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By

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This monograph is dedicated to the memory of all the African children who have died from severe malaria

CONTENTS

PREFACE

The landmark studies on the medicinal properties of *Artemisia annua*, the use of which dates back to at least 500 B.C., by the Chinese Traditional Medicine Group finally led to the discovery of artemisinin (Qinghaosu) in 1969. Its chemical structure was reported in 1972 and its antimalarial (blood schizonticidal) properties were finally reported in 1979 by Chinese medicinal chemists who were part of the Qinghaosu Antimalaria Coordinating Research Group. The initial toxicity study on artemisinin showed that the drug was fairly safe on the basis of LD_{50} per mouse in a murine study with the following doses:

5,105 mg/kg orally;
2,800 mg/kg as oil suspension (intramuscular route);
1,556 mg/kg as oil suspension (intraperitoneal route).

The Chinese group also established blood schizonticidal activity in clinical cases of *Plasmodium falciparum* and *Plasmodium vivax*. A clinical study of 141 cases of cerebral malaria (chloroquine resistant *P. falciparum*) treated with artemisinin (1974-1978) saw a cure rate of 92.9 % (with 10 deaths). Initially, since these cerebral malaria cases were comatose, the drug was administered nasally and found to be effective. Later, administration was by intramuscular (IM) injection (0.3 g once daily IM x 3 days)

Plasmodium falciparum produces high mortality in young children who are rendered comatose/unconscious due to the severity of the infection. Cerebral malaria can kill children within 48 hours (h) in remote settings and rural areas where medical facilities are not available for emergency intranasal or intramuscular treatment. Li *et al.* (1985) were the first to study alternative forms of delivery of qinghaosu/other artemisinin derivatives, such as artesunate suppositories, in the emergency treatment of 100 cases of *P. falciparum*. Delivery of artesunate, which is a water soluble derivative, have been found effective in severe/comatose malaria cases, as reported in a large number of clinical trials (see reviews by Professor Melba Gomes *et al.* 2008; Professor Karunajeewa *et al.* 2007; and the World Health Organization (WHO) 2002, 2006). Extensive trials have also been undertaken with a variety of rectal suppositories (artemisinin,

artesunate, artemether and dihydroartemisinin (DHA)) with fast delivery of antimalarial treatment through rectal administration of one or two suppositories. As shown by pharmacokinetic studies, this procedure ensures adequate blood plasma levels of these antimalarials in controlling the complications of severe malaria, which are responsible for high mortality in children (Karunajeewa *et al.* 2007).

In the authors' opinion, most of the rectal suppositories in current clinical use (initial treatment) are not radical curatives (because they are used as emergency therapy to suppress parasitaemia only for one or two days) and most of the suppositories currently prescribed need a second consolidation treatment with mefloquine or sulfadoxin/pyrimethamine, with or without an additional dose of mefloquine plus artesunate/artemether/artesunate + sulfadoxine + pyrimethamine. The antimalarials prescribed as a consolidation treatment are ones for which clinical drug resistance was reported in field studies carried out in the 1990s. Clinical resistance against mefloquine, sulfadoxine/pyrimethamine and artesunate have been reported for Southeast Asia and Africa. Treatment of children/infants with these drugs may not achieve a radical cure following initial suppression of parasitaemia with an artesunate, artemisinin, dihydroartemisinin, or quinine-based suppository.

This book on the use of rectal suppositories provides experimental evidence for the identification of new rectal suppository drug regimens that can be administered over three to five days or more to achieve a radical cure against drug-resistant *P. falciparum* infection. Such infections are responsible for a high level of mortality among child under five in African countries where recent WHO (2014) reports show continued mortality due to ineffective antimalarial therapy.

Finally, an update/review of rectal suppositories recommended and approved by the World Health Organization for clinical use as an emergency life-saving treatment in cases of severe, complicated, cerebral malaria in comatose children, is made. A review is also made of the use of one or two consecutive administrations of artesunate-based rectal suppositories, which can reduce parasitaemia by 90 % or more within 12-24 hours of treatment. This is accepted as a life-saving emergency treatment for comatose children who cannot be administered oral medication. Artesunate, used as a suppository/or through IM/IV administration, is known to be rapidly metabolized in the body to dihydroartemisinin (DHA), which is the active antimalarial drug. The artesunate absorbed from the suppository enters the blood stream and has a very short half-life (of 5-15 minutes) in

the blood, rapidly being converted to DHA, which exerts strong blood schizonticidal activity against malaria and is effective in further reducing blood parasitaemia to less than 90 % within 12-24 hours. The author of this book has patented DHA (the synthesized drug) for its curative efficacy as a blood schizonticide and its antimalarial activity by intramuscular, oral, and rectal routes of drug administration (Dutta, Jain *et al.* 2001, U.S. Patent 6214864 on dihydroartemisinin filed March 5, 1999). Besides its blood schizonticidal activity, DHA has an additional gametocytocidal action, which can help reduce malaria transmission by destroying gametocytes ensuring that they fail to be passed on to mosquitoes. Although more than 100 clinical efficacy studies on artemisinin rectal suppositories have been published in the literature, only three clinical trials on rectal DHA-based suppositories have been carried out (Esamal *et al.* 2000; Wilairatna *et al.* 2000; Alaxin 40 mg DHA suppository; Green Life Pharmaceuticals Ltd.). In the opinion of the authors, there is a need to conduct extensive clinical trials on DHA-based rectal suppositories, which can be administered for two, five, or even seven days, as a life-saving treatment for children suffering from severe malaria.

