EFFICACY OF ARTEMISININ DERIVATIVES IN TREATING SEVERE MALARIA IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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A Research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master Science in Medicine in the field of Epidemiology and Biostatistics.

Johannesburg, April 2006.

DECLARATION

I, GEORGE PRAYGOD declare that this research report is my own work. It is submitted for the degree of Master of Science in Medicine in the field of Epidemiology and Biostatistics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

SIGNED: _____

DATE: 28th April 2006

DEDICATION

This research report is dedicated to my wife Sharifa for her loving care, understanding, encouragement and support.

ABSTRACT

Background

Evidence shows that the efficacy of intravenous quinine, which is the mainstay for treating severe malaria in children, is decreasing. Artemisinin derivatives are the potential replacement for quinine. Their efficacy compared to quinine in treating severe malaria in children is not well known.

Objective

To assess the efficacy of parenteral artemisinin derivatives versus parenteral quinine in treating severe malaria in children.

Search strategy

The Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 4, 2005), MEDLINE (1966 to October 2005), EMBASE (1980 to October 2005), and LILACS (1982 to October 2005) were searched. Malaria researchers and a pharmaceutical company were contacted. In addition, conference proceedings were also searched.

Selection criteria

Randomised controlled studies comparing parenteral artemisinin derivatives with parenteral quinine in treating severe malaria in children. All trials had to report mortality as an outcome.

Data collection

After data were extracted, two individuals independently assessed the trial quality. In addition, information on adverse effects from the studies was also collected.

Main results

Eleven trials were selected (1455 subjects), nine of them from Africa and the rest from Asia. Allocation concealment was adequate in seven trials (1238 subjects). Overall there was no difference in mortality between artemisinin derivatives and quinine (Risk Ratio= 0.89, 95% confidence interval 0.71 to 1.1). There was no difference in mortality between adequately concealed and inadequately concealed /unconcealed trials (Risk Ratio = 0.93, 95% confidence interval 0.74 to 1.16 and Risk Ratio=0.66, 95% confidence interval 0.36 to 1.22). In Parasite Clearance Time (PCT), though there was no statistical difference between the two groups there was a tendency towards favouring the artemisinin derivatives (weighted mean difference among studies which reported PCT as mean was -4.76 with 95% confidence interval -9.68 to 0.17 and all three studies which reported PCT as median showed that artemisinin derivatives cleared parasites faster than quinine, each had $p<0.001$). However; when only trials with adequate concealment were considered this potential advantage disappeared. In exploring heterogeneity for PCT, it was shown that study settings (Asia versus Africa) might have been a cause for heterogeneity. The artemisinin derivatives resolved coma faster than quinine (weighted mean difference=-5.32, 95%CI: -8.06 to -2.59), but when only trials with adequate concealment were considered this difference disappeared. Other secondary outcomes i.e. Fever clearance time, Incidence of neurological sequelae, and 28^{th} day cure rate showed no significant difference between artemisinin derivatives and quinine. There was no enough data to make meaningful comparison of adverse effects between the two groups.

Conclusions

The available evidence suggests that parenteral artemisinin derivatives are as efficacious as quinine in preventing mortality from severe malaria in children.

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LIST OF ABBREVIATIONS

CI	Confidence Interval
CRT	Coma Resolution Time
FCT	Fever Clearance Time
i.m	Intramuscularly
IQR	Inter-quartile Range
i.v	Intravenously
PCT	Parasite Clearance Time
SD	Standard Deviation
UNICEF	United Nations Children's Fund
WHO	World Health Organization

1.0 INTRODUCTION

1.1 BACKGROUND

1.1.1 Burden of malaria

Malaria remains a major public health threat globally. It is estimated that there are between 350-500 million cases of malaria worldwide annually.[1] Malaria is a public health problem in Africa south of the Sahara, and other tropical areas such as South East Asia, India, Indonesia, Papua New Guinea and the Amazon region of Latin America.[1] Approximately 1 million people die of malaria each year in sub-Saharan Africa.[2] This is about 90% of all malaria deaths which occur worldwide. Most of these deaths occur in children under the age of 5 years.[2] This figure translates into one child malaria death every 40 seconds and about 2100 deaths daily. This makes malaria one of the top child killers in the world[3] and the number one killer of children in Sub-Saharan Africa.

There are two reasons for this level of malaria mortality in Africa. The first is the fact that the majority of infections are caused by *Plasmodium falciparum* which is the most virulent of the four human malaria parasites and thus causes a severe form of malaria with the highest mortality.[2] The second reason is the mosquito *Anopheles gambiae,* which is a very effective vector, most difficult to control and widely present in Africa.[2, 3]

Malaria is known to be responsible for more than 40% of the burden on health systems in Africa.[2] It is estimated that between 30 and 50% of all hospital admissions and deaths in malaria endemic countries are attributed to malaria.[2] Malaria implicated as the cause of poverty at household and national levels.[3,4] It has been estimated that between 1965 and 1990 the annual economic growth rate of *P. falciparum* endemic countries was 1.3% lower than

that of *P. falciparum* non-endemic countries.[5] It also causes growth and development deficits in children, which result into short and long term negative biological and socio-economic repercussions in the populations of endemic countries.[2]

In recent times it has been argued that malaria morbidity and mortality have been on the increase worldwide.[5,6] Several factors have contributed to the worsening situation including: population increase especially in poor malaria endemic countries, international travel, climatic changes, environmental changes, war and civil disturbances in war torn countries in Africa and elsewhere, insecticide resistance in West and South Africa, poverty, poor health systems and most importantly drug resistance of the *P. falciparum* parasite to cheap and effective drugs i.e. chloroquine and sulfadoxine/pyrimethamine.[5,6] It has further been predicted that if effective interventions against malaria are not found and put in place and if the current population growth rate in malaria endemic countries remains constant, the number of malaria cases will double within the next 20 years.[7] This will mean more paediatric deaths from severe malaria.

Whether the incidence of malaria remains static or increases, the disease has a huge impact on the lives, growth and development of children, more than in any other population group. This is because they are susceptible to develop severe malaria, a form of malaria, which causes severe morbidity and highest case fatality rate. The control of malaria in children therefore needs to be a priority in malaria control strategies.

1.1.2 Burden of severe malaria in children

Severe malaria is characterised by manifestations of various symptoms and signs of vital organs dysfunction.[8] Though its exact pathophysiology remains a subject of controversy it has been suggested that the sequestration of mature parasitised erythrocytes into microvasculature and subsequent obstruction of vital organs circulation may lead to evolution of signs and symptoms of severe malaria which may include: prostration, loss of consciousness, respiratory distress, convulsions, severe anaemia, jaundice etc.[8] The presence of above symptoms plus identification of asexual forms of malaria parasites (mainly *P. falciparum*) are the criteria used for diagnosing severe malaria.[8]

Nearly all one million malaria deaths that are reported yearly occur amongst children under the age of five years in sub-Saharan Africa following severe *P. falciparum* infection and are localised in areas with high malaria transmission intensity.[8] The rest of the mortality occurs among non-immune adults and children residing in areas outside Africa which are characterised by low to moderate *P. falciparum* malaria transmission intensity.[8] However because sub-Saharan Africa carries the heaviest burden of severe malaria, most of the epidemiological and clinical data on severe malaria come from African children.[8]

Studies have suggested that in areas of sub-Saharan Africa with intense malaria transmission severe malarial anaemia is the predominant form of severe malaria in children aged 1 to 3 years, whereas in areas with moderate to intense transmission cerebral malaria is the predominant form of severe malaria and occurs in much older children.[8]

It has been estimated that in Africa cerebral malaria affects about 575,000 children under the age of five years annually, with a 19% case fatality rate.[9,10] Also in the same age group, about 1.42 to 5.66 million cases of severe malarial anaemia occur annually with a 13% case fatality rate. [9,10] In addition about 17% of children who recover from cerebral malaria suffer from learning impairments and disabilities due to brain damage, including epilepsy and spasticity.[9,10] In general it is estimated that malaria causes 20% of all deaths of children under the age of five years in Africa.[2,7]

In Africa about 1 to 2% of children, who develop uncomplicated malaria each year, will eventually develop severe malaria.[11] Apart from factors related to health systems i.e. drug resistance or delayed treatment, it has been stated that the occurrence of severe malaria is largely determined by unknown complex interactions of host, parasite and socio-environmental factors.[11,12] To date, epidemiological and molecular research efforts have not been able to comprehensively elucidate risk factors that could be manipulated to prevent evolution of severe malaria in children[13-15] and there is yet no vaccine against malaria or severe malaria.

In the absence of specific risk factors that could be manipulated to prevent the development of severe malaria, control of severe malaria depends entirely on the application of general malaria control strategies. Proper application of malaria control strategies will prevent and control both non-severe and severe malaria disease.

1.1.3 Control of severe malaria in children

The ultimate purpose of malaria control in malaria endemic countries is to reduce malaria to a level where the disease is no longer a public health problem. Control of malaria therefore involves measures, which reduce its transmission, prevent manifestation of the disease, and alleviate suffering of those who have the disease. These measures include:[16] vector control strategies aimed at reducing contacts between mosquitoes and human beings (e.g. source reduction, in door residual spraying and use of insecticide treated bed nets), prompt diagnosis and treatment of malaria cases with effective drugs, and intermittent presumptive treatment of malaria in pregnancy during second and third trimesters to reduce the health impact of malaria on mothers and their newborns in endemic countries.

Source reduction is a strategy of choice for vector control in areas where mosquitoes breeding sites are localised in a few habitats.[16] The strategy is implemented by filling pits that collect water, draining swamps, and removing water standing in cans and broken tiles. In areas where removal of breeding sites can not be implemented, larval destruction may be carried out using chemical or biological agents.[16] Unfortunately, in Africa where *A. gambiae* is a major vector, source reduction strategy has not been implemented in large scale, because the mosquito breeds in numerous sites and the larva grows fast into adulthood thus making it difficult to trace all breeding sites and implement the strategy before the larva grows into adult mosquito.[16]

In door house spraying with insecticides, is another strategy for vector control. The strategy is implemented by applying residual insecticides to the wall and other surfaces of the house. The insecticide kills those mosquitoes, which rest on the wall after taking blood. To be effective

(in order to reduce mosquito bites and malaria transmission), the strategy must be applied to at least 70% of the households in an intervention area.[16] However, with exception of a few countries in Southern Africa, other malaria endemic countries in sub-Saharan Africa have not applied it widely due to high operational/logistics costs, and emerging resistance of the residual insecticides.[1,16] In other areas outside Africa especially those with frequent malaria epidemics the strategy has been used very successfully to prevent malaria transmission.[1]

The use of Insecticide-Treated Nets (ITNS) has also been advocated as a strategy for vector control. Studies have shown that their use can reduce up to 20% of all-cause under five mortality rate, and reduce child and maternal morbidity. [2] In order to achieve this level of efficacy, the ITNS coverage among under fives should be 60% or above. [2] Due to high cost, poor social marketing, weak supply and distribution mechanisms, the ITNS coverage has remained low in many African malaria endemic countries. [2] Recent ITNS surveys in some African countries have revealed that their use among under fives stood at 5%.[2] This level is not adequate to have an impact on malaria control.[2]

Prompt and effective treatment of malaria has been recommended as a key malaria (including severe malaria) control strategy.[2] In areas where *P. falciparum* malaria is endemic, this strategy could save lives by halting the progression of severe malaria to death.[2] Importantly, the strategy will continue to be a key control measure, since as explained above other measures are either weak or non-functional.

Chemotherapeutic treatment of severe malaria in children

The chemotherapeutic control of severe malaria in children requires a drug that is effective and acts very fast. This normally should be accompanied by good supportive care and blood transfusion in severe malarial anaemia. For many years quinine has been one of the major drugs meeting these conditions for treating severe malaria. The drug has been widely available in many national malaria control programs in malaria endemic countries for treating the disease. Recently artemisinin derivatives, drugs originally derived from the *Artemisia annua* plant in China have shown potential for treating severe malaria in children; however they are not widely used yet because of the controversy regarding their efficacy in comparison to quinine. Though it is difficult to elucidate the treatment costs of quinine versus the artemisinin derivatives, one study indicated that the cost of using a standard dose for quinine in treating severe malaria might be comparable to the cost of using intramuscular artemether. In that study the cost for quinine was estimated at $22.15 while that for artemether was $ 18.26.[45] However this may vary depending on products under consideration and market forces.

Pharmacology of quinine

In severe malaria quinine is administered intravenously, although the oral and intramuscular routes have also been reported to have rapid absorption.[8,17] The oral route is not normally used, as many children with severe malaria can not swallow and the intramuscular route is associated with the development of sterile abscesses. After quinine administration plasma peak concentration is achieved after 3 hours.[8] Studies have shown that after absorption about 70 to 85% of the drug is bound to proteins and it has been noted that the drug has high bioavailability (about 80%).[17] About 80% of the drug is metabolised in the liver and its

metabolites are excreted in urine as hydroxyl derivatives.[17] Plasma elimination half life of quinine in children aged 1 to 12 years who have malaria is eleven to twelve hours.[17]

Quinine is a blood schizonticidal agent which acts against the asexual erythrocytic forms of Plasmodia.[17] Though its complete mechanism of action is not clearly understood, it has been suggested that its antimalarial activity is mediated through binding to plasmodial Deoxribose Nucleic Acid (DNA) to prevent protein synthesis[17] and consequently inhibiting parasite growth. In treating severe malaria in children, the drug is administered for seven days starting at a loading dose of 20mg/kg followed by 10mg/kg every 12 hours until the child is able to swallow then the drug is given orally every eight hours.[8] In settings with no intravenous drug administration facilities, it can also be administered intramuscularly, however as with intravenous administration, it must be changed to the oral route when the child is able to swallow. The drug is known to cause some side effects like ringing ears, cardiac arrhythmias, and hypoglycaemia.[8]

Pharmacology of artemisinin derivatives

Artemisinin and its derivatives (e.g. dihydroartemisinin, artemether, arteether and artesunate) are another group of antimalarial drugs with potential for treating severe malaria in children.[18] Because of the influence of their chemical structure, artemisinin and dihydroartemisinin are sparingly soluble in water and fat and thus they can only be administered orally and rectally.[18,19] Artemether and arteether can be administered orally and intramuscularly, and artesunate can be administered orally, rectally, and parenterally (intramuscularly and intravenously).[18,19] Studies have shown that in uncomplicated malaria the absorption of intramuscular formulations of artemether and arteether is poor compared to their respective

oral formulations and studies in acute malaria have shown that their absorption after intramuscular injection is extremely variable and may take hours to reach parasiticidal concentrations.[18,20] In contrast, artesunate seems to have excellent pharmacokinetics properties whether administered orally, intramuscularly or intravenously.[18] Absorption of artesunate from the intramuscular site in children with severe malaria seems to be rapid and maximum concentration achieved within one hour with its bioavailability reaching 80%.[18,21] Thus compared to other derivatives(e.g. artemether) artesunate seems to be a better choice for childhood severe malaria treatment.[21] Available data on rectal artesunate in African children with severe malaria show that it has variable absorption with peak concentration achieved after two hours and its bioavailability ranging from 20 to 60%.[18]

Once absorbed the artemisinin derivatives (artemether, arteether and artesunate) are converted to dihydroartemisinin and other inactive metabolites in the liver.[18] Dihydroartemisinin is a potent antimalarial with an elimination half-life of about 45 minutes. Artemisinin itself is not metabolised but acts as a primary antimalarial, while artesunate is rapidly hydrolysed to dihydroartemisinin, which mediates its antimalarial activity. Apart from their conversion to dihydroartemisinin, artemether and arteether themselves contribute to their antimalarial activity.[18] In one study, the elimination half-life for artesunate among adults with severe malaria was estimated to be 25 minutes while that for artemether among adults with severe malaria was between four to seven hours.[18]

Artemisinin and its derivatives act against small and large ring stages of plasmodia infection.[18] In addition, studies have shown that they kill early stages of gametocytes and hence they may reduce malaria transmission especially in areas with low transmission intensities.[18] Studies

have found that they act faster than other known malaria drugs.[18] The antimalarial activity of artemisinin and its derivatives is attributed to their peroxide containing structure.[18] It is believed that upon reaction with Iron (Fe^{2+}), artemisinins are first converted into oxygen centred free radicals and then into carbon centred free radicals.[18] The carbon centred free radicals are thought to be the main mediators of the artemisinin parasiticidal process.[18] However a more recent theory has suggested that the drugs' mechanism of action is mediated through inhibition of the malaria parasite's calcium ATPase (sarcoplasmic endoplasmic reticulum calcium ATPase).[18] These observations may only serve to indicate that this is an area that requires more research.

