Dr Hendrik V. Hogerzeil, Director, Medicines Policy and Standards Department; e-mail: hogerzeilh@who.int

Dr Janis Karlin Lazdins-Helds, Coordinator, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases; e-mail : lazdinsj@who.int

Mrs Françoise Mas, Procurement Officer, Contract and Procurement Services; e-mail: masf@who.int

Dr Lulu Mussa Muhe, Medical Officer, Child and Adolescent Health and Development Department; e-mail: muhel@who.int

Dr Peter Olumese, Medical Officer, Global Malaria Programme; e-mail: olumese@who.int

Dr Clive Ondari, Coordinator, Medicines Policy and Standards Department; e-mail: ondaric@who.int

Dr Franco Pagnoni, Medical officer, UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases; e-mail: pagnonif@who.int

Dr Wilson Milton Were, Medical Officer, Global Malaria Programme; e-mail: werew@who.int

For further information, please contact:

**Global Malaria Programme
World Health Organization
20. avenue Appia – CH-1211 Geneva 27
infogmp@who.int
www.who.int/malaria**