Rectal suppositories containing a dose that is 3-4 times higher than single dose DHA, or in combination with longer acting antimalarials such as piperaquine, can serve as a very powerful antimalarial combination therapy. This therapy has now been approved by the WHO (2010) as a radical cure for uncomplicated *P. falciparum*. Rectal suppositories based on combinations of DHA + long-acting piperaquine can serve as a life-saving emergency drug for children and their extended use for 3-5 days can provide a curative treatment for children who cannot take oral medication.

Recently, artesunate induced reproductive toxicity in male rats has been reported after long-term administration (Stephen and Yinusa 2013). There is a need for caution regarding long-term use of artesunate at high doses in suppository or IV/oral administration.

Another artemisinin based drug, α/β-arteether (30:70), has been identified through CSIR-CDRI/CIMAP collaboration as a very fast-acting blood schizonticide. It was brought to market in 1997 and has the potential to be used in rectal suppository/emergency therapy for the treatment of comatose cerebral malaria cases.

The authors wish to acknowledge the contribution of the WHO to global efforts in the fight against malaria and sponsoring the development of antimalarial-based rectal suppository technology, which has saved the

lives of millions of malaria-infected children in Africa and Southeast Asia over the last two decades. The updates on policy decisions framed and published from time to time by the WHO-associated International Expert Panels have immensely benefitted the development of a pre-referral strategy to save the lives of children under five suffering from severe cerebral malaria.

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CHAPTER 1

INTRODUCTION

1.1 World Health Records of malaria mortality

According to the latest WHO Epidemiological Assessment (2018), infection with malaria caused an estimated 435,000 deaths in 2017 and an estimated 219 million malaria cases were detected in 90 countries:

i) According to the latest report (December 2014), approximately 198 million malaria cases (with a range of 124 million to 283 million cases) were recorded globally. In 2017, the WHO-African Region accounted for 92 % of malaria cases and 93 % of malaria deaths.
ii) Most malaria cases due to *Plasmodium falciparum* (99.7 %) occur in children living in Africa; it is estimated that a child dies every minute from malaria infection.
iii) It is encouraging to report that according to WHO (2015) estimates, global malaria mortality rates decreased by 47 % during the period 2000-2014. In the WHO-African Region, there was a 54 % decrease in the reported mortality rate.
iv) Clinical relapse can occur in infection with *P. vivax* and *P. ovale*, caused by the activation of hypnozoites (which remain dormant in the liver). In addition, some cases of human-transmissible simian malaria (*P. knowlesi*), with zoonotic transmission, has been recorded in Southeast Asian jungle zones.
v) According to a WHO (2014) media report, nearly half of the world's population continues to be at risk from malaria infection.
vi) Most malaria cases, as well as malaria mortality, are reported in sub-Saharan Africa, with the incidence of malaria in Asia and Latin America being much lower.
vii) If the placenta is heavily parasitized with *P. falciparum* in pregnant women, it can lead to abortion and higher mortality.
viii) Intermittent treatment with sulfadoxin/pyrimethamine is recommended for pregnant women.

ix) Monthly administration of amodiaquine plus sulfadoxin/pyrimethamine is recommended for all children under five, especially in high transmission areas.
x) For vector control, pyrethroids (insecticide), in the preparation of insecticide treated/impregnated bed nets **(**ITNs) or long-lasting insecticidal nets (LLINs), have been widely used to reduce transmission levels in India and sub-Saharan Africa. They have been extensively used to protect millions of children/pregnant women and interrupt mosquito-borne malaria transmission in Southeast Asia, where mortality and malaria transmission have not been controlled due to a lack of safe gametocytocidal drugs discovered or approved by the WHO. The World Health Organization has not yet been able to develop a safe gametocytocidal drug to replace primaquine (the only drug available to stop malaria transmission).
xii) The WHO (2014) also reports that 55 countries have managed to reduce malaria cases by 75 % in line with World Health Assembly targets for 2015. The WHO (2014) highlighted that "ITNs and LLINs remain highly effective tools in almost all settings."
xiii) Judging from the current scenario, the authors wish to put in record that malaria eradication will not be practical or achievable without the development of: safe and effective drugs to treat emerging artemisinin drug resistance; effective treatment for MDR malarias; radical curative anti-relapse drugs; safe transmission blocking drugs; safe blood schizonticides for children and pregnant women; and causal prophylactic drugs to protect international travelers.
xiv) In addition, there is an urgent need to develop safe pre-referral antimalarial rectal suppositories to protect and cure millions of African children.