Clinical administration: Artemether-3.2mg/kg intramuscular dose is administered as a loading dose, followed by 1.6mg/kg daily for a minimum of the three days.[8] For artesunate, 2.4mg/kg as a loading dose is administered intramuscularly or intravenously followed by 1.2mg/kg daily for a minimum of three days until the patient can take oral drugs.[8] As artemisinin derivatives monotherapy for malaria has been associated with recrudescence rates of up to 20% (attributed to their short half lives), continuation of treatment for five days in all regimens has been recommended to check recrudescence.[18] Despite the pre-clinical evidence that the drugs have a potential to cause neuro-toxicity and feto-toxicity, there is yet no evidence that they have any meaningful clinical toxicity at normal doses.[18] However, due to inadequate safety data on their use during pregnancy, they are not recommended during the first trimester.[18]

1.2 PROBLEM STATEMENT, JUSTIFICATION AND OBJECTIVES

1.2.1 Problem statement and justification

It has been reported that the efficacy of quinine a key drug for severe malaria in children, is declining especially in some parts of Africa and South East Asia.[22-25] These reports were an alert to malaria experts especially when experience shows that it takes about ten years or more to develop new malaria drugs. Additionally, drug companies hesitate to invest money in developing drugs for diseases of the poor, as they might not be able to sell the drugs at prices that will recover development costs.[26] Lessons learned from treating uncomplicated malaria with chloroquine have shown that not developing a replacement drug until the main drug for treatment is completely unresponsive could be disastrous. It has been documented that between year 1978 and 1988 mortality attributable to malaria increased by up to six times in some parts of Africa due to chloroquine resistance.[27-29] If the same were to happen to quinine in treating severe malaria in children, the mortality would be higher as it is known that even in the current situation where cure rates are still high with quinine, the mortality rate for severe malaria in children is up to 40%.[30]

This knowledge necessitated the launch of a series of studies to find alternative drugs for severe malaria treatment in children that are effective and superior to existing drugs. Most of the studies focused on finding an alternative from artemisinin derivatives,[31-42] a group of drugs with no known *P. falciparum* resistance and which act faster than all known malaria drugs.[18,19] In addition, compared to quinine, which may induce hypoglycaemia, cardiac arrthymias, and ringing ears, they seem to have few clinical side effects. As opposed to quinine for which the recommendation is that in treating severe malaria, it should be administered intravenously, some artemisinin derivatives may also be administered

intramuscularly, a route that may be the only option in rural settings. In view of the above features, artemisinin derivatives showed potential for replacing quinine in treating severe malaria in children, in the face of emerging quinine ineffectiveness.

Most of these studies showed mixed findings on the superiority of artemisinin derivatives over quinine in mortality and other endpoints[31-42] and therefore did not provide sufficient evidence on superiority of artemisinin derivatives over quinine. It has been argued that where there are uncertainties regarding the effectiveness of any particular intervention, a systemic review and meta analysis of randomised controlled trials could help to clarify evidence for such an intervention and thus hasten the introduction of effective intervention in healthcare[43]. To date two meta-analyses of published trials have looked at the efficacy of artemisinin derivatives for treating severe malaria.[44,45] The first, looked at the efficacy of artemether versus quinine in treating severe malaria,[44] and the second evaluated the efficacy of artemisinin derivatives versus standard drugs used for treating severe malaria (e.g. quinine, chloroquine, and others).[45] Both reviews pooled data from adults and children. The first meta-analysis showed that there was no significant difference between artemether and quinine in mortality rate when data from all continents were considered (Odds Ratio 0.76,95% confidence interval 0.5 to 1.14, random effects model), but when the data from South east Asia alone was pooled, a trend towards reduction in mortality (by artemether) became evident (Odds Ratio 0.38, 95% confidence interval 0.14 to 1.02, random effects model). The second meta-analysis showed artemisinin derivatives were better than quinine, but the difference was marginal when only data from high quality trials were pooled together (Odds Ratio 0.72,95% confidence interval 0.54 to 0.96, random effects model). While the findings seem to suggest that artemisinin derivatives are either equal to, or have marginal advantage over quinine in mortality reduction, both

reviews did not consider the efficacy of the drugs on childhood severe malaria separately, thus making it difficult to apply the findings to children.

Studies have shown that severe malaria develops and kills faster in children than in adults.[8] It has also been shown that most deaths from severe malaria in children occur within 24 hours of hospital admission while deaths in adults occur much later.[8] Therefore while there may be enough time for drugs to act and save lives in adults, there may not be enough time in children.[46] In theory this might lead to a difference in post-treatment mortality rates between children and adults. On the other hand it has been suggested that upon treatment children with cerebral malaria tend to resolve coma faster (1 to 2 days) than adults (2 to 4 days), a phenomenon which in theory might lead to lower mortality in children relative to adults.[8] It is not clearly known how these phenomena might affect response to treatment. These controversies point to the fact that there are basic differences between children and adults that may predict the way the two population groups respond to treatment for severe malaria. Therefore findings obtained from pooling data from children and adults can not provide an answer to the question, which seeks to find the drug which works better in children. Hence a need to evaluate data arising from trials conducted among children.

One Individual Patient Data (IPD) review on efficacy of artemether versus quinine in severe malaria found that artemether was not more efficacious than quinine in severe malaria in children.[47] While this review may have provided some information on this area, the information provided was not adequate as it included studies from Africa alone, and it evaluated one drug alone i.e. artemether. In addition, it included only four trials. There was therefore an urgent need to conduct a comprehensive review that would include potential

randomised controlled trials from all continents, which compared the efficacy of artemisinin derivatives versus quinine in treating severe malaria in children, with mortality as a primary end point and parasite clearance time, fever clearance time, coma resolution time, incidence of neurological sequelae, 28th day cure rate, and incidence of adverse effects as secondary end points. It was expected that the findings would assist policy makers in malaria endemic countries to decide whether based on their efficacy, artemisinin derivatives should or should not replace quinine in treating severe malaria in children.

1.2.2 Objectives

1.2.2.1 Primary aim

To compare the efficacy of parenteral artemisinin derivatives with quinine in treating severe malaria in childhood through systematic review and meta-analysis of randomised controlled trials.

1.2.2.2 Specific objectives

(1) To compare the efficacy of parenteral artemisinin derivatives to quinine in terms of mortality attributable to severe malaria in children.

(2) To compare the efficacy of parenteral artemisinin derivatives to quinine in terms of parasite clearance time, fever clearance time, coma resolution time, incidence of neurological sequelae, 28th day cure rate, and incidence of adverse effects.

1.3 Definition of terms and significance of outcome measures used.

Severe malaria: This is diagnosed in patients with *P. falciparum* asexual parasitaemia, who in addition also present with any of the following: impaired consciousness, prostration, severe anaemia, renal failure, respiratory distress, pulmonary oedema, jaundice, circulatory collapse, abnormal bleeding, multiple convulsions, acidosis, and macroscopic haemoglobinuria.[8]

Artemisinin derivatives: In this review they denoted the pharmaceuticals derived from artemisinin compound that can be administered either intramuscularly or intravenously: These are Artemether, β-arteether or artemotil, and artesunate.

Mortality: In this review, mortality was defined as any death occurring in a study participant from the time the participant is randomised to a particular study arm to the time the trial follow-up schedule is completed.

Significance: Severe malaria is a life threatening medical condition. In children it is associated with a high case fatality rate even when treatment with an effective antimalarial and good supportive care is provided. Any efficacious anti-malaria drug should therefore be able to reduce the case fatality rate. This is the reason why mortality was taken as a primary efficacy outcome.

Parasite Clearance Time (PCT)

Definition: PCT was defined as the mean or median time taken for either an artemisinin derivative or quinine to clear malaria parasites from study participants. However, because it was anticipated that there would be slight differences in the way the investigators assessed the PCT it was decided to adapt the PCT ascertainment criteria for each study.

Significance: Malaria drugs kill parasites by inhibiting various parasite metabolic processes. The removal of malaria parasites from the circulation of a malaria patient should ideally lead to a relief of malaria signs and symptoms. An efficacious drug should clear parasites very quickly and consequently relieve malaria symptoms.

Fever Clearance Time (FCT)

Definition: FCT was defined as the mean or median time taken for an artemisinin derivative or quinine to bring temperature to normal in study participants. However, because it was anticipated that there would be slight differences in the way the investigators assessed the FCT it was decided to adapt FCT ascertainment criteria for each study.

Significance: Fever is a key symptom of malaria. A drug, which is efficacious, should clear fever faster.

Coma Resolution Time (CRT)

Definition: CRT time was defined as the mean or median time taken for an artemisinin derivative or quinine to resolve loss of consciousness among study participants. However, because it was anticipated that there would be slight differences in the way the investigators assessed the CRT resolution it was decided to adapt CRT ascertainment criteria for each study.

Significance: Coma or loss of consciousness is a cardinal feature of cerebral malaria (a form of severe malaria). Studies have shown severe malaria patients with coma tend to have a poor prognosis. An antimalarial, which can resolves coma faster, should in theory improve the prognosis of a cerebral malaria patient.

Neurological sequelae

This outcome measure was defined as the evolution of neurological abnormalities following treatment. This review included all neurological abnormalities, which were detected clinically at discharge, or by day seven of the follow up schedule**.**

Significance: All human drugs including antimalarials have the potential to cause harm to those who use them. This includes neurological sequelae or disabilities. An antimalarial drug with frequent and serious neurological sequelae should be avoided.

28th day cure rate: This was defined as the percentage of children who remained parasite free by day 28 of follow up, in each arm of a particular trial. This is one of the WHO recommended efficacy outcomes in determining cure rates for malaria drugs.

Adverse effects

Definition: This was defined as mild or serious discomfort or consequence observed after commencement of treatment. The mild discomfort included weakness, vomiting, and pruritis while serious adverse effects were defined as life threatening conditions or death.

Significance: Apart from efficacy another parameter, which determines the acceptability of the drug for widespread clinical use, is its safety and tolerability. An efficacious drug with serious adverse effects can not pass safety and tolerability tests and is unaccepted for widespread clinical use.

2.0 METHODS

This study was approved by Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Ethical clearance number: M040816). Methodology was based on Cochrane collaboration recommendations on conducting systematic reviews and meta-analysis of randomised control trials.[48-50]

2.1 Study design & population

The design involved the systematic review and meta- analysis of the results of randomised clinical trials on the efficacy of parenteral artemisinin derivatives versus quinine in the treatment of severe malaria in children. The population consisted of children aged 0 to 14 years diagnosed with severe malaria and who were included in these randomised trials worldwide.

2.2 Criteria for considering studies for this review

Types of studies

Randomised controlled trials of treatment comparisons

Types of participants

Children aged 0 to 14 years with any form of severe malaria as defined by the World Health Organization. [8] Trials including both adults and children were excluded.

Types of interventions

Only one intravenous or intramuscular artemisinin derivative was compared with intravenous or intramuscular quinine. Studies were not considered if: an artemisinin derivative was combined with another antimalarial and compared with quinine, comparison was between two

or more artemisinin derivatives, comparison was between regimens and routes of administration of one artemisinin derivative or the trial included more than two arms.

Types of outcome measures

Trials measuring mortality as an outcome.

Primary outcome/end point

Mortality

Secondary outcomes/end points

Parasite clearance time, fever clearance time, coma resolution time, incidence of neurological sequelae, 28th day cure rate, and incidence of adverse effects.

2.3 Search strategy for identification of studies

Electronic databases and non-electronic sources were used to search for studies to include in the review. Both controlled vocabulary terms and free text words were used. Published as well as unpublished studies were sought and the search was not restricted to any language. The detailed search strategy for each source is described below.

Electronic databases

(i)The Cochrane Central Register of Controlled Trials (CENTRAL), host: The Cochrane Library issue 4, 2005, search date: October 23rd 2005, years covered by search: 1966 to 2005

The complete search strategy is listed in Table 2.1

Table 2.1 Search strategy for CENTRAL

Search No	Search terms
#1	Artemisinins (MeSH descriptor)
#2	Artemether(All fields)
#3	Artesunate(All fields)
#4	Arteether(All fields)
#5	Dihydroartemisinin (All fields)
#6	Artemotil (All fields)
#7	Artelinic acid(All fields)
#8	Artemisimic acid(All fields)
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10	Quinine(MeSH descriptor)
#11	Quinine(All fields)
#12	(#10 OR #11)
#13	(#9 AND #12)
#14	Malaria(MeSH descriptor)
#15	Malaria, Cerebral(MeSH descriptor)
#16	Malaria, Falciparum(MeSH descriptor)
#17	Malaria(All fields)
#18	Severe malaria(All fields)
#19	Complicated malaria(All fields)
#20	Cerebral malaria(All fields)
#21	(#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22	(#13 AND #21)

Searches using Medical Subject Headings (MeSH) are followed by the words "MeSH descriptor" in brackets. In all MeSH searches all trees were exploded. Search terms followed by the words "all fields" in brackets, were free text words, and in these all fields e.g. title, abstract and key words were searched. Searches numbered 1 to 9 were used to identify studies, which involved artemisinin derivatives, searches numbered 10 and 12 identified studies which involved quinine, search number 13 identified studies which involved both artemisinin derivatives and quinine, and searches 14 to 21 identified studies which involved malaria. Search number 22 identified malaria trials involving artemisinin derivatives as well as quinine.

(ii)MEDLINE, host: National Library of Medicine (USA), search date: October 23rd 2005, years covered by search: 1966 to October 2005)

The complete search strategy is listed in Table 2.2

Table 2.2 Search strategy for MEDLINE

Search No	Search terms
#1	"Artemisinins"/all subheadings
#2	"Artemether"[Substance Name]
#3	"Artesunate"[Substance Name]
#4	"Arteether"[Substance Name]
#5	"Dihydroquinghaosu"[Substance Name]
#6	Artemether[tw]
#7	Artesunate[tw]
#8	Arteether[tw]
#9	Dihydroartemisinin[tw]
#10	Artemotil[tw]
#11	Artelinic[tw]
#12	Artemisimic[tw]
#13	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14	"Quinine"/all subheadings
#15	Quinine[tw]
#16	(#14 OR #15)
#17	(#13 AND #16)
#18	"Malaria"/all subheadings
#19	"Malaria, Cerebral"/all subheadings
#20	"Malaria, Falciparum"/all subheadings
#21	Severe malaria[tw]
#22	Complicated malaria[tw]
#23	Malaria[tw]
#24	Cerebral malaria[tw]
#25	(#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
#26	(#17 AND #25)
#27	Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebo[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:Noexp] OR comparative study[mh] OR evaluation studies[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteeer*[tw]) NOT (animals [mh] NOT human[mh])
#28	(#26 AND #27)

For search number 1 to 26 words which are followed by "/" are MeSH terms while words followed by "[tw]" are text words. Terms indexed as substance names are followed by the words "substance name" in brackets. All searches using MeSH terms were exploded. For search #27 the abbreviations used have the following meanings: [mh] = MeSH term, [pt] = publication type, [tw] = text word, [mh:Noexp] = MeSH term no explosion. Searches numbered 1 to 13 were used to identify studies which involved artemisinin derivatives, searches number 14 to 16 identified studies which involved quinine, search number 17 identified studies involving artemisinin derivatives and quinine, searches 18 to 25 identified studies involving malaria, search number 26 identified malaria studies involving artemisinin derivatives and quinine. Search number 27 identified randomised controlled studies and is the Cochrane highly sensitive search strategy (all phases).[50] Search number 28 identified all possible randomised trials which compared artemisinin derivatives with quinine for the treatment of malaria.

(iii)The EMBASE, host: Ovid technologies Inc, search date: October 23rd 2005, years covered by search: 1980 to October 2005)

The complete search strategy is listed in Table 2.3

Table 2.3 Search strategy for EMBASE

Search No	Search terms
1	exp ARTEMISININ/
2	exp Artemisinin Derivative/
3	exp ARTEMETHER/
4	exp ARTESUNATE/
5	exp ARTEETHER/
6	ARTEMISININ.tw.
7	ARTEMETHER.tw.
8	ARTESUNATE.tw.
9	ARTEETHER.tw.
10	(1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9)
11	exp QUININE/
12	QUININE.tw.
13	(11 or 12)
14	(10 and 13)
15	exp MALARIA/
16	exp Brain Malaria/
17	exp Malaria Falciparum/
18	MALARIA.tw.
19	(15 or 16 or 17 or 18)
20	(14 and 19)
21	Randomized Controlled Trial/
22	exp RANDOMIZATION/
23	Controlled Study/
24	Multicenter Study/
25	Phase 3 Clinical Trial/
26	Phase 4 Clinical Trial/
27	Double Blind Procedure/
28	Single Blind Procedure/
29	(21 or 22 or 23 or 24 or 25 or 26 or 27 or 28)
30	(RANDOM$ or CROSS?OVER$ or FACTORIAL$ or PLACEBO$ or VOLUNTEER).ab,ti.
31	(SINGL$ or DOUBL$ or TREBL$ or TRIPL$ or BLIND$ or MASK$).ab,ti.
32	(29 or 30 or 31)
33	(20 and 32)

Words followed by "/" were controlled vocabulary terms in EMBASE, while those followed by ".tw." were text words. Searches numbered 1 to 10 were used to identify studies involving artemisinin derivatives, searches 11 to 13 identified studies which involving quinine, search number 14 identified studies involving artemisinin derivatives and quinine, 15 to 19 identified studies involving malaria, and search number 20 identified malaria studies involving artemisinin derivatives and quinine. Searches 21 to 32 identified randomised controlled

studies. Search number 33 identified randomised controlled studies comparing artemisinin derivatives and quinine for the treatment of malaria.

(iv)LILACS, host: Latin American and Caribbean Centre on Health Sciences Information, search date: October 23rd 2005, years covered by search: 1982 to October 2005. The complete search strategy is listed in Table 2.4

Table 2.4 Search strategy for LILACS

Search	Search term
1	Artemisinin AND quinine
2	Artemether AND quinine
2	Artesunate AND quinine
4	Arteether AND quinine
5	Dihydroartemisinin AND quinine
6	(Artemisinin AND quinine) OR (Artemether AND quinine) OR (Artesunate AND quinine) OR (Arteether AND quinine) OR (Dihydroartemisinin AND quinine)
7	((Artemisinin AND quinine) OR (Artemether AND quinine) OR (Artesunate AND quinine) OR (Arteether AND quinine) OR (Dihydroartemisinin AND quinine)) AND Malaria
8	((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal)))
9	(((Artemisinin AND quinine) OR (Artemether AND quinine) OR (Artesunate AND quinine) OR (Arteether AND quinine) OR (Dihydroartemisinin AND quinine)) AND Malaria) AND ((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal)))

Using the advanced search facility in the LILACS search interface, searches numbered 1 to 6 were conducted to identify studies involving artemisinin derivatives and quinine. Search number 7 identified studies involving malaria, artemisinin derivatives and quinine. Search number 8 identified randomised controlled studies and is the highly sensitive search strategy for LILACS.[51] Search number 9 identified all possible randomised trials which compared artemisinin derivatives with quinine for the treatment of malaria.

Other sources

Conference proceedings

National Institute for Medical Research: Proceedings of the 11th annual joint scientific conference with a seminar on malaria control research. 22-25th February 1993, Arusha, Tanzania.

Efforts to identify unpublished studies

A number of malaria researchers were contacted to find out if they had any information on unpublished trials for possible inclusion in the review.

Those contacted were: Dr P Olumese (WHO/Roll back malaria), Prof A Bjorkman (Karolinska Institute, Sweden), Dr J Tomas (Institute of Tropical Medicine, Berlin Germany), Dr I Adam (Khartoum University, Sudan), Prof JK Tumwine (Makerere University, Uganda), Prof Z Premji (Muhimbili University, Tanzania), Dr JF Doherty (Medical Research Council Laboratories, The Gambia), Prof NJ White (Mahidol University, Thailand**)**, Dr L von Seidlein (Medical Research Council Laboratories, The Gambia), Dr EA Gomez **(**Catholic University, Ecuador), Dr H Barennes (Epidemiology Intervention Center, Burkina Faso), Dr G Priotto (MSF, France), Dr SB Sirima (Burkina Faso), Dr CO Obonyo (Kenya Medical Research

Institute, Kenya), Dr H Van der Meersch (France), Dr TA Eggelte **(**Amsterdam Academic Medical Center, Netherlands), Dr M Rowland (London School of Hygiene and Tropical Medicine, UK), Dr. F Nosten (Shoklo Malaria Research Unit,Thailand), Dr TE Taylor (United States of America), Dr R Moyou-somo (Cameroon), Dr P Thuma (United States of America), Prof Mohanty (India), Dr Ojuawo (Nigeria), Prof I Afza (India), and Prof O Doumbo, (Bamako University, Mali). Noelle Jude of Norvatis Pharmaceutical Company in Geneva, Switzerland was also contacted.

2.4 Study selection, data extraction and quality assessment

Selection of studies

After the literature search was completed the results were sorted to include abstracts, which had the potential of being included in the study. Complete articles of the potential abstracts were retrieved or ordered. If a trial was published more than once, only one publication was presented for assessment and if an interim analysis of a particular major study was published, only the final publication was presented for assessment. In order to minimize selection bias, two reviewers (The author of the report and a fellow student) independently assessed the suitability of each paper for inclusion in the study using specific predetermined eligibility criteria (Appendix A). Where there was disagreement on whether to include a particular trial, the advice of a third person was sought.

Data extraction and management

After eligible trials were identified, data were extracted using specially prepared form (Appendix B). Study site, study year, type of severe malaria, study methods, sample size, settings, interventions and outcomes (primary and secondary outcomes) were extracted. For

the *binary* outcomes (mortality, incidence of neurological sequelae and 28th day cure rate) the number of participants experiencing the event was recorded for each trial and for the *continuous* outcomes (parasites clearance time, fever clearance time and coma resolution time) means and standard deviations were extracted. If the reporting was not in means and standard deviations, respective medians and inter-quartile ranges were also extracted. In each case a sample size from which a particular outcome was measured was also recorded. A pilot data collection was carried out to ascertain the suitability of data collection tools and uniformity of outcomes to be collected. Two articles were used in pilot data extraction and as a result "name of artemisinin derivative" and "type of severe malaria" were added to the form before proper data collection commenced.

Assessment of methodological quality of included studies

All eligible studies were assessed for their quality in design and conduct. Four key criteria were employed to assess the quality of studies[48,49]; these included generation of allocation sequence, allocation concealment, blinding and loss to follow up/exclusion from analysis. Generation of allocation sequence was graded as "adequate" if methods used could not predict allocation sequence, "inadequate" if methods used could predict allocation sequence or "unclear" if methods used were not clear. Allocation concealment was graded as "adequate" if methods used could not predict assignment, "inadequate" if methods used could predict assignment or "unclear" if methods used were not clear. Blinding was described as "open" if all parties were aware of the treatment, "single" if participant *or* investigators were not aware of the treatment and "double" blind if *both* participant *and* investigators were not aware of the treatment given. If loss to follow up was not greater than 20% this was considered as "adequate". If it was more than that, it was considered as "inadequate". In order to minimize

bias in assessment of methodological quality two independent assessors (The author of the report and a fellow student) did an assessment of the quality of each paper independently, using specific pre-determined quality criteria (Appendix C). Where there was disagreement or difficulty in assessing the quality of a particular trial, the advice of a third person was sought. Also previous quality reviews[45,52] by other workers helped in deciding whether there was adequate generation of random numbers in two articles and whether there was adequate allocation concealment in another two articles. The result of this assessment was then used for sensitivity analysis.

2.5 Data analysis

Before data entry all data collection forms were checked for missing data or inappropriate filling, and then necessary corrections were made using the collected original study publications. Data were entered in *Epi Info* and analysed using *STATA release 8.2.* Special STATA meta-analysis commands were downloaded from the Oxford Centre for Statistics in Medicine website.[53] Binary outcomes were compared by Risk Ratio (RR) using the Mantel-Haenszel method.[54] and continuous outcomes by Weighted Mean Difference (WMD) using the inverse variance method[54,55] where the fixed effect model was used. For both outcomes where the random effects model was used, the DerSimonian and Laird method was employed in computing summary estimates.[55] Where continuous outcomes were reported as medians and interquartile ranges, they were not included in summary estimate calculations, because currently there are no methods for combining data reported in that form. The 95% confidence interval was used and $P < 0.05$ was assumed to be showing evidence for a statistically significant difference.

Assessment of heterogeneity and publication bias

To assess heterogeneity among trials, the chi-squared test for heterogeneity was used. A chi-squared test for heterogeneity with p value<0.05 was assumed to be showing significant heterogeneity among trials. The fixed effect model was employed in pooling data where a chi-squared test for heterogeneity showed no evidence of heterogeneity. Where the test showed significant heterogeneity, the random effects model was used instead. While during the protocol writing stage the need for doing subgroup analysis for exploring heterogeneity was not anticipated, later in the research process it was decided to do subgroup analysis on detection of heterogeneity. The study setting (Asian versus non-Asian studies) was chosen as a possible source of heterogeneity. The rationale for choosing this characteristic was that in Asia, evidence suggested that the level of quinine resistance is higher than on other continents[1] and therefore artemisinin derivatives are likely to be more efficacious in Asia than on other continents; a situation that might introduce heterogeneity in summary estimates. The difference in confidence intervals was used to ascertain the difference in effect measures between the two sub-groups. Other characteristics like study designs and population were thought not have major impact on study outcomes. Evidence for publication bias was explored using a funnel plot.[56]

Sensitivity analysis

Also sensitivity analysis for adequately concealed trials and inadequately or unclear concealed trials was carried out for all outcomes. The sensitivity analysis was limited to one factor as all other factors were similar i.e. all trials but one were open and all trials had overall follow-up rates that were adequate/satisfactory.

3. RESULTS

3.0 DESCRIPTION OF STUDIES

3.1 Results of the search

The search strategy for CENTRAL produced 78 articles, the search strategy for MEDLINE resulted in 160 articles, the search strategy for EMBASE resulted in 212 articles, and the search strategy for LILACS did not produce any article. Search from conference proceedings did not produce any article. All researchers and a pharmaceutical company that produces an artemisinin based combination drug, replied that they had no information on any unpublished trial. After carefully going through abstracts in each of the sources searched fourteen potential studies were identified, eleven of which met the inclusion criteria and were included in the review. All retrieved articles were publications in the English language journals of the studies conducted between 1990-2002 in Africa and Asia and published from 1993 to 2004. Study names, countries where trials were conducted and names of articles selected are presented in table 3.1, baseline characteristics of selected studies in table 3.2, and characteristics of included studies in Appendix D

3.1.1 Included studies

Location and participants

Nine studies were conducted in African countries i.e. Nigeria-Walker(1993)[31], Ojuawo(1998)[35], and Olumese(1999)[36]. Others were; Malawi-Taylor(1998)[34], Kenya-Murphy(1996)[32], Gambia-Van-Hensbroek(1996)[33], Zambia-Thuma(2000)[37], Cameroon-Moyou-somo(2001)[38], and Sudan-Adam(2002)[39]. Two were conducted in India i.e. Huda(2000)[40] and Mohanty(2004)[41]. Age range was from 0 to 14 years and a total of 739

children receiving artemisinin derivatives were compared with 716 children receiving quinine. In terms of sex distribution there were 765 male and 690 female children. See Tables 3.1 and 3.2

Type of severe malaria

Eight studies i.e. Walker(1993)[31], Murphy(1996)[32], Van Hensbroek(1996)[33], Taylor(1998)[34], Ojuawo(1998)[35], Olumese(1999)[36], Thuma(2000)[37], Moyou-somo(2001)[38] recruited children with cerebral malaria. In these studies cerebral malaria was defined as a Blantyre Coma Scale of ≤ 2 and the presence of *P. falciparum* or according to WHO cerebral malaria diagnosis criteria.[8] Three studies i.e. Adam(2002)[39], Huda(2003)[40], and Mohanty(2004)[41] recruited children with any form of severe malaria as defined by WHO.[8]

Intervention drugs used

Eight trials i.e. Walker(1993)[31], Murphy(1996)[32], Van Hensbroek(1996)[33], Taylor(1998)[34], Ojuawo(1998)[35], Olumese(1999)[36], Adam(2002)[39], and Huda(2003)[40] used intramuscular artemether while the Mohanty(2004)[41] trial used intramuscular artesunate. Two studies i.e. Thuma(2000)[37] and Moyou-somo(2001)[38] used intramuscular artemotil/β-arteether. The duration of artemisinin derivatives treatment ranged from 3-6 days while that of quinine ranged from 1 to 7 days. In all trials quinine was administered intravenously except in one trial i.e. Van Hensbroek(1996)[33] where it was administered intramuscularly. See table 3.2

Table 3.1 Selected studies

Study name &Country	Study article
Walker(1993)[31] Nigeria	Walker O, Salako LA, Omukhodion SI, Sowunmi A. An open randomized comparative study of intramuscular artemether and intravenous quinine in cerebral malaria in children. *Trans Roy Soc Trop Med Hyg* 1993;87:564-56
Murphy(1996)[32] Kenya	Murphy S, English M, Waruiru C, Mwangi I, Amukoye E, Crawley J et al. An open randomized trial of artemether versus quinine in the treatment of cerebral malaria in African children. *Trans Roy Soc Trop Med Hyg* 1996;90:298-301
Van Hensbroek(1996)[33] Gambia	Van Hensbroek MB, Onyiorah E, Jaffar S, Schneider G, Palmer A, Frenkel J et al. A trial of artemether or quinine in children with cerebral malaria. *N Engl J Med* 1996;335(2):69-75
Taylor(1998)[34] Malawi	Taylor TE, Wills BA, Courval JM, Molyneux ME. Intramuscular artemether vs intravenous quinine: an open, randomized trial in Malawian children with cerebral malaria. *Trop Med Int Health* 1998;3(1):3-8
Ojuawo (1998)[35] Nigeria	Ojuawo A, Adegboye AR, Oyewalo O. Clinical response and parasite clearance in childhood cerebral malaria: A comparison between intramuscular artemether and intravenous quinine. *East Afr Med J* 1998;75(8):450-452
Olumese(1999)[36] Nigeria	Olumese PE, Bjorkman A, Gbadegesin RA, Adeyemo AA, Walker O. Comparative efficacy of intramuscular artemether and intravenous quinine in Nigerian children with cerebral malaria. *Acta Trop* 1999;*73:231-236*
Thuma(2000)[37] Zambia	Thuma PE, Bhat GJ, Mabeza GF, Osborne C, Biemba G, Shakankale GM et al. A Randomized controlled trial of artemotil(β-arteether) in Zambian children with cerebral malaria. *Am J Trop Med Hyg* 2000;62(4):524-29
Moyou-somo(2001)[38] Cameroon	Moyou-somo R, Tietche F, Ondoa M, Kouemeni LE, Ekoe T, Mbonda E et al. Clinical trial of β-arteether versus quinine for the treatment of cerebral malaria in children in Yaounde, Cameroon. *Am J Trop Med Hyg* 2001;64(5,6):229-232
Adam(2002)[39] Sudan	Adam I, Idris HM, Mohamed-Ali AA, A/Elbasit, Elbashir MI. Comparison of intramuscular artemether and intravenous quinine in the treatment of Sudanese children with severe falciparum malaria. *East Afr Med J* 2002;79(12):621-625
Huda(2003)[40] India	Huda SN, Shahab T, Ali SM, Afzal K, Khan HM. A comparative clinical trial of Artemether and quinine in children with severe malaria. *Indian Pediatr* 2003;40:939-945
Mohanty(2004)[41] India	Mohanty AK, Rath BK, Mohanty R, Samal AK, Mishra K. Randomized control trial of quinine and artesunate in complicated malaria. *Indian J Pediatr* 2004;71:291-295

Note: The names of the studies in this review are identified by the name of the correspondent author followed by the year the study was published. The year is denoted in brackets.