1.2 Malaria incidence in India

The malaria incidence in India, based on the slide positivity rate of blood smears, as reported by the Directorate of National Vector Borne Disease Programme (Govt. of India) for the year 2010 to 2018 is presented in Table 1. The mortality rate according to the official report showed a significant decline from 2010 to 2018. This suggests that the overall incidence of malaria is being brought under control. Since this malaria epidemiological data is based on the malaria slide positivity rate, the

conclusion may be drawn that the current malaria control policy in India is showing credible results.

Table 1: Total malaria cases of diagnosed *P. falciparum* and mortality due to malaria (deaths). Incidence of malaria in India: 2010-2018

Year	Total malaria cases	*P. falciparum*	Deaths
2010	1.60 million	0.83 million	1018
2011	1.31 million	0.67 million	754
2012	1.07 million	0.53 million	519
2013	0.88 million	0.46 million	440
2014	1.10 million	0.72 million	562
2015	1.17 million	0.78 million	384
2016	1.09 million	0.71 million	331
2017	0.84 million	0.53 million	194
2018	3,75,845	18,83,889	77

Note: data taken from: www.malariasite.com/malaria-India

1.3 Malaria: World Health Report 2014-2019

According to a WHO report released on 9 December 2014, global malaria mortality rates were reduced by 47 % between 2000 and 2013. Additionally, it is commendable that the WHO has achieved unprecedented progress in malaria control and malaria deaths have declined dramatically worldwide, but especially so in sub-Saharan Africa. Another significant conclusion of the report is that "fewer people are carriers of symptomatic or asymptomatic infection," which suggests a reduction in gametocyte carriers of *P. falciparum*. The WHO report also focuses on future "opportunities and challenges in controlling and eliminating the disease."

Dr. Margaret Chan (2012), former Director-General of the WHO, has also emphasized the identification of new foci of continuing malaria transmission, which need to be interrupted to fight their expansion. The WHO has launched a new initiative, known as T3: Test; Treatment with appropriate antimalarials; and Track (i.e. conduct malaria surveillance), to help stop the spread of malaria.

The author wishes to record the views of distinguished international malaria experts as recently published in their Malaria Eradication Agenda.

This document argues that malaria eradication may not be possible during their lifetimes because of the paucity of safe and effective antimalarials.

The international malaria control strategy should focus on reducing child mortality in terms of: (i) stopping malaria transmission, particularly of *P. falciparum*; (ii) developing blood schizonticides to treat expanding foci of emerging artemisinin resistance; (iii) developing anti-relapse treatments (radical curative drugs for the control of *P. vivax*); (iv) developing causal prophylactic agents; (v) and the non-availability of prophylactic malaria vaccines. Several antimalarial drug discovery projects have been sponsored by the Medicines for Malaria Venture (Switzerland); these are still in the drug development stages. However, there is a paucity of safe fast-acting antimalarials that can be used as rectal suppositories to reduce child mortality in cases of severe malaria.

1.4 Historical overview of the use of artemisinins

Professor Nicholas White and colleagues (Newton *et al.* 2000) have published an authoritative document on the pathophysiology of cerebral malaria. Based on extensive clinical experience, Professor White and colleagues reported that the neurological complications in cases of malaria not only include the pathogenesis of cerebral malaria, but also: multisystem failure and dysfunction and the role of sequestration of red cells; mechanisms of cytoadherence rosetting; the tumour necrosis factor (TNF-α) and interleukins in comas; and high fever, hypoglycaemia, hyponatraemia, and uraemia, associated with a sharp rise in parasitaemia in most *P. falciparum* cases and rare incidences of *P. vivax*, which contribute to a comatose condition. The role of cerebral malaria in causing high mortality in African children and persistant neurological sequelae have been listed as a long-term neurological complication. Besides classical treatment with quinine and quinidine, this publication also emphasizes the important role of artemisinins, particularly the use of intravenous artesunate for the emergency control of cerebral malaria complications. The WHO (2007) also reports the adoption of artesunate rectal suppositories/intravenous artesunate for the emergency treatment of cerebral malaria. The Central Drug Research Institute has developed another artemisinin-based injectable drug, α/β-arteether, for the emergency treatment of cerebral malaria. This drug was patented in 1990 (Dutta *et al.* CSIR-CDRI patent). A large number of pharmaceutical companies are manufacturing α/β-arteether in India, which is exported for treatment of malaria in Africa.