3.1.2 Excluded studies

Three potential trials were excluded from the review: All trials were conducted in African continent and published in 1992, 1994, and 2000 respectively. All three examined the efficacy of artemether versus quinine in treating moderate severe malaria or cerebral malaria in children. One trial i.e. Taylor(1992)[58] was excluded because it was an interim analysis of another included trial i.e. Taylor (1998)[34]. The second one i.e. Salako (1994)[59] was excluded because literature review revealed that this trial was wrongly claimed as randomised, and the last was excluded because the full article of this trial could not be retrieved despite efforts made to get the paper through the Wits Health Science Library, the Journal editor and one author of the article. Characteristics of excluded trials are found in appendix E.

Table 3.2 Baseline characteristics of the selected studies

Study name	Artemisinin derivatives group			Quinine group			Type of malaria
	Mean age(SD)	Drug&(route)	Duration (maximum)	Mean age (SD)	Drug&(route)	Duration (maximum)	
Walker(1993)[31] Nigeria	3.0(1.3)	Artemether (i.m)	5 days	3.0(1.1)	Quinine (i.v)	7 days	Cerebral malaria
Murphy(1996)[32] Kenya	2.1(0.4-9) Ψ	Artemether (i.m)	3 days	2.5(0.4-12) Ψ	Quinine (i.v)	7 day	Cerebral malaria
Van Hensbroek(1996)[33] Gambia	4.0(1.8)	Artemether (i.m)	4 days	3.8(1.8)	Quinine (i.m)	5 days	Cerebral malaria
Taylor(1998)[34] Malawi	2.9(1.9)	Artemether (i.m)	5 days	3.2(1.9)	Quinine (i.v)	7 days	Cerebral malaria
Ojuawo (1998)[35] Nigeria	3.7(1.7)	Artemether (i.m)	3 days	4.1(1.9)	Quinine (i.v)	7 days	Cerebral malaria
Olumese(1999)[36] Nigeria	3.1(1.7)	Artemether (i.m)	5 days	3.2(1.7)	Quinine (i.v)	7 days	Cerebral malaria
Thuma(2000)[37] Zambia	3.9(2.2)	β-arteether (i.m)	5 days	3.3(1.8)	Quinine (i.v)	7 days	Cerebral malaria
Moyou-somo(2001)[38] Cameroon	3.4( )	β-arteether (i.m)	5 days	3.2( )	Quinine (i.v)	7 days	Severe malaria
Adam(2002)[39] Sudan	4.1(2.5)	Artemether (i.m)	5 days	3.6(3.2)	Quinine (i.v)	7 days	Severe malaria
Huda(2003)[40] India	6.6(3.5)	Artemether (i.m)	6 days	5.8(2.4)	Quinine (i.v)	7 days	Severe malaria
Mohanty(2004)[41] India	7.3(3.4)	Artesunate (i.m)	6 days	8.1(3.2)	Quinine (i.v)	7 days	Cerebral malaria

Note: All ages are in years. All studies involved both male and female children.

Ψ = Median and range

In Moyou-somo(2001)[38] trial standard deviations of the mean age were not reported

Outcomes measures

All trials reported on mortality, parasite clearance time, fever clearance time and coma resolution time. Nine trials i.e. Walker(1993)[31], Murphy(1996)[32], Van Hensbroek(1996)[33], Taylor(1998)[34], Olumese(1999)[36], Thuma(2000)[37], Moyou-somo(2001)[38], Huda(2003)[40] and Mohanty(2004)[41] were designed to measure mortality rate between artemisinin derivative and quinine as a primary outcome, whilst Ojuawo(1998)[35] and Adam(2002)[39] trials were not designed to measure mortality as a primary outcome but did report the mortality rates between the two drug groups. Not all studies reported on incidence of neurological sequelae, 28th cure rate and incidence of adverse effects. Outcomes were reported on day of discharge from the hospital, day 7, 14, 21 or 28. None of the trials reported on malaria transmission intensity or quinine resistance levels.

3.2 Methodological quality

Six trials i.e. Murphy(1996)[32], Van Hensbroek(1996)[33], Taylor(1998)[34], Olumese(1999)[36], Thuma(2000)[37] and Moyou-somo(2001)[38] had adequate generation of random numbers and allocation concealment methods. Random numbers were generated using either computer software or table of random numbers. The Adam(2002)[39] trial had an "unclear" description of the generation of random numbers but adequate concealment. Two trials i.e. Walker(1993)[31] and Ojuawo(1998)[35] had an "unclear" descriptions of the generation of random numbers and allocation concealment. The Mohanty(2004)[41] study had inadequate generation of random numbers and allocation concealment and the Huda(2003)[40] study had an "unclear" generation of random numbers and inadequate concealment. In three trials i.e. Walker(1993)[31], Murphy(1996)[32] and Taylor(1998)[34] the procedures were described as open, in Mohanty(2004)[41] trial there was blinding of the assessor with regard to parasite clearance,

fever clearance and coma resolution time. In four trials i.e. Van Hensbroek(1996)[33], Thuma(2000)[37], Adam(2002)[39] and Huda(2003)[40] it was stated that there was blinding of microscopists. In the remaining three trials i.e. Ojuawo(1998)[35], Olumese(1999)[36], and Moyou-somo(2001)[38] there was no description with regard to blinding. In all trials where there were no description of blinding of interventions, it was assumed that the trials were not blinded as they all involved interventions with different routes of administration and/or different durations.

Losses to follow up or exclusion from analysis of the primary outcome ranged from 0% to 20%. Murphy(1996)[32] study had the highest percentage of subjects excluded from analysis, however since the overall exclusion was not more than 20%, the study is classified as having an adequate number of children who were analysed. In the Walker(1993)[31] study only one patient was excluded from analysis for fever clearance time whilst in the Ojuawo(1998)[35], Adam(2002)[39], Huda(2003)[40], and Mohanty(2004)[41] studies, there were no loss to follow-up or exclusions from analysis. Table 3.3 summarises these findings.

Table 3.3 Results of methodology quality assessment

Study name	Generation of allocation sequence	Allocation concealment	Blinding	Loss to follow up (%)		
				Artemisinin derivatives	Quinine	Overall
Walker(1993)[31]	unclear	unclear	open	0.00%	0.00%	0.00%
Murphy(1996)[32]	adequate	adequate	open	13.50%	26.80%	20.00%
Van Hensbroek(1996)[33]	adequate	adequate	open	-	-	0.50%
Taylor(1998)[34]	adequate	adequate	open	12.60%	7.90%	10.40%
Ojuawo(1998)[35]	unclear	unclear	open	0.00%	0.00%	0.00%
Olumese(1999)[36]	adequate	adequate	open	0.00%	9.20%	4.70%
Thuma(2000)[37]	adequate	adequate	open	1.05%	2.10%	3.20%
Moyou-somo(2001)[38]	adequate	adequate	open	1.88%	1.88%	3.80%
Adam (2002)[39]	unclear	adequate	open	0.00%	0.00%	0.00%
Huda(2003)[40]	unclear	inadequate	open	0.00%	0.00%	0.00%
Mohanty(2004)[41]	inadequate	inadequate	single blinded	0.00%	0.00%	0.00%

Note: In Van Hensbroek(1996)[33] trial percentage lost to follow up in each arm could not be calculated.

3.3 Primary efficacy outcome

3.3.1 Mortality

A total of 739 children were evaluated in the artemisinin derivatives group, among them 17.6% (130/739) died whilst in the quinine group 716 children were evaluated, 19.8%(142/716) of whom died. Among trials with adequate concealment there was an 18.3%(116/633) mortality in the artemisinin derivatives group and 19.8%(120/605) in the quinine group. In inadequate or unclear concealed trials 13.2%(14/106) of children died in the artemisinin derivatives and 19.8%(22/111) in the quinine group. Tables 3.4, 3.5 and 3.6 present these descriptive observations. Nine trials i.e. Walker(1993)[31], Van Hensbroek(1996)[33], Taylor(1998)[34], Ojuawo(1998)[35], Olumese(1999)[36], Moyou-somo(2001)[38], Adam(2002)[39], Huda(2003)[40], and Mohanty(2004)[41] showed that artemisinin derivatives had a lower mortality compared to quinine but none of these findings were statistically significant. The other two trials i.e. Murphy(1996)[32] and Thuma(2000)[37] showed that the quinine groups had a lower mortality compared to the artemisinin groups; however, these differences were again not statistically significant (intention to treat analysis for the Murphy(1996)[32] trial showed the difference was significant) .

Because heterogeneity test showed no evidence of heterogeneity among trials, the fixed effect model was used in calculating summary estimates. Overall the pooled analysis showed that, compared to quinine, artemisinin derivatives were not better at preventing mortality (Risk Ratio= 0.89, 95%CI: 0.71 to 1.10). Of the three artemisinin drugs i.e. arteether, artemether and artesunate none was better than the others. When sensitivity analysis was done based on adequacy of concealment, studies with adequate concealment showed that there was no statistical difference in mortality between artemisinin derivatives and quinine (Risk Ratio=

0.93, 95%CI: 0.74 to 1.16). Again those with inadequate or unclear concealment showed similar findings (Risk Ratio=0.66, 95%CI: 0.36 to 1.22). Figures 3.1 and 3.2 present these findings.

Table 3.4 Comparison of mortality

Study name	Artemisinin derivatives			Quinine			Risk Ratio	95%CI
	Sample size	Death	Death (%)	Sample size	Death	Death (%)		
Walker(1993)[31]	25	3	12.0	29	6	20.7	0.58	0.16, 2.08
Murphy(1996)[32]	89	18	20.2	71	8	11.3	1.79	0.83, 3.89
Van Hensbroek(1996)[33]	288	59	20.5	288	62	21.5	0.95	0.69, 1.31
Taylor(1998)[34]	83	10	12.0	81	12	14.8	0.81	0.37, 1.78
Ojuawo(1998)[35]	18	1	5.5	19	2	10.5	0.53	0.05, 5.33
Olumese(1999)[36]	54	11	20.4	49	14	28.6	0.71	0.36, 1.42
Thuma(2000)[37]	48	10	20.8	44	9	20.5	1.02	0.46, 2.27
Moyou-somo(2001)[38]	51	8	15.7	51	14	27.5	0.57	0.26, 1.24
Adam (2002)[39]	20	0	00.0	21	1	4.7	0.35	0.02, 8.10
Huda(2003)[40]	23	5	21.7	23	6	26.0	0.83	0.30, 2.35
Mohanty(2004)[41]	40	5	12.5	40	8	20.0	0.63	0.22, 1.75
Overall	739	130	17.6	716	142	19.8	0.89	0.71, 1.10

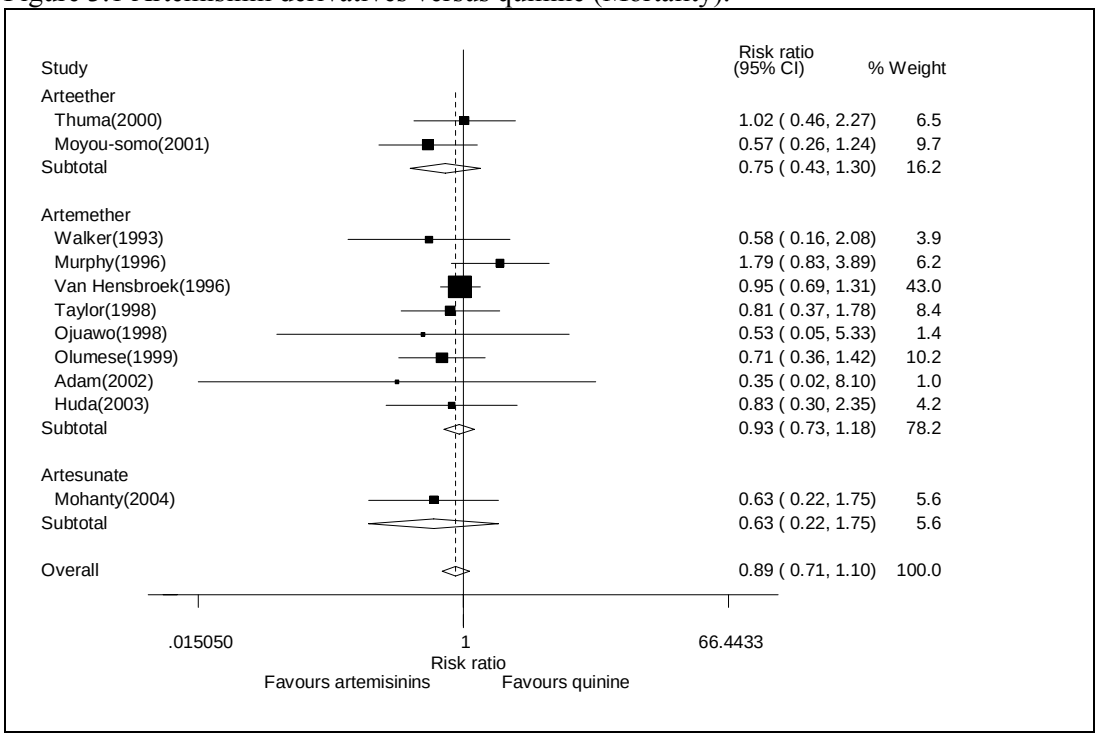
Table 3.5 Comparison of mortality for adequately concealed trials

Study name	Artemisinin derivatives			Quinine			Risk Ratio	95%CI
	Sample size	Death	Death (%)	Sample size	Death	Death (%)		
Murphy(1996)[32]	89	18	20.0	71	8	11.3	1.79	0.83, 3.89
Van Hensbroek(1996)[33]	288	59	20.5	288	62	21.5	0.95	0.69, 1.31
Taylor(1998)[34]	83	10	12.0	81	12	14.8	0.81	0.37, 1.78
Olumese(1999)[36]	54	11	20.4	49	14	28.6	0.71	0.36, 1.42
Thuma(2000)[37]	48	10	20.8	44	9	20.5	1.02	0.46, 2.27
Moyou-somo(2001)[38]	51	8	15.7	51	14	27.5	0.57	0.26, 1.24
Adam (2002)[39]	20	0	0.0	21	1	4.7	0.35	0.02, 8.10
Overall	633	116	18.3	605	120	19.8	0.93	0.74, 1.16

Table 3.6 Comparison of mortality for inadequately/unclear concealed trials

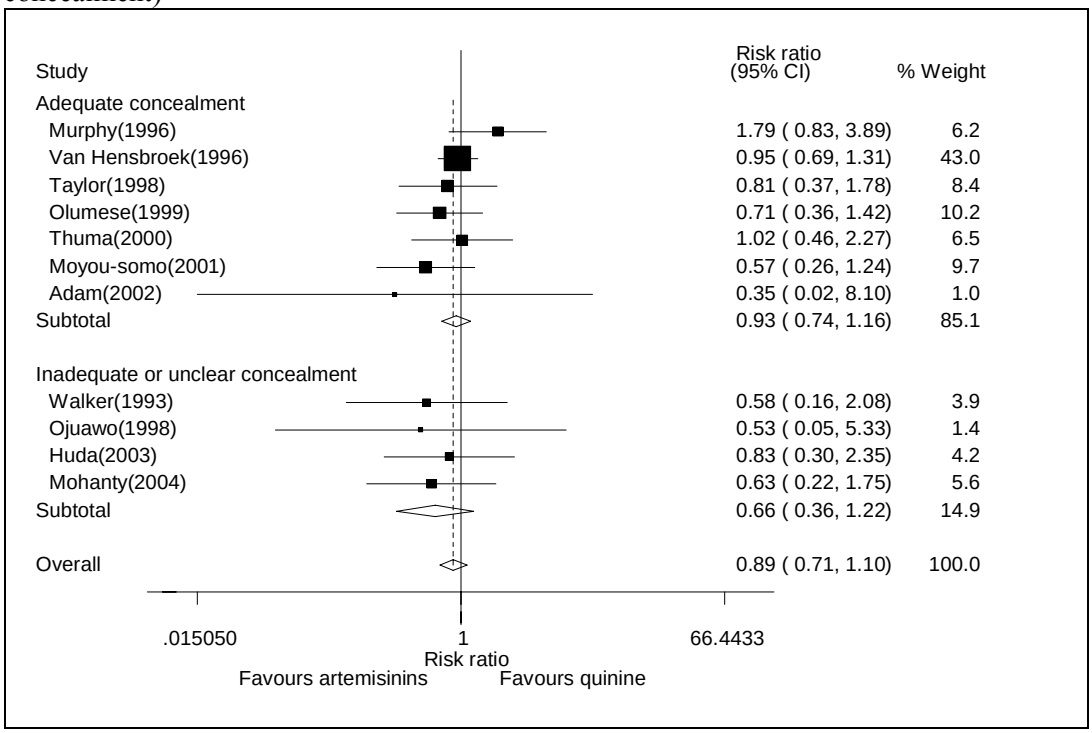
Study name	Artemisinin derivatives			Quinine			Risk Ratio	95%CI
	Sample size	Death	Death (%)	Sample size	Death	Death (%)		
Walker(1993)[31]	25	3	12.0	29	6	20.7	0.58	0.16, 2.08
Ojuawo(1998)[35]	18	1	5.5	19	2	10.5	0.53	0.05, 5.33
Huda(2003)[40]	23	5	21.7	23	6	26.0	0.83	0.30, 2.35
Mohanty(2004)[41]	40	5	12.5	40	8	20.0	0.63	0.22, 1.75
Overall	106	14	13.2	111	22	19.8	0.66	0.36, 1.22

Figure 3.1 Artemisinin derivatives versus quinine (Mortality).