Three artemisinin medicines: (i) artemisinin (qinghaosu); (ii) artesunate; and (iii) artemether; as well as Cinchona quinine, for use in rectal suppositories, were comprehensively reviewed by Professor Melba Gomes and colleagues (2008) and Professor Karunajeeva and colleagues (2006 and 2007). WHO reports (2002, 2006) have also endorsed the use of artesunate suppositories as an emergency life-saving/pre-referral rectal treatment for children suffering from severe/comatose/cerebral malaria. Chinese clinical/medical experts and medicinal chemists were the first to report the chemistry of the above three artemisinins, while chemists in the USA first synthesized quinine, as well as their use as emergency medication/life-saving drugs for the treatment of cerebral malaria in children and adults. They published their results in Chinese publications between 1972 and 1982 (Anonymous 1979, 1982a, 1982b; Guoqiao *et al.* 1982). Cerebral malaria cases included in trials were characterized by fever, coma, lethargy, delirium, convulsions, rigidity of neck, and high parasitaemia. Antimalarial qinghaosu (artemisinin) was isolated from *Artemisia annua*, a medicinal plant, described as a new type of sesquiterpene lactone with a peroxy group, and first used in the treatment of emerging chloroquine resistant *P. falciparum* in China around 1960. In a clinical study, 41 cases of cerebral malaria with chloroquine resistant *P. falciparum* were treated between 1974 and 1978 with qinghaosu (artemisinin) given nasally; patient response and recovery was reported to be satisfactory. In published reports, the IM injection of artemisinin cured 92.9 % of cerebral malaria cases. Recovery from coma was recorded in 21.5-30.8 hours after treatment with artemisinin/artesunate and artemether. Professor Li Guoqiao and colleagues (1982) reported results of clinical studies on 140 diagnosed cerebral malaria cases (aged 2-80) with: (i) qinghaosu (artemisinin) at doses of 1-1.5 g administered through nasal feeding; (ii) artemether 1,200 mg oil-based IM injection (over three days); and (iii) sodium artesunate 400 mg total dose in distilled water over three days. All three drugs were reported to cure cerebral malaria in patients. The cure rate with qinghaosu was 91.7 %; with sodium artesunate it was 86.7 %; and with artemether it was 94.1 %. The cure rate of cerebral malaria cases with chloroquine was 92.5 %, while with quinine it was 97.5 % (1972-1973). The overall mortality rate for the above three treatments was 8.65 %. It is important to note that in this study, cerebral malaria with *P. falciparum* was reported to be chloroquine resistant in most cases before they were treated with various artemisinins.

1.5 WHO Clinical studies on rectal artemisinins

Gomes *et al.* (2008) published an extensive review of the literature on the safety and efficacy of rectal artemisinins, with a special focus on the efficacy and safety from individual patient data in clinical studies. They presented a global overview on individual patient data from 1,167 patients suffering from malaria. The review was based on 15 clinical trials of rectal artemisinin therapy prepared and evaluated by international groups who used suppositories made from three artemisinins: (i) artesunate; (ii) artemisinin; and (iii) artemether.

The results of earlier reviews were pooled in order to compare: (1) the rapidity of clearance of *P. falciparum* parasitaemia; (2) the incidence of reported adverse effects/events with these suppositories; (3) further data from patients who had received comparator treatments (parenteral artemisinin derivatives or quinine therapy) was also reviewed; (4) the criteria for evaluating suppository efficacy included: (a) primary endpoints, including percentage reduction in malaria parasitaemia at 12 hours and 24 hours. A further criterion of reduction of > 90 % parasitaemia at 24 hours was regarded as a parasitological success.

The main conclusions of this exhaustive analysis were:

1. Artemisinin and artesunate rectal suppository treatment cleared parasites more rapidly when compared to parenteral treatment with quinine during the first 24 hours of treatment.
2. A single high dose of rectal artesunate treatment was five times more likely to achieve more than 90 % parasite reduction at 24 hours than clinical use of multiple lower doses of artesunate (i.e., repeated administration of suppositories), or a single lower dose of a rectal artemether suppository.

This extensive overview of the data on individual suppositories clearly established that artemisinin, as well as artesunate suppositories, resulted in rapid elimination of malaria parasitaemia and this therapy was judged to be clinically safe in the treatment of severe malaria. The primary conclusion was that more rapid parasite clearance using a single (high-dose) regimen, which was very efficient in achieving immediate high drug concentration (plasma levels), would offer an optimal strategy for saving the lives of children in remote malaria endemic areas. Finally, the authors stated that the WHO strategy over the past 10 years had achieved this objective by developing artemisinin/artesunate as suppositories, which

could be given rectally as a clinically effective substitute for injectable therapy with quinine. The rationale for standardizing the suppository formulations was that without fast acting/effective treatment of severe *P. falciparum* malaria, comatose children can die within a matter of hours. Rectal formulations of artesunate show a dramatic effect in killing off the early trophozoite stages and have the ability to rapidly reduce rising *P. falciparum* parasitaemia, which can prove fatal, especially in young children.

The major advantage of a rectal suppository is the ease with which it can be administered into the rectum by unskilled/rural family caretakers, particularly in remote settings, as a life-saving therapy to "buy time" through its rapid blood schizonticidal action in areas of emerging chloroquine resistant *P. falciparum* or even *P. vivax* malaria. Although severe *P. falciparum* is a cause of mortality, there are numerous reports of the emergence of chloroquine resistant *P. vivax* and several episode of cerebral malaria have been reported from malaria endemic areas where *P. vivax* prevalence is high. Professor Melba Gomes (2008) also emphasized that during emergency treatment of severe *P. falciparum*, parasite reduction (as seen in blood smears) is "a well-established indicator of clinical effect in the evaluation of antimalarial drugs."

A major conclusion of this study was that early clearance of parasites could be better achieved by the use of rectal artemisinins compared to quinine therapy. In addition, the rectal artemisinins used for treatment of severe malaria were shown to be safe and did not raise concerns about neurotoxicity. In addition, the superior efficacy of a single dose rectal suppository in parasite reduction, compared to multiple low artemisinin dosing schedules, was highlighted. The comprehensive review, after analysis of clinical data on rectal formulations, recommended the use of artemisinin and artesunate rectal formulations (suppositories) and their particular use as a pre-referral treatment/emergency medicine for children in malaria-infested countries, such as those in Africa and the Asia-Pacific. According to the authors, antimalarial rectal suppositories can be "effectively used to reduce malaria incidence and mortality in Asia—an approach which holds great promise for malaria control elsewhere."

Professor Melba Gomes *et al.* (2008), in an exhaustive review, covered the intra-rectal (IR) application of artemether (IR); artemisinin (IR); artesunate (IR) and artesunate per os (by mouth); artemisinin parenteral; quinine parenteral; and quinine parenteral + artesunate IR in a total of 1,167 individual cases (see Table 5 in Gomes *et al.* 2008). These artemisinins

have been reported to have a fast antimalarial action leading to rapid control and reduction of developing parasitaemia in children. Gomes *et al.* (2008) focused on rectal antimalarial technology for the arrest of severe malaria infection within the first 12-24 hours. This WHO approved approach for children under five is recommended as a reliable life-saving drug delivery treatment for children who cannot take drugs orally. Besides primary emergency life-saving initial rectal treatment, the authors also recommended a second consolidated treatment comprising: artemether IR/mefloquine/mefloquine + sulphadoxine + pyrimethamine; artesunate + sulphadoxine-pyrimethamine; chloroquine or sulphadoxine + pyrimethamine; artesunate + mefloquine; chloroquine or sulphadoxine + pyrimethamine; artesunate + mefloquine/quinine, to achieve a long-term cure. Professor Gomes and colleagues quoted treatments used by former clinical investigators, including Vinh (1992-94); Looareesuwan *et al*. (1995, 1996); Karunajeewa *et al*. (2007, 2003-4); Phuong (1992-5); Barnes *et al* (1998); Aceng (2002-3); and Than (1998).

Previous data on rectal suppositories containing various antimalarials, such as artemether (single or multiple dose), artesunate (single or multiple dose), artesunate per os, artemisinin parenteral, quinine parenteral, or quinine parenteral + artesunate, was published in Gomes *et al.* (2008) and they were designated an initial form of treatment. In addition to the above treatment, a second consolidated antimalarial treatment was administered to achieve long-term cure and ensure full recovery from *P. falciparum* infection.

In view of the widespread emergence of drug-resistant strains of *P. falciparum* in malaria endemic countries, particularly in African and Asia-Pacific countries (cited by Gomes *et al.* 2008), it may not be feasible to achieve a radical cure of MDR strains of malaria with the exclusive use of the drugs listed in the second consolidated drug regimes, as drug resistance has already appeared.

Initial treatment options

Artesunate is the most widely used rectal suppository drug for children with severe malaria. It is effective in reducing parasitaemia to less than 90 % within 12-24 hours. Its beneficial antiplasmodial activity has been extensively cited in literature reviews (Gomes *et al.* 2008; Karunajeewa *et al.* 2007). It is safe to administer two consecutive artesunate suppositories in young children; however, numerous reports of *P. falciparum* resistance against artesunate are found in the literature (in addition to its sertoli cell

reproductive toxicity in male rats; Olumide Stephen & Raji Yinusa 2013). Its major drawback is that it has a very short half-life of around 5-15 min, so its antimalarial action may not last beyond 15 minutes in the body. It is now well-known that the major antimalarial component in the blood, i.e. the active antimalarial metabolite of artesunate, is dihydroartemisinin (DHA). This metabolite is considered one of the most active blood schizonticide and is probably responsible for a significant reduction in parasitaemia within 15 minutes to 24 h following rectal administration. A higher dose of 80 mg/kg artesunate in suppository form achieves a very fast acting schizonticidal action (suppressing 100 % of parasitaemia after 24 h). The drastic action of DHA is responsible for complete parasite clearance in 24 h. Another drawback of artesunate is its ineffectiveness in controlling MDR *P. falciparum* malaria. In the author's experience, artesunate is not able to radically cure MDR *P. yoelii nigeriensis* infection in mice (Dutta *et al.* 1989).

It has been claimed that artesunate IR and artemisinin IR administered as a single or multiple dose treatment (Hien 1998; Phuong 1992-5; Vinh 1992-4) are able to control severe *P. falciparum* infection through the initial suppression of rising parasitaemia, but it must be followed by administration of mefloquine (as a consolidation treatment).