Heterogeneity chi-squared: p = 0.764 Test of Risk Ratio=1: p = 0.268

Figure 3.2 Artemisinin derivatives versus quinine (Sensitivity analysis based on adequacy of concealment)

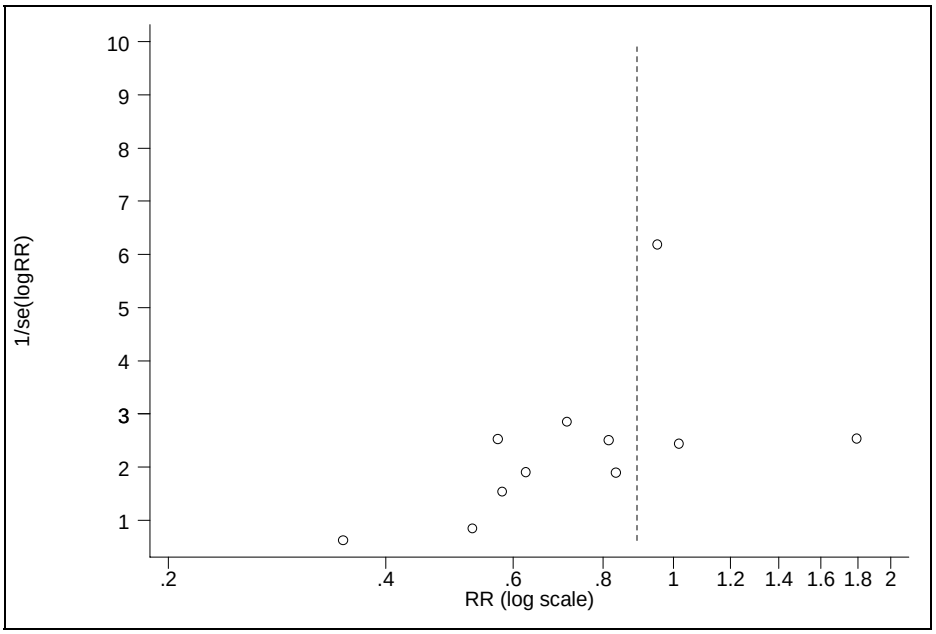


Heterogeneity chi-squared (concealed): p = 0.49 Test of Risk Ratio=1: p = 0.506
Heterogeneity chi-squared (unconcealed): p = 0.964 Test of Risk Ratio=1: p = 0.187

3.3.2 Graphical test for publication bias

In order to test whether these findings have been influenced by publication bias, a funnel plot is presented. This is the graph of risk ratio for each study in natural logarithmic scale against the inverse of standard error of risk ratio in natural logarithmic scale; it is normally used as a simple test for publication bias. Asymmetry of the two sides of the dotted line may be an indication of publication bias. The funnel plot below i.e. Figure 3.3 shows marked asymmetry- this shows that there may have been some publication bias. This could have happened if studies with negative findings were not published. However, other known causes of asymmetry plot e.g. inclusion of studies with poor methodological quality, citation and language biases may have been the cause for the asymmetry.

Figure 3.3 Funnel plot for mortality.



3.4 Secondary efficacy outcomes

3.4.1 Parasite clearance time

Ten studies reported this outcome. Six studies reported the mean parasite clearance time with its standard deviation, three studies reported this outcome in terms of median and interquartile range and one study reported in mean, standard deviation, median and interquartile range. Taylor(1998)[34] trial indicated that data was taken from all admissions while Olumese(1999)[36], Thuma(2000)[37], Moyou-somo(2001)[38], and Adam(2002)[39] trials reported that data came from survivors and the rest did not report their denominator. In those, which did not report the denominator, it was assumed that data were taken from the survivors. Table 3.7 shows some of these findings. Across the trials there were slight variation in definitions, ascertainment and reporting of this outcome. Five studies i.e. Walker(1993)[31], Olumese(1999)[36], Thuma(2000)[37], Moyou-somo(2001)[38] and Adam(2002)[39] showed no statistically significant difference in parasite clearance mean times between artemisinin derivatives and quinine whilst two studies Huda(2003)[40] and Mohanty(2004)[41] showed that artemisinin derivatives cleared parasites faster than quinine(p values <0.001 and <0.05). The Ojuawo(1998)[35] trial showed that the percentage of children with parasite clearance at day 7 was significantly higher in the quinine group than in the artemether group (p value <0.05).

Due to significant heterogeneity among trials, which reported this outcome as mean, a random effects model was used to calculate the summary estimate. The weighted mean difference for the parasite clearance time for the seven studies that reported mean parasites clearance times, showed that artemisinin derivatives cleared parasites faster than quinine, however the difference was not significant (Weighted mean difference=-4.76, 95%CI: -9.68 to 0.17) and p=0.058. Figure 3.4 illustrates this finding. Sensitivity analysis based on adequacy of

concealment showed that artemisinin derivatives cleared parasites faster in trials, which were either inadequately concealed or not concealed (see Figure 3.5). Subgroup analysis revealed heterogeneity between Asian and African studies and showed parasite clearance time was shorter for artemisinin derivatives in Asian studies but not in African studies (Weighted mean difference=-10.9, 95%CI: -14.33 to -7.47 and Weighted mean difference=-1.38, 95%CI: -6.34 to 3.58 see Figure 3.6 below). Three studies i.e. Van Hensbroek(1996)[33], Murphy (1996)[32], and Taylor(1998)[34] all with adequate concealment, which reported parasite clearance time as median and thus used non-parametric tests found that artemisinin derivatives cleared parasites faster than quinine(p values<0.001,<0.001 and <0.001). Table 3.8 presents these findings.

Table 3.7 Parasite clearance time (mean, standard deviation and weighted mean difference)

Study name	Artemisinin derivatives		Quinine		Weighted mean difference	95%CI
	Sample size	Mean(SD)	Sample size	Mean(SD)		
Walker(1993)[31]	22	39.3(28)	23	37.2(21.2)	2.10	-12.46, 16.66
Olumese(1999)[36]	43	44.5(26.6)	35	42.0(22.8)	2.50	-8.47, 13.47
Thuma(2000)[37]	38	53.0(26.4)	34	57.0(24.1)	-4.00	-15.67, 7.67
Moyou-somo(2001)[38]	43	46.3(28.5)	37	40.7(18.9)	5.60	-4.87, 16.07
Adam (2002)[39]	20	16.0(09.2)	20	22.4(11.5)	-6.40	-12.85, 0.05
Huda(2003)[40]	18	40.9(08.4)	17	51.9(01.2)	-11.00	-14.92, -7.08
Mohanty(2004)[41]	35	41.7(16.8)	32	52.2(12.7)	-10.57	-17.66, -3.48
Overall					-4.76	-9.68, 0.17

Mean in hours SD= Standard Deviation

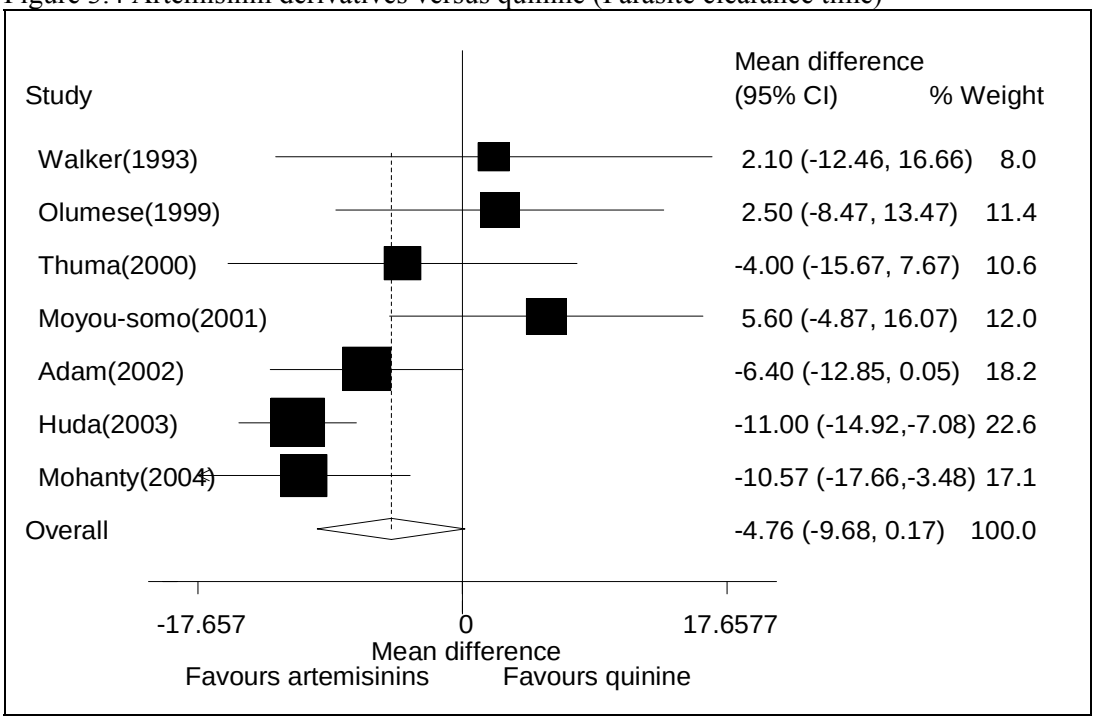
Table 3.8 Parasite clearance time (median and interquartile range)

Study name	Artemisinin derivatives		Quinine		P value
	Sample size	Median(IQR)	Sample size	Median(IQR)	
Murphy(1996)[32]	71	39.5(24-45)	63	48(37-56)	<0.001
Van Hensbroek(1996)[33]	-	48.0(36-60)	-	60(48-72)	<0.001
Taylor(1998)[34]	83	32.0(25-36)	81	40(32-48)	<0.001

Median in hours IQR=Interquartile Range

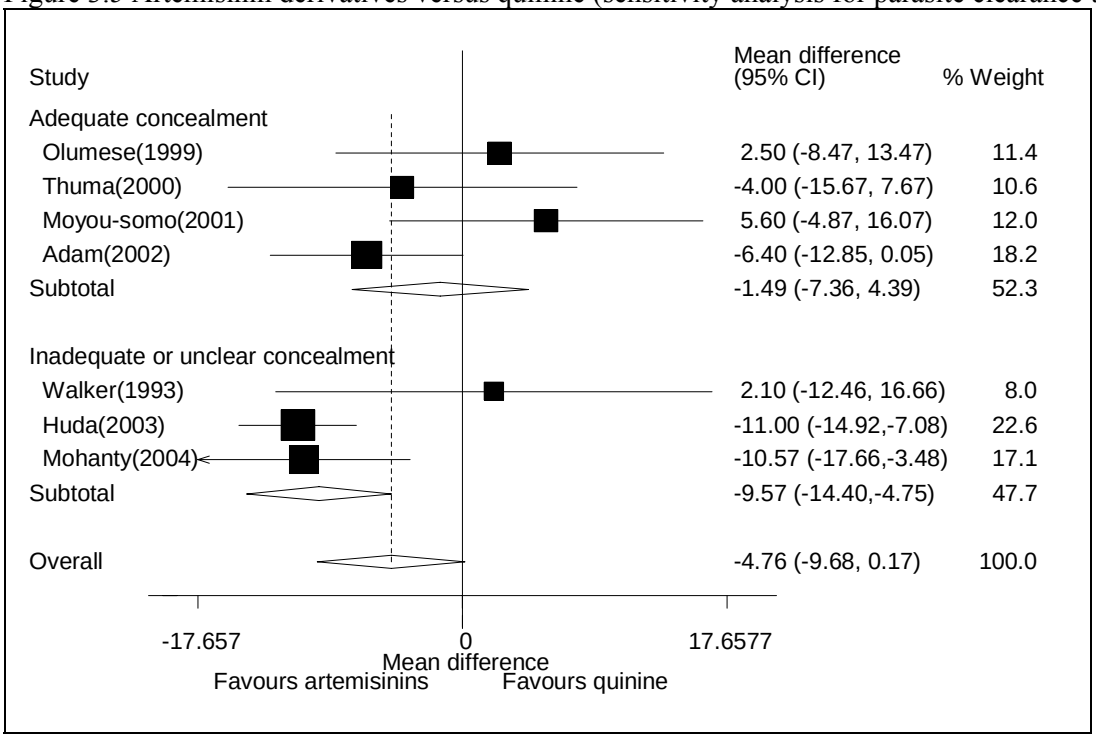
Note: Van Hensbroek(1996)[33] trial did not report sample sizes from which median parasite clearance times were derived from.