Artemisinin, in addition to its blood schizonticidal action at very high doses, has shown exceptional gametocytocidal action at very low doses against *P. cynomolgi* B infection in *Anophlese stephensi*, as shown in another study and supported by SEM photographic evidence (Dutta *et al.* 1990; Figs. 1-6). Figs. 3 and 4 show an absence of *P. cynomolgi* B oocysts in the mid-gut of a mosquito following an IM dose of 5 mg/kg of artemisinin administered to a gametocyte carrying monkey. This indicates the complete sterilization (absence) of oocysts in the mid-gut of the dissected mosquito 18 hours after artemisinin injection. It needs to be emphasized that artemisinin at very high doses is required to suppress severe complicated *P. falciparum* infection in children in 24 hours; whereas a very low dose (5 mg/kg) of artemisinin (IM) has been shown to exhibit gametocytocidal action against *P. cynomolgi* B infection in a rhesus monkey model. The first report on the gametocytocidal action of artemisinin against simian malaria (*P. cynomolgi* B) was published by the author (Dutta *et al.* 1989).

1.6 Professor Melba Gomes, UNDP/World Bank, WHO report

Subject: ARTESUNATE RECTAL CAPSULES

Professor Gomes (2010) discussed the urgent need to develop and standardize pre-referral treatment with artesunate rectal suppositories for emergency control and management of severe and complicated *P. falciparum* in comatose malaria cases. This is particularly the case with children who cannot take oral medication and for whom parenteral treatment is not available in rural areas. These areas see high rates of child mortality due to complications from rising parasitaemia within the first 24-48 h of infection. Treatment with artesunate rectal suppositories, as initiated around 2002 by the WHO, is considered superior to standard quinine therapy. Gomes (2010) reported that a single dose rectal artesunate suppository cannot cure severe malalria, but it can reduce the parasite count half within 6-12 h (Simpson *et al.* 2006; Krishna *et al.* 2001; Barnes *et al.* 2004).

Gomes (2010), in an analysis of 3,000 malaria cases, reported that in those cases not treated in a clinic more than 6 hours after insertion of an 100 mg artesunate suppository, the trial treatment did not have time to make much difference. The median time of arrival at a clinic was 15 h and the risk of death or serious permanent disability was approximately halved: 1.9 % for artesunate (9/1,568) vs 3.8 % for the placebo (57/519) ($p = 0.001$). According to Gomes, the 100 mg single dose rectal artesunate suppository, on which extensive clinical evaluation has been conducted in children under six, could be given only as a research drug as it had not yet been approved by the FDA.

The FDA (US Agency/Advisory Committee) recommends the administration of a “100 mg single-dose artesunate rectal suppository to treat patients ages 6 or younger who have suspected malaria, are unable to take oral medications and lack access to empiric IV therapy.” In addition, “more data are needed before they could recommend a 400 mg formulation to treat patients older than 6 years,” The committee’s recommendations were based on 12,068 people in Bangladesh, Ghana and Tanzania. A 100 mg artesunate suppository administered to 6,072 children saw 154 fatalities (mortality in this group was 2.5 %). In the placebo cohort of 5,996 patients (with no artesunate given in the suppository), the mortality rate was 3.0 % ($p = 0.1$). There was a lack of safety/efficacy data on treatment with a 400 mg suppository proposed for adult severe malaria cases.

1.7 Review of clinical use of rectal artesunate derivatives

Professor Karunajeewa *et al.* published a comprehensive review titled "Rectal Administration of Artemisinin Derivatives for the Treatment of Malaria" (2007). The main emphasis of Karunajeewa *et al.* (2007) was on how to save lives in cases of severe/complicated/cerebral malaria, which carry the risk of death, particularly in *P. falciparum* infection, unless effective antimalarial treatment is provided within 24 h. Rectal antimalarial treatment can be a valuable public health strategy in rural India where the majority of adult morbidity and mortality occurs and in African countries where child mortality due to severe malaria is very high. According to WHO reports (WHO 2002-2010), child mortality is highest in sub-Saharan African countries where nearly 20 % of deaths in children under five are due to complications from severe malaria. Rectal antimalarial suppositories can be administered to children in rural settings in Africa and Southeast Asia who cannot be provided with oral medication due to vomiting, prostration, or coma. Coma is frequently seen in cerebral malaria and in such situations death is highly likely within 24 h unless emergency rectal suppositories are provided to arrest and clear parasitaemia. Rectal suppositories can be used for emergency therapy in rural areas where facilities for injectable drugs are not available. Artemisinin-based suppositories, containing artemisinin or artesunate, can be used as an emergency treatment because of their rapid absorption through rectal tissue and their rapid antimalarial action.

Professor Karunajeewa *et al.* (2007) compiled an exhaustive review of the use of currently available suppositories and their clinical efficacy as an emergency antimalarial therapy, as documented in the literature over the past 25 years. They documented the work of international investigators in establishing the clinical efficacy and the dose schedule used in more than a hundred research publications; as well as the efficacy of suppositories in arresting parasitaemia within 12 h and eliminating parasites completely in 24 h. Karunajeewa *et al.* (2007) pointed out that suppositories containing artemisinin or artesunate appear to be a very effective emergency treatment and these treatments provide adequate plasma blood levels and bioavailability. Their review also established that rectal suppositories for emergency malaria treatment can be considered to have acceptable therapeutic efficacy for treating children suffering from severe malaria and revive comatose children.