Figure 3.4 Artemisinin derivatives versus quinine (Parasite clearance time)



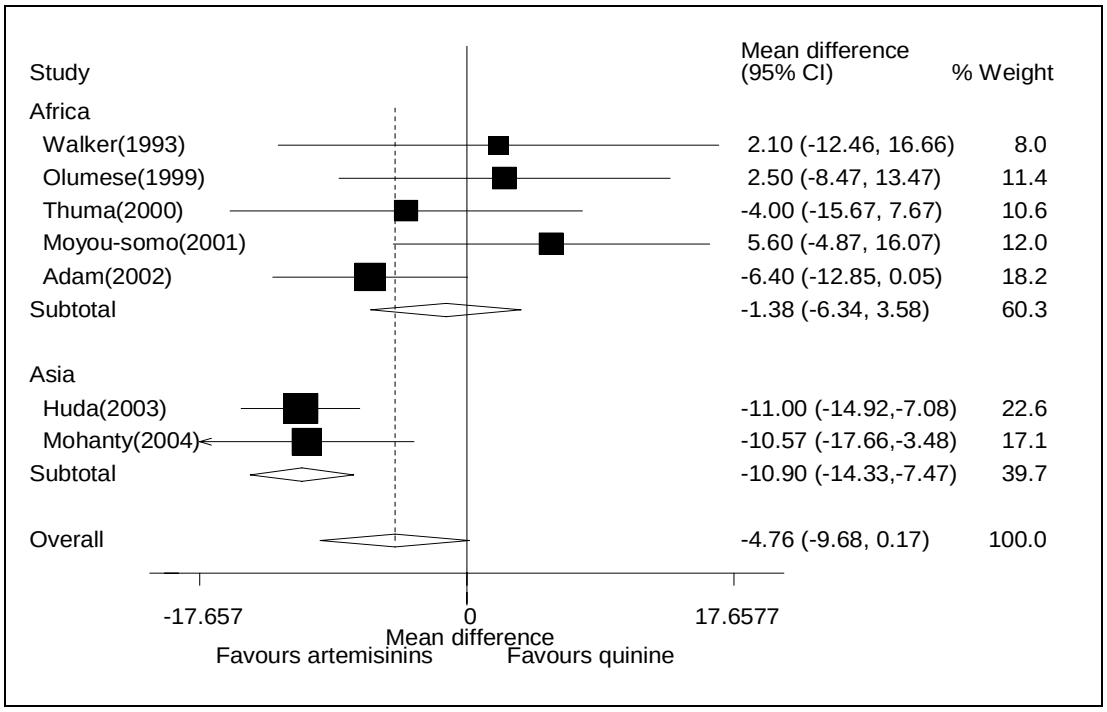
Heterogeneity chi-squared: p = 0.019 Test of weighted mean difference=0: p = 0.058

Figure 3.5 Artemisinin derivatives versus quinine (sensitivity analysis for parasite clearance time)



Tests of heterogeneity: Adequate concealment: p=0.207 Inadequate or unclear concealment: p= 0.233
Significance tests of weighted mean difference=0 Adequate concealment: p = 0.620 Inadequate or unclear concealment: p = 0.000

Figure 3.6 Artemisinin derivatives versus quinine (subgroup analysis for parasite clearance time)



Test of heterogeneity between subgroups: p=0.001
Significance tests of weighted mean difference=0 Africa: p = 0.586 Asia: p = 0.000

3.4.2 Fever clearance time

All eleven studies reported this outcome, seven of them reported it as mean with standard deviation, three reported as median and inter-quartile range and one study reported in mean, standard deviation, median and inter-quartile range. The Taylor(1998)[34] study indicated that the data came from all admissions. The Olumese(1999)[36], Thuma(2000)[37], Moyou-somo(2001)[38] and Adam(2002)[39] trials reported that the data came from the survivors and the rest did not report their denominator. In those, which did not report the denominator, it was assumed that the data were sourced from the survivors. Table 3.9 shows some of these observations. Across the trials there were slight variation in definitions, ascertainment and reporting of this outcome. Of the eight studies which reported mean fever clearance time, five of them i.e. Walker(1993)[31], Olumese(1999)[36], Thuma(2000)[37], Moyou-somo(2001)[38], and

Huda(2003)[40] showed no statistical significant difference in fever clearance times among the two interventions, while two studies i.e. Ojuawo(1998)[35]and Mohanty(2004)[41] showed that artemisinin derivatives cleared fever faster than quinine. The Adam(2002)[39] showed that quinine cleared fever faster than the artemisinin derivatives. Due to significant heterogeneity a random effects model was used in computing the summary estimate. Weighted mean difference of all eight studies which reported mean fever clearance times, showed that artemisinin derivatives did not clear fever faster than quinine (Weighted mean difference=-4.33, 95%CI: -12.64 to 3.97) and p value=0.3. Figure 3.7 present these findings. However, sensitivity analysis showed that artemisinin derivatives cleared fever faster than quinine in trials, which were inadequately concealed or unconcealed (see Figure 3.8). Subgroup analysis revealed no evidence of heterogeneity between Asian and African studies (Weighted mean differences=-9.63, 95%CI: -26.54 to 7.29 and Weighted mean difference=-2.06, 95%CI: -13.51 to 9.38 see Figure 3.9 below). The Murphy (1996)[32] and Van Hensbroek(1996)[33] trials which reported fever clearance time as median, showed no statistical difference between fever clearance times of the two drug groups, while Taylor(1998)[34] trial reported that artemether cleared fever faster than quinine. Table 3.10 shows these findings.

Table 3.9 Fever clearance time (mean, standard deviation and weighted mean difference)

Study name	Artemisinin derivatives		Quinine		Weighted mean difference	95%CI
	Sample size	Mean(SD)	Sample size	Mean(SD)		
Walker(1993)[31]	22	46.7(20.0)	23	57.8(27.3)	-11.10	-25.04, 2.84
Ojuawo(1998)[35]	17	34.7(12.7)	17	53.3(16.6)	-18.60	-28.54, -8.66
Olumese(1999)[36]	43	44.6(26.6)	35	51.3(25.6)	-6.70	-18.32, 4.92
Thuma(2000)[37]	36	50.0(48.6)	35	33.0(19.9)	17.00	-0.19, 34.19
Moyou-somo(2001)[38]	39	42.2(34.9)	36	45.0(26.7)	-2.80	-16.80, 11.20
Adam (2002)[39]	20	30.5(20.9)	20	18.0(8.15)	12.50	2.67, 22.33
Huda(2003)[40]	18	44.5(07.7)	17	45.9(7.20)	-1.40	-6.34, 3.54
Mohanty(2004)[41]	35	43.55(20.12)	32	62.23(16.99)	-18.68	-27.57, -9.79
Overall					-4.33	-12.64, 3.97

Mean in hours SD= Standard Deviation

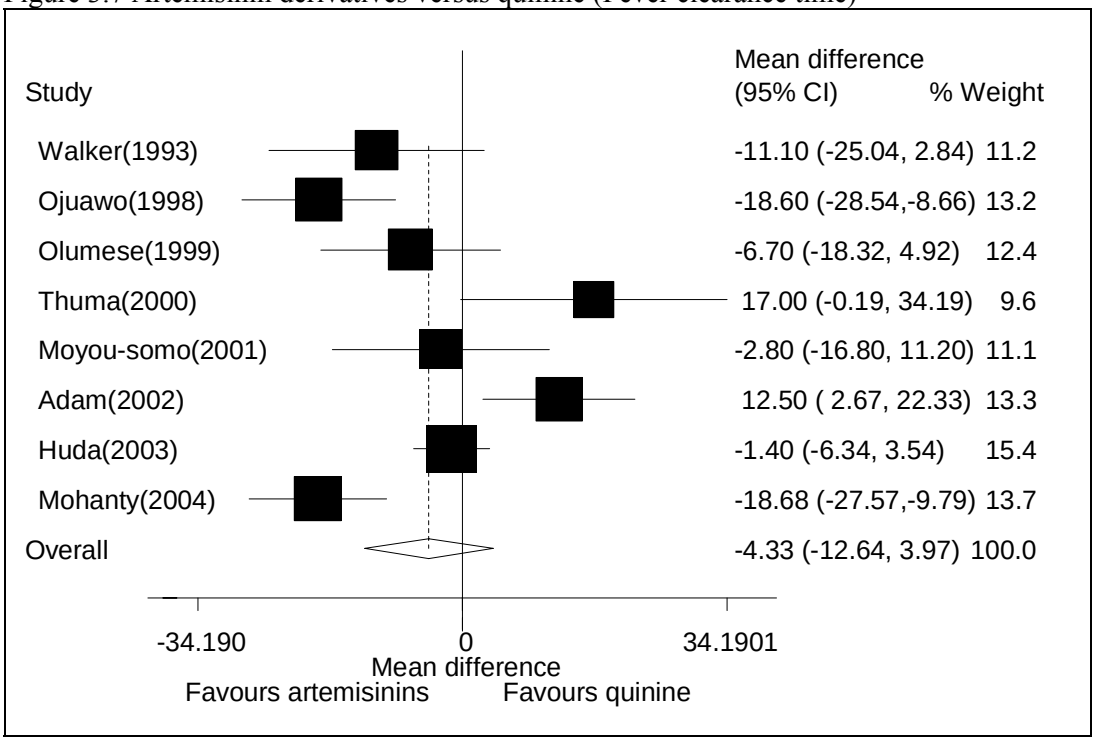
Table 3.10 Fever clearance time (median and interquartile range)

Study name	Artemisinin derivatives		Quinine		P value
	Sample size	Median(IQR)	Sample size	Median(IQR)	
Murphy(1996)[32]	71	32(04-86)	63	32(04-96)	>0.05
Van Hensbroek(1996)[33]	-	30(16-48)	-	33(12-60)	0.8
Taylor(1998)[34]	83	31(24-52)	81	45(33-60)	<0.05

Median in hours IQR=Interquartile Range

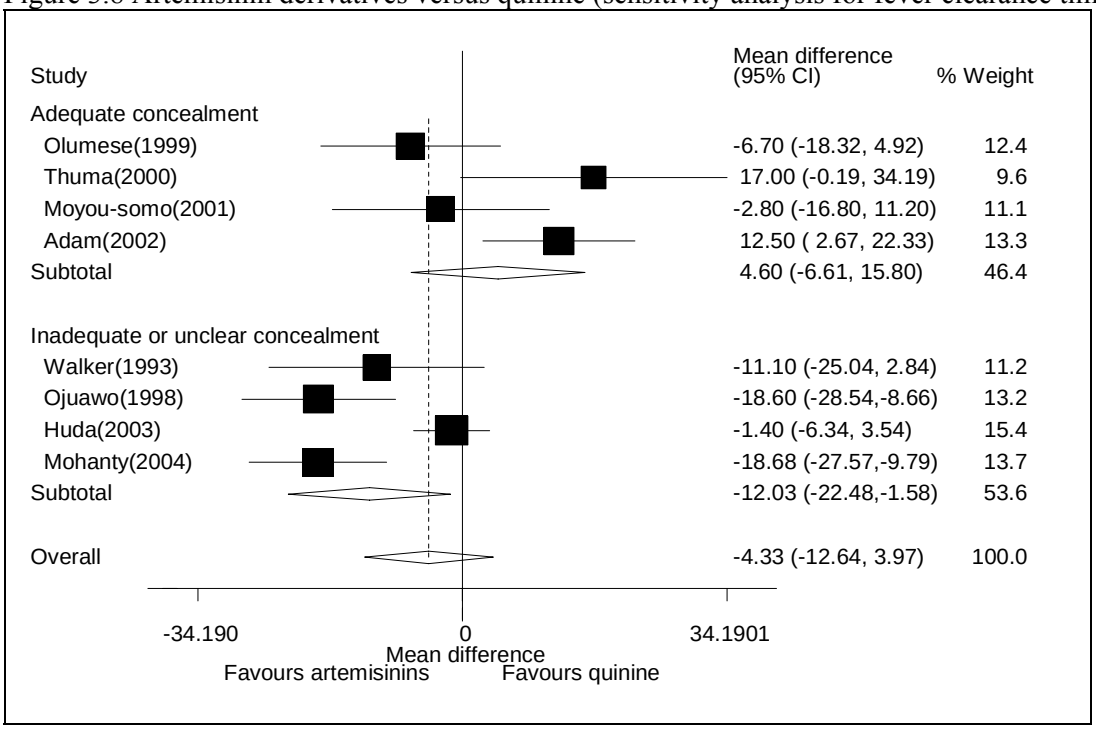
Note: Exact p values for Murphy(1996)[32] and Taylor(1998)[34] trials were not available.
Van Hensbroek(1996)[33] trial did not report sample sizes from which median parasite clearance times were derived from.

Figure 3.7 Artemisinin derivatives versus quinine (Fever clearance time)



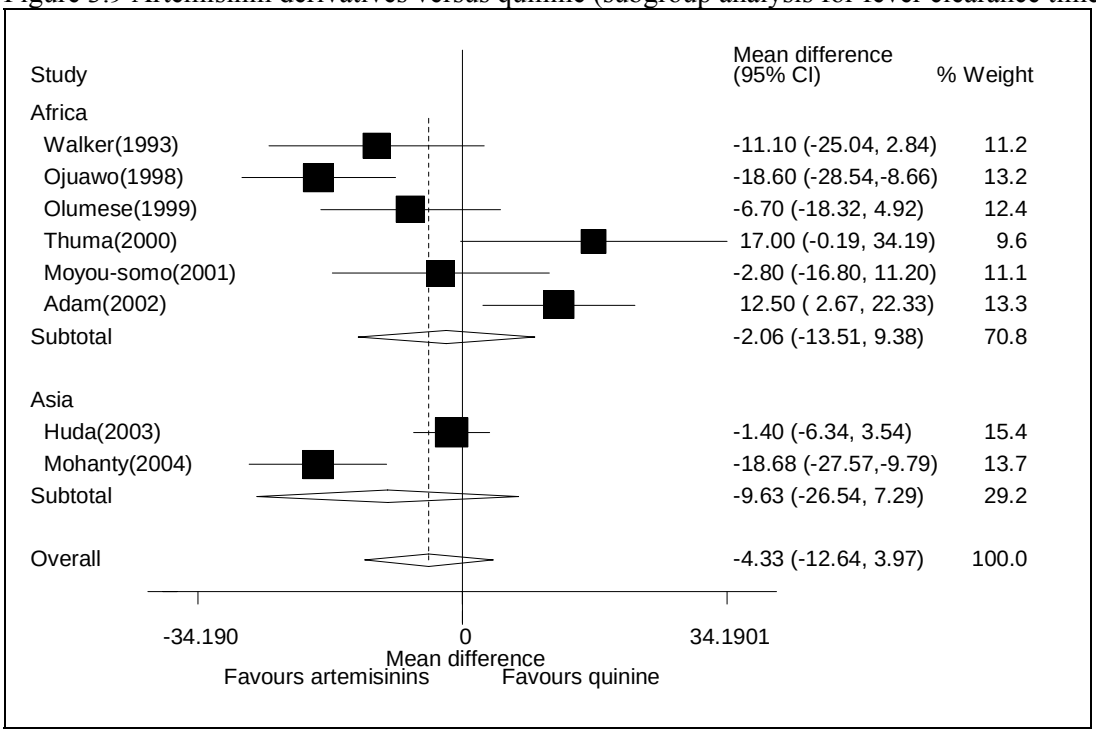
Heterogeneity chi-squared: p <0.0001 Test of Weighted mean difference=0: p = 0.306

Figure 3.8 Artemisinin derivatives versus quinine (sensitivity analysis for fever clearance time)



Test(s) of heterogeneity: Adequate concealment: p=0.027 Inadequate or unclear concealment: p= 0.001 Weighted mean difference=0 Adequate concealment: p = 0.421 Inadequate or unclear concealment: p = 0.024

Figure 3.9 Artemisinin derivatives versus quinine (subgroup analysis for fever clearance time)



Test for heterogeneity between sub-groups: p=0.450 Significance test(s) of Weighted mean difference=0 Africa p = 0.724 Asia p = 0.265 Overall p = 0.306

3.4.3 Coma resolution time

All eleven trials reported this outcome. Seven reported mean and standard deviation, three reported median and inter-quartile range and the last one reported both mean and median. In Taylor(1998)[34] trial it was indicated that the reporting arose from all admissions while Olumese(1999)[36], Thuma(2000)[37], Moyou-somo(2001)[38], and Adam(2002)[39] trials reported that this was among the survivors and the other five did not report their denominator. In those, which did not report the denominator, it was assumed that the reporting was among the survivors. Table 3.11 summarises some of these observations. Across the trials there were slight variation in ascertainment of this outcome.

Among studies which reported coma resolution time as mean, five i.e. Walker(1993)[31], Olumese(1999)[36], Thuma(2000)[37], Moyou-somo(2001)[38] and Adam(2002)[39] showed no statistical significant difference between artemisinin derivatives and quinine whilst the rest i.e. Ojuawo(1998)[35], Huda(2003)[40], and Mohanty(2004)[41] trials showed that coma resolution time was significantly faster in the artemisinin group than in the quinine group. The weighted mean difference which was computed using a fixed effect model, showed that overall artemisinin derivatives resolved coma faster than quinine (Weighted mean difference=-5.32, 95%CI: -8.06 to -2.59) and $p<0.0001$. Figure 3.10 illustrates these findings. On sensitivity analysis it was revealed artemisinin derivatives resolved coma faster in trials, which were either not concealed or inadequately concealed while there was no difference in coma resolution time in trials, which were adequately concealed (see Figure 3.11). Among those which reported median coma resolution times only Van Hensbroek(1996)[33] trial showed that quinine resolved coma faster than the artemether($p=0.046$). Table 3.12 summarises these observations.

Table 3.11 Coma resolution time (mean, standard deviation and weighted mean difference)

Study name	Artemisinin derivatives		Quinine		Weighted mean difference	95%CI
	Sample size	Mean(SD)	Sample size	Mean(SD)		
Walker(1993)[31]	22	40.1(30.7)	23	36.7(29.6)	3.40	-14.23, 21.03
Ojuawo(1998)[35]	17	12.5(05.8)	17	17.4(07.2)	-4.90	-9.29, -0.51
Olumese(1999)[36]	43	35.1(27.1)	35	42.4(31.6)	-7..30	-20.54, 5.94
Thuma(2000)[37]	38	61.0(57.6)	35	44.0(44.9)	17.00	-6.59, 40.59
Moyou-somo(2001)[38]	43	34.8(18.8)	37	30.3(28.9)	4.50	-6.38, 15.38
Adam (2002)[39]	20	12.5(05.2)	20	20.0(16.9)	-7.50	-15.25, 0.25
Huda(2003)[40]	18	34.8(08.2)	17	40.8(07.0)	-6.00	-11.04, -0.96
Mohanty(2004)[41]	35	50.4(31.5)	32	70.15(17.6)	-19.75	-31.83, -7.67
Overall					-5.32	-8.06, -2.59

Mean in hours SD= Standard Deviation

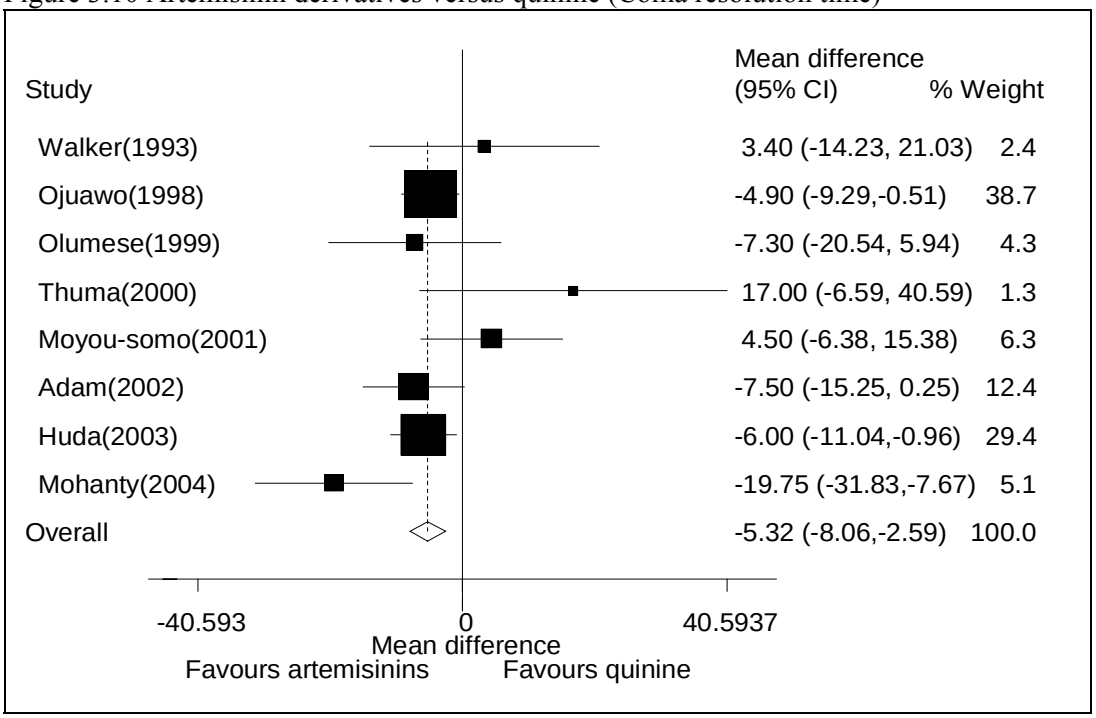
Table 3.12 Coma resolution time (median and interquartile range)

Study name	Artemisinin derivatives		Quinine		P value
	Sample size	Median(IQR)	Sample size	Median(IQR)	
Murphy(1996)[32]	71	12(02.8-96)	63	13(02.83-96)	>0.05
Van Hensbroek(1996)[33]	229	26(15.0-48)	226	20(12.00-43)	0.046
Taylor(1998)[34]	83	18(08.0-30)	81	20(10.00-54)	>0.05

Median in hours IQR=Interquartile Range

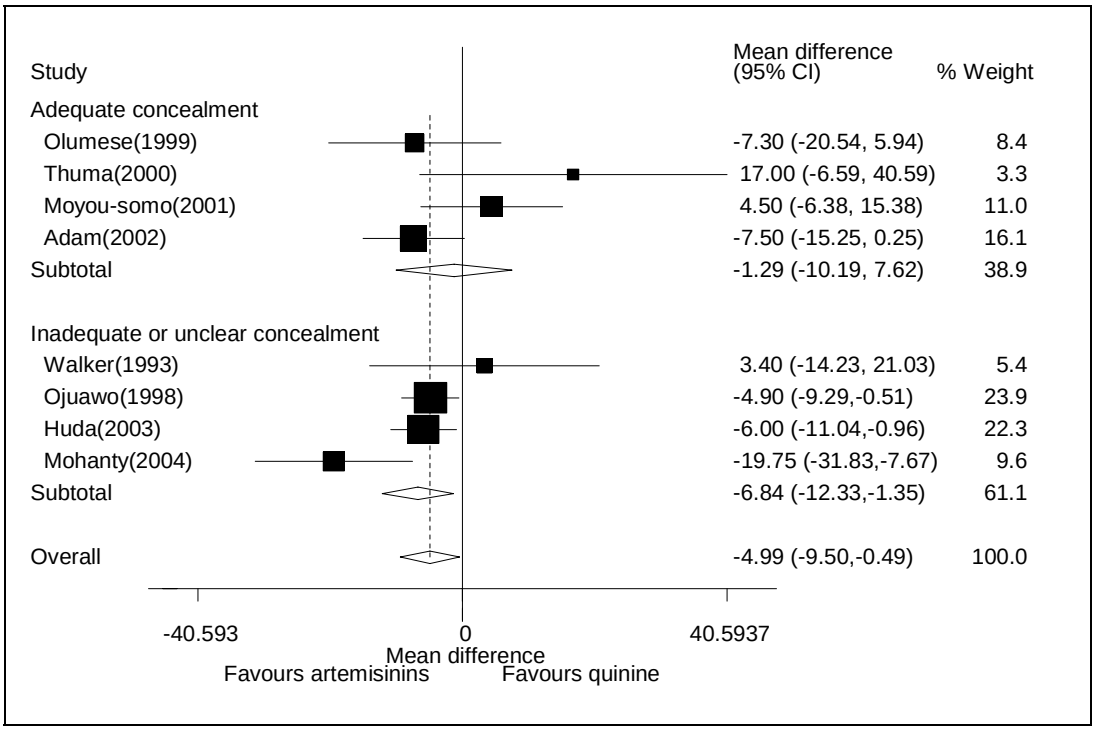
Note: Exact p values for Murphy(1996)[32] and Taylor(1998)[34] trials were not reported.

Figure 3.10 Artemisinin derivatives versus quinine (Coma resolution time)



Heterogeneity chi-squared: p = 0.061 Test of weighted mean difference=0: p = <0.0001

Figure 3.11 Artemisinin derivatives versus quinine (sensitivity analysis for coma resolution time)



Tests of heterogeneity:
Adequate concealment: p= 0.098 Inadequate or unclear concealment: p= 0.097
Significance tests of weighted mean difference=0
Adequate concealment: p = 0.777 Inadequate or unclear concealment: p = 0.015

3.4.4 Incidence of neurological sequelae

Eight trials i.e. Walker(1993)[31], Murphy(1996)[32], Van Hensbroek(1996)[33], Taylor(1998)[34], Ojuawo(1998)[35], Olumese(1999)[36], Thuma(2000)[37] and Moyou-somo(2001)[38] reported or had data on incidence of neurological sequelae at discharge or at day seven. Except for Ojuawo(1998)[35] trial in which subjects with neurological sequelae were reported as percentage of admissions, in all other trials the data were from the survivors. Two other trials i.e. Adam(2002)[39] and Huda(2003)[40] reported that neurological sequelae had not been observed during follow up and Mohanty(2004)[41] trial did not report any data. In total, among 518 survivors in the artemisinin derivatives group who were evaluated for this outcome, 18.3%(95/518) developed neurological problems whilst among 485 survivors in the quinine

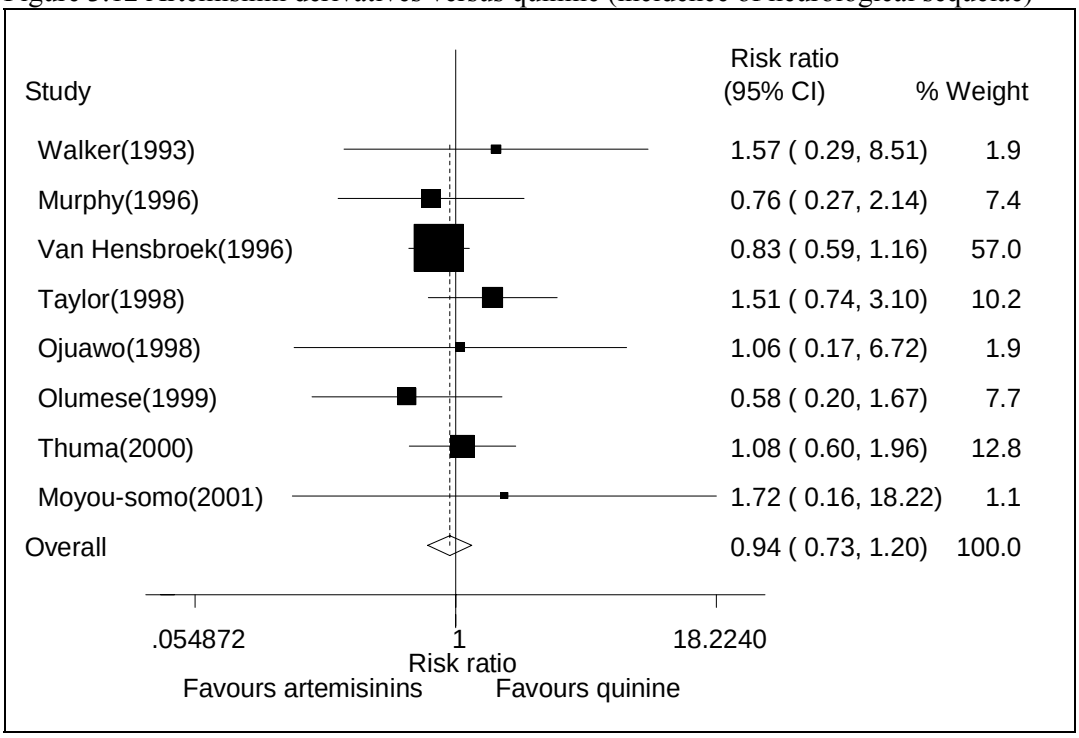
group, 19.8%(96/485) developed neurological problems. Table 3.13 summarises these observations. The sequelae reported included motor deficits, severe hypotonia, aphasia, abnormality in gait, cortical-deafness, blindness, mental-retardation, hallucinations, hemiplegia and quadriparesis.

Studies which followed-up children for at least one month i.e. Van Hensbroek(1996)[33], Taylor(1998)[34], Olumese(1999)[36] and Thuma(2000)[37] reported that most of the sequelae had subsided by that time. Murphy(1996)[32], Van Hensbroek(1996)[33], Taylor(1998)[34], Ojuawo(1998)[35] and Thuma(2000)[37] trials showed that, there was no statistical difference in neurological sequelae incidence among the two groups at discharge or one month. When the data from studies that recorded incidences of neurological sequelae at discharge or by day seven among the survivors were pooled together using a fixed effect model, the results showed that there was no statistical difference among the two groups for this outcome (Risk Ratio=0.94, 95%CI: 0.73 to 1.20) and p=0.604. Figure 3.12). Sensitivity analysis showed no difference between concealed and inadequately concealed/unconcealed trials (see Figure 3.13).

Table 3.13: Incidence of neurological sequelae (At discharge or by day seven)

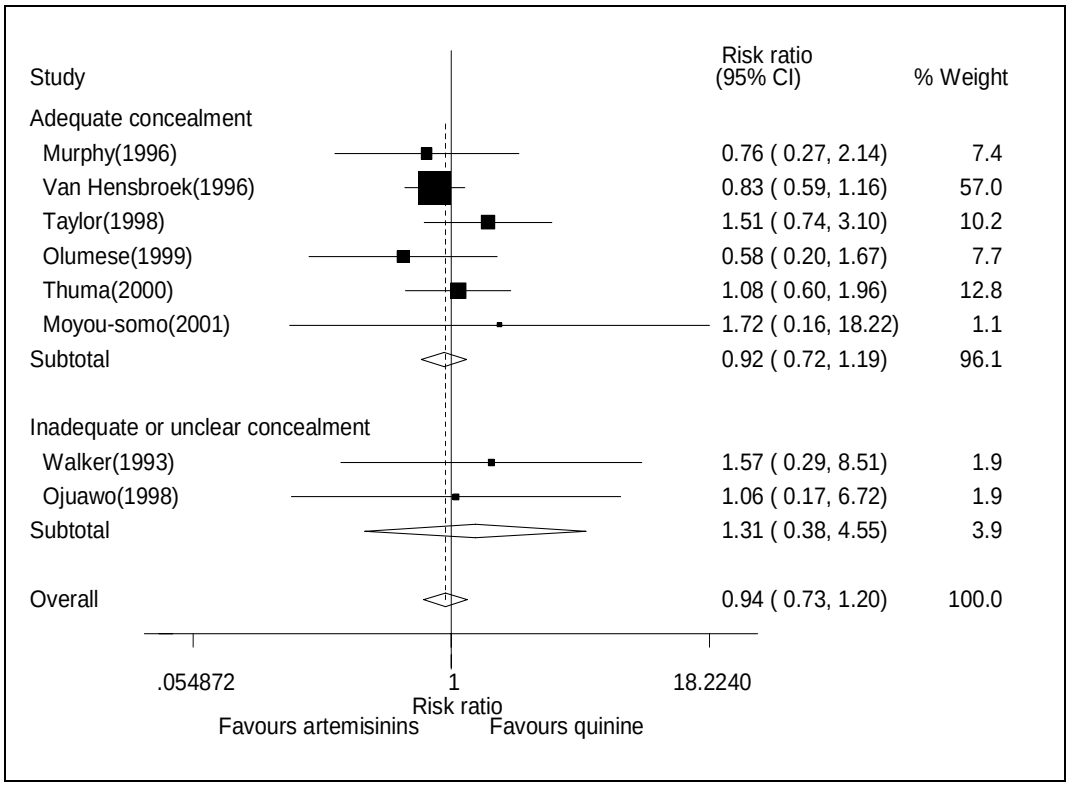
Study name	Artemisinin derivatives		Quinine		Risk Ratio	95%CI
	Sample size	Number with neurological sequelae	Sample size	Number with neurological sequelae		
Walker(1993)[31]	22	3	23	2	1.57	0.29, 8.51
Murphy(1996)[32]	71	6	63	7	0.76	0.27, 2.14
Van Hensbroek(1996)[33]	229	48	226	57	0.83	0.59, 1.16
Taylor (1998)[34]	73	16	69	10	1.51	0.74, 3.10
Ojuawo(1998)[35]	18	2	19	2	1.06	0.17, 6.72
Olumese(1999)[36]	43	5	35	7	0.58	0.20, 1.67
Thuma(2000)[37]	37	15	32	12	1.08	0.60, 1.96
Moyou somo(2001)[38]	43	2	37	1	1.72	0.16,18.22
Overall	518	95(18.3%)	485	96(19.8%)	0.94	0.73, 1.20

Figure 3.12 Artemisinin derivatives versus quinine (incidence of neurological sequelae)



Heterogeneity chi-squared: p = 0.782 Test of Risk Ratio=1:p = 0.604

Figure 3.13 Artemisinin derivatives versus quinine (sensitivity analysis for neurological sequelae)



Tests of heterogeneity:
Adequate concealment:p= 0.609 Inadequate or unclear concealment: p= 0.757
Significance tests of Risk Ratio=1
Adequate concealment: p = 0.525 Inadequate or unclear concealment: p = 0.668

3.4.5 Cure rate (28th day cure rate)

Six trials ((Walker(1993)[31], Van Hensbroek(1996)[33], Taylor(1998)[34], Olumese(1999)[36], Moyou-somo(2001)[38] and Mohanty(2004)[41])) reported or had data that could be extracted on 28th day cure rates. Of 442 survivors who were evaluated in the artemisinin derivatives group, 84% (371/442) were cured while of 421 survivors in the quinine group who were evaluated, 86%(363/421) were cured. In all the trials almost all survivors were followed for 28 days and none of trials used molecular methods to differentiate between recrudescence and re-infection. Table 3.14 shows these observations.