Karunajeewa *et al.* (2006) also compared the antimalarial potential and clinical efficacy of artesunate rectal suppositories and IM artemether

injection in the management of severe *P. falciparum* malaria infection in young children in Papua New Guinea. Forty-one children suffering from severe malaria were administered rectal suppositories containing artesunate (8 to 16 mg/kg of body weight) at hour 0; after 12 h; and then daily. The antimalarial efficacy of this group was compared to another group of 38 children with severe malaria who were treated initially with a 3.2 mg/kg artemether injection at hour 0 and then 1.6 mg/kg of artemether daily.

The response to antimalarial treatment in the artesunate rectal suppository group of children was compared to the artemether (IM) injected group by recording parasite density and fever level in both groups every 6 h up to a total of 72 h. The primary endpoints of drug efficacy were monitored by recording the time required for a reduction of parasitaemia in treated children to 50 % and to 90 % (PCT_{50} and PCT_{90}), and the time required for the fever (temperature) to return to normal following both the treatments. The treated children's parasite clearance time to PCT_{50}/PCT_{90} levels and temperature returning to normal were compared after artesunate suppository and IM artemether injection.

The authors reported that the rectal artesunate treatment group of children saw reduced parasitaemia with a PCT of 50 % (9.1 versus 13.8 h; $p = 0.008$) and a PCT of 90 % (15.6 versus 20.4 h; $p = 0.011$). The authors recorded the clinical efficacy endpoints in the artesunate suppository group and IM artemether group. In general, the rectal artesunate suppository treatment cleared parasitaemia faster than the artemether treatment:

1. The PCT_{50} was faster (9.1 ± 4.9 h) in the suppository group compared to the artemether group.
2. PCT_{90} was also faster (15.6 ± 7.4 h) in the suppository group compared to the artemether group.
3. Total parasite clearance was achieved in 30.3 ± 14.2 h in the artemether group and 38 ± 12.0 h in the rectal suppository group.
4. The FCT was shorter, 15.6 ± 9.2 h, with artemether injection than the rectal artesunate treatment (18.3 ± 10.7 h).

Earlier studies on the drug sensitivity of *in vitro* malaria (*P. falciparum*) cultures indicated that artemether might be intrinsically less potent than either artesunate or DHA (Ringwal *et al.* 1996, 1999). The pharmacokinetic data presented by Karunajeewa *et al.* (2006) for severe malaria cases showed that artesunate rectal suppositories given to malaria patients saw

active DHA produced in plasma reaching a level of 3,509 (222-5,218) nmol/l at one hour after and a level of 2,487 (120-14,613) nmol/l two hours after suppository administration; this is explained by the rapid absorption of rectal artesunate and its conversion to the highly active metabolite DHA. In contrast, the IM artemether was very slowly metabolized to DHA, as shown by plasma levels in severe malaria patients of 69 (21-4,314) nmol/l at one hour and 57 (18-4,186) nmol/l at two hours after injection. The data further showed that the DHA plasma level at six hours post-rectal artesunate suppository was 819 (84-2,690) nmol/l, while the DHA produced at six hours following artemether injection was extremely low at 53 (29-509) nmol/l. This pharmacokinetic data shows that the antimalarial effect produced by rectal artesunate suppositories is much superior in severe malaria patients than the antimalarial activity of IM artemether up to six hours after treatment. In this clinical study, a second artesunate suppository was recommended six hours after administration of the first, further potentiating the action of the first suppository. This second suppository has been reported to clear PCT_{50} in 9.1 ± 4.9 h and PCT_{90} in 15.6 ± 7.4 h. In this study, one of the 29 severe malaria children from Papua New Guinea died within two hours of admission and artesunate suppository administration, but the remaining 28 severe malaria cases recovered after treatment with rectal artesunate suppositories. This data is fully supported by pharmacokinetic evidence on plasma levels of the active principal, DHA.

1.8 WHO recommendations for rectal suppositories in cerebral malaria

The WHO report “Artemisinin-based Suppositories: Use of Rectal Artemisinin-based Suppositories in the Management of Severe Malaria,” published by the Global Malaria Programme, focused on the standardization of artesunate rectal suppositories for reducing mortality from severe malaria among infants in endemic countries (World Health Organization Report 2007). The major emphasis of this report was on the control of child mortality from severe/cerebral/*P. falciparum* malaria through the use of artesunate rectal suppositories. Rectal artesunate has been used successfully in Southeast Asia, China, Thailand, Vietnam and Africa. Rectal DHA has also been successfully used to treat severe malaria, in addition to rectal artemisinin and artemether suppositories. A 24 hour survey revealed that in severe malaria cases, artemisinin and artesunate suppositories were superior to quinine (parenteral treatment). The WHO (2007) report strongly emphasized “artemisinin based suppository treatment

… [should be] used and marketed specifically as pre-referral treatment" for severe malaria cases. The report further cautioned that a pre-referral suppository should be followed by a course of artemisinin-based combination therapy (ACT) to maximize cure rates and minimize the selection of artemisinin-resistant malaria (special report by Krishna *et al.* 2006). Reevaluation of how artemisinins work in the light of *in vitro* evidence on emerging resistance needs to be undertaken. Wilairatna *et al.* (2000) also emphasized that pre-referral treatment of severe malaria cases using DHA suppositories should be followed by mefloquine for appropriate curative antimalarial therapy and to avoid the emergence of artemisinin resistance. In addition to the pre-referral use of rectal suppositories in the treatment of children suffering from severe *P. falciparum*, several distinguished malariologists have also noted the importance of a secondary curative malaria therapy with mefloquine (Looareesuwan *et al.* 1995; Eduardo, A. & Gomez-Landires, E. A. 1996; Birku *et al.* 1999).

Prior to the publication of the WHO's 2007 comprehensive report, a large number of malaria experts formulated a policy for using rectal artemisinin suppositories as an emergency measure in the treatment of *P. falciparum* cases who had become comatose or had developed symptoms of cerebral malaria. These reports show that severe malaria cases should be administered an initial malaria treatment before receiving a second consolidation treatment, as summarized in Table 2.

A variety of rectal suppositories for pre-referral emergency treatment of severe/cerebral malaria/*P. falciparum* in children and adults were extensively used in malaria endemic areas between 1992 and 2005. As summarized in Table 2, these comprised artemether IR, artemisinin IR, artesunate IR, artesunate per os assessed by a number of malaria experts as an emergency pre-referral medication followed by a consolidation treatment (curative therapy) comprising artemether IR, mefloquine + sulfadoxin, pyrimethamine, mefloquine, artesunate + SP, mefloquine, chloroquine or SP, artesunate + mefloquine, chloroquine or SD-P, artesunate + mefloquine, chloroquine or SD. In addition to artemisinins, parenteral therapy was also given initially, followed by artesunate + SD/P, mefloquine and chloroquine or SD/P as a consolidation treatment (1992-2004).

Table 2: Consolidation (curative) treatments administered in different clinical studies to achieve complete cure

Initial treatment group	Consolidation treatment	Follow-up period	Study identification/year of enrolment (Ref)	Total patients
Artemether IR*, single dose	Artemether IR	7 days	Aceng 2002-3[32]	51
Artemisinin IR, Single dose	Mefloquine + SP	72 hours	Hien 1998	46
Artemisinin IR, multiple dose	Mefloquine	None post discharge	Phuong 1992-5 [31] Vinh 1992-4 [33]	46
Artesunate IR, multiple dose	Artesunate + SP Mefloquine Chloroquine or SP	72 hours 28 days None post discharge None post discharge	Karunajeea 2003-4 [34] Looareesuwan 1995 [35] Than 1998 Bhatt 1994-5 [36] Karunajeewa 2001 [37]	41 60 100 23 48
Artesunate IR, single dose	Aartesunate + Mefloquine Mefloquine Chloroquine or SP SP Mefloquine-SP	28-42 days 28 days 28 days 30 days 28-42 days 72 hours	Van Vugt 1997-9 Looareesuwan 200 Looareesuwan 1996 Krishna 1996 [10] Molyneux 1997-8 [30] Hien 1998	44 69 26 23 113 44
Artesunate per os	Artesunate + Mefloquine	28-42 days	Van Vugt 1997-9	17
Artemisinins parenteral	Artesunate + SP Mefloquine	72 hours 28 days None post discharge	Karunajeewa 2003-4 [34] Looareesuwan 1996	38 24

	Chloroquine or SP	30 days	Phuong 1992-5 [31] Vinh 1992-4 [33] Krishna 1996 [10]	 40 123 11
Quinine parenteral	Quinine SP	7 days 28-42 days None post discharge	Aceng 2002-3 [32] Barnes 1998 [30] Phuong 1992-5 [31]	52 36 35
Quinine parenteral +Artesunate ir	SP	42 days	Barnes 1998 [30]	5
Total				1167

*IR: intra-rectal

Note: The author recommends additional consolidation treatment with a combination of dihydroartemisinin + piperaquine, as recommended by the WHO (2010) report: "Rectal Artemisinins for Malaria: a Review of Efficacy and Safety from Individual Patient Data in Clinical Studies" Melba Gomes*1, *et al.*

The Global Malaria Programme of the World Health Programme (2017) recommends the use of artesunate rectal suppositories as an emergency pre-referral treatment for severe malaria, including cerebral malaria cases. Untreated cerebral malaria in children under six can lead to very high mortality in rural areas. The WHO have emphasized that rectal artesunate is a key approach to reducing mortality. The WHO has strongly recommended it for the treatment of severe/cerebral malaria cases showing a variety of clinical features, including impaired consciousness, unrousable coma, prostration, convulsions, deep breathing/respiratory distress, acute pulmonary oedema, and circulatory collapse/shock.

1.9 Global malaria programme review May 2018

According to this review, rectal artesunate is key to reducing mortality from severe/cerebral malaria mortality and preserving artemisinin treatments from the risk of developing resistance. The Global Malaria Programme has cautioned malariologists that there is a risk of emerging artesunate resistance, which "would have devastating consequences on the people's health in malaria endemic countries and could reverse the progress in malaria control achieved in many countries over the past decade."