In Van Hensbroek(1996)[33] trial participants received Sulfadoxine/pyrimethamine(SP) before they were discharged from hospital in year two and year three of the trial. In this trial, recrudesce rates in the first year were not statistically different (p=0.4) and in the following two years, the rates were similar (10.6%, 9.4%). In the Murphy(1996)[32] and Taylor(1998)[34] trials children received SP after parasites were cleared and the children were conscious. In these three trials, which used SP after coma resolution, parasite clearance or at discharge, the criterion for its use was the same among trials' interventions.

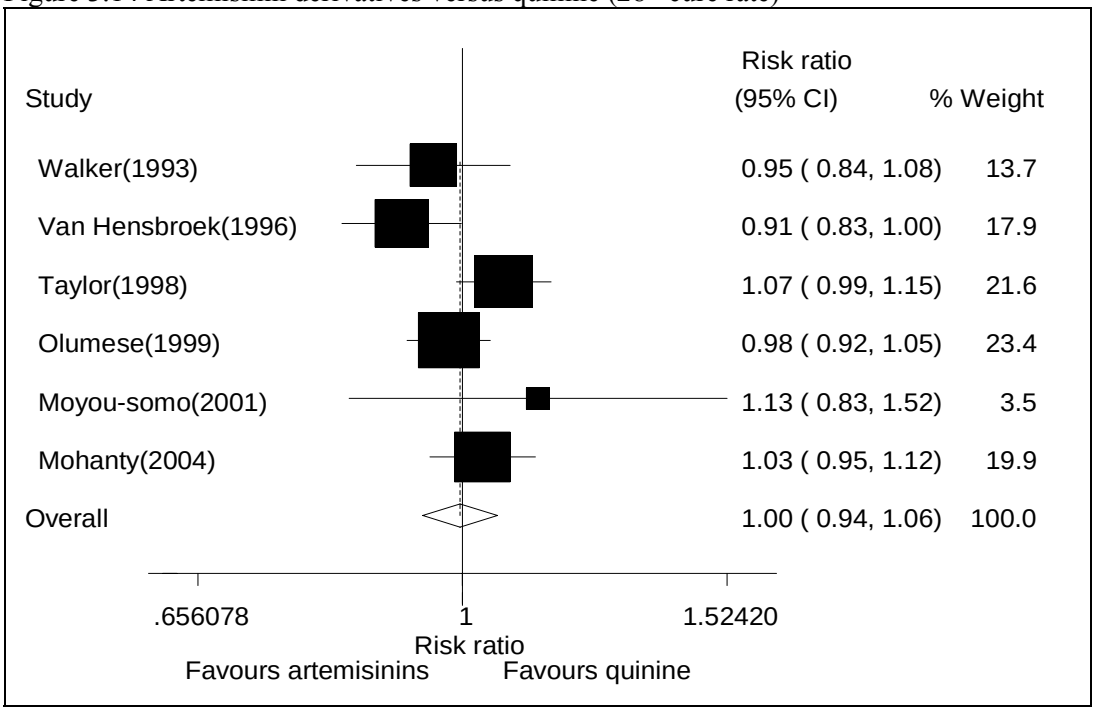
In the Walker(1993)[31] and Olumese(1999)[36] trials only one child in each trial in the artemether group developed parasitaemia on day 14. These children were treated successfully. When the results were pooled together using a random effects model, there was no statistical difference in cure rates between the two drug groups (Risk Ratio=1.00, 95%CI: 0.94 to 1.06).

Figure 3.14 presents these findings. Subgroup analysis revealed no evidence of heterogeneity between Asian and African studies (Risk Ratio=1.03, 95%CI: 0.95 to 1.12 and Risk Ratio=0.99, 95%CI: 0.92 to 1.06 see Figure 3.15 below). Also sensitivity analysis revealed no difference between adequately concealed and inadequately/unconcealed trials (Figure 3.16).

Table3.14: 28th day cure rate (Artemisinin derivatives versus quinine)

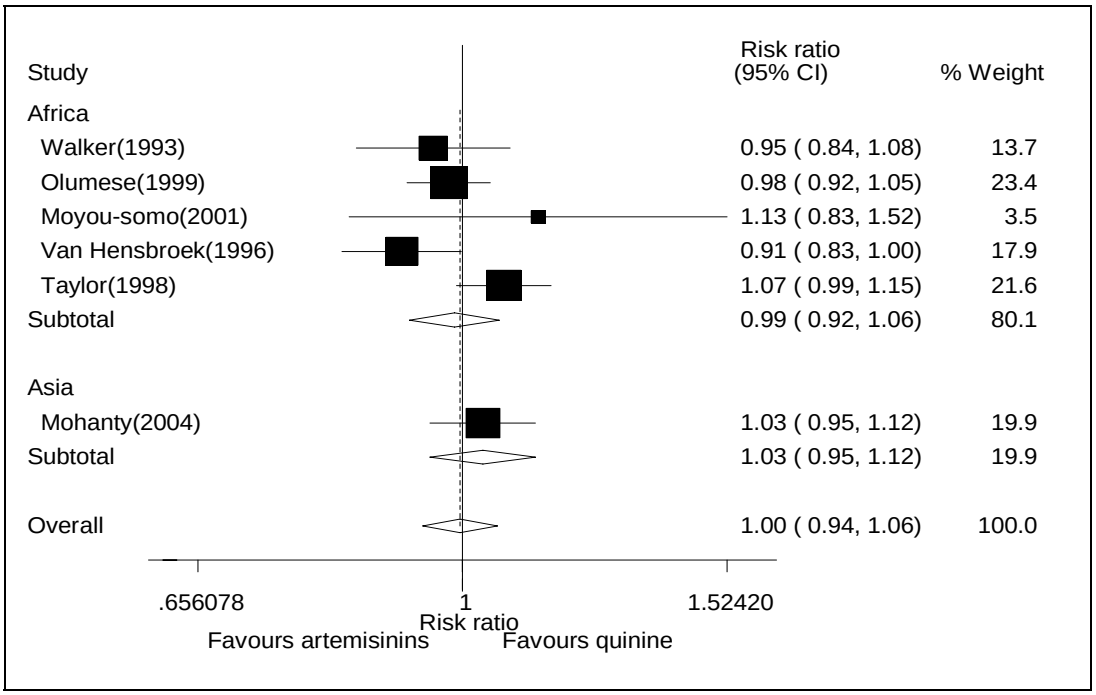
Study name	Artemisinin derivatives		Quinine		Risk Ratio	95%CI
	Sample size	Number cured	Sample size	Number cured		
Walker(1993)[31]	22	21	23	23	0.95	.84, 1.08
Van Hensbroek(1996)[33]	229	172	226	187	0.91	.83, 1.00
Taylor (1998)[34]	72	71	65	60	1.07	.99, 1.15
Olumese(1999)[36]	43	42	38	38	0.98	.92, 1.05
Moyou-somo(2001)[38]	41	30	37	24	1.13	.83, 1.52
Mohanty(2004)[41]	35	35	32	31	1.03	.95, 1.12
Overall	442	371(83.9%)	421	363(86.2%)	1.00	.94, 1.06

Figure 3.14 Artemisinin derivatives versus quinine (28th cure rate)



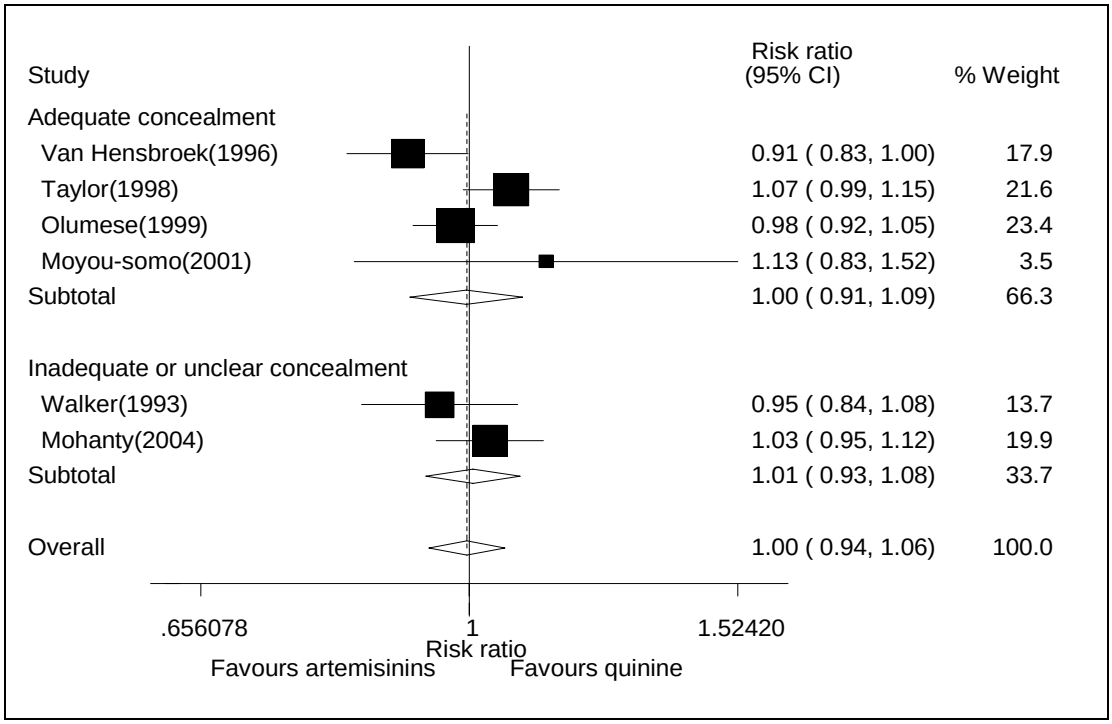
Heterogeneity chi-squared: p = 0.048 Test of Risk Ratio=1: p = 0.9

Figure 3.15 Artemisinin derivatives versus quinine (subgroup analysis for 28th day cure rate)



Test(s) of heterogeneity: between sub-groups: p= 0.231
Significance test(s) of Risk Ratio=1 Africa p = 0.725 Asia p = 0.447 Overall p = 0.900

Figure 3.16 Artemisinin derivatives versus quinine (sensitivity analysis for 28th day cure rate)



Test(s) of heterogeneity:

Adequate concealment: p=0.022 Inadequate or unclear concealment: p= 0.291

Significance test(s) of Risk Ratio=1

Adequate concealment: p = 0.918 Inadequate or unclear concealment: p = 0.877

3.4.6 Adverse effects

Most of the trials were not designed to evaluate differences in adverse effects amongst the two groups. Those, which reported this outcome, reported it either incompletely or in a way that hindered thorough comparison among the interventions, thus only a descriptive narrative of the data is given. The adverse effects reported included: weakness, fevers/rigors, anorexia, nausea, vomiting, diarrhoea, cough, pneumonia, conjunctivitis, cardiac signs, skin irritation, headache, tinnitis, vertigo, circulatory failure, sudden blindness, hypoglycaemia and black water fever.

The Moyou-somo(2001)[38] study reported one fatal case of black water fever among the quinine group while Adam(2002)[39] trial reported one case of hypoglycaemia among the quinine group. Thuma(2000)[37] trial reported that 75%(36/48) of children in the β-arteether group had adverse effects while in the quinine group 77%(34/44) had adverse effects. Van Hensbroek(1996)[33] trial reported that local reactions at the site of injection were more common in the quinine group than in the artemether group(p= 0.0001). The Walker(1993)[31] study reported two cases of supraventicular tachycardia in the quinine group. The rest of the studies either did not report or reported that there were no significant differences in adverse effects between the two groups.

4. DISCUSSION

4.1 Summary of main results

This review has shown that compared to quinine artemisinin derivatives are not superior in preventing mortality from childhood severe malaria. This review also revealed that none of the artemisinin derivatives was more efficacious (in terms of mortality reduction) than others. The review has also shown that parasite clearance time (PCT) tended to be shorter in artemisinin derivatives in comparison to quinine (though weighted mean difference among studies which reported PCT as mean showed no statistical difference but there was a tendency towards favouring the artemisinin derivatives and all three studies which reported PCT as median showed that artemisinin derivatives cleared parasites faster than quinine). However, this advantage (for the pooled studies) waned off when only adequately concealed trials were considered. In exploring causes for heterogeneity for PCT, it was evident that study settings (Asia versus Africa) may have been a cause for heterogeneity. Artemisinin derivatives resolved coma significantly faster than quinine, however when only adequately concealed trials were considered this difference disappeared. In other secondary outcomes (fever clearance time, 28th day cure rates, incidence of neurological sequelae), there were no differences between the two drug groups. This review lacked adequate data for assessing the safety profile of artemisinin derivatives in comparison to quinine.

4.2 Strength of the evidence

4.2.1 Methodological quality assessment

In this review there was variation in the way, in which some secondary outcomes were defined, ascertained and reported. For example the Olumese(1999)[36] study referred to parasite clearance time(PCT) as the time taken from commencement of treatment until parasites are

not detected in two consecutive slides and remain so for 7 days while in the Thuma(2000)[37] trial the parasite clearance time (PCT) was defined as time taken from starting treatment until parasites are not detected and remain so for 24 hours. In addition, these studies had different parasites ascertainment schedules. These differences may have affected comparability of the trials. In reporting the outcomes; three trials (i.e. Murphy(1996)[32], Van Hensbroek(1996)[33], and Taylor(1998)[34]) consistently reported the medians and not the means of parasite clearance time (PCT), fever clearance time (FCT) and coma resolution time (CRT). Original reports show that this reporting was either used deliberately or the data were not normally distributed. However reporting in medians does not confer any statistical or clinical advantage in interpreting drug efficacy parameters.

This review included eleven trials involving 1,455 children aged 0 to 14 years, 1238 (85%) of whom were from seven adequately concealed trials. Adequacy of concealment before allocation is known to prevent selection bias in randomised trials.[57] In this review the difference in mortality between artemisinin derivatives and quinine remained the same when summary estimates were computed separately for adequately concealed trials and those which were either not adequately concealed or were unconcealed. This testifies to the fact that the overall summary estimate for mortality was not influenced by trials, which were insufficiently concealed. However, in parasite clearance time and coma resolution time, it was evident that inadequately concealed trials had influenced the overall summary estimates, as the estimates were pushed towards showing no difference when only adequately concealed trials were considered.

Seven trials were indicated as open, one as single blinded and in the other three, their blinding status was not stated. However, since the drugs were administered using different routes and had different durations of administration, this precluded the possibility of blinding in these three studies. Though most studies were not blinded, the possibility that there was any detection bias in assessing the outcomes is very small since all of the outcomes, except neurological sequelae and adverse effects, were assessed objectively. In addition, there was blinding of the microscopists in four trials (i.e. Van Hensbroek(1996)[33], Thuma(2000)[37], Adam(2002)[39] and Huda(2003)[40]) to ensure that malaria slide reading was not biased. A small chance exists that some detection bias was introduced in the assessment of neurological sequelae as in some trials there was no blinding of the assessors and the assessment was possibly subjective.

The percentages of subjects, which were lost to follow-up or excluded from analysis in all trials, were within the pre-determined range. However this does not rule out the possibility that attrition bias was introduced in the trials. There was differential loss to follow up/exclusion from analysis in Murphy (1996)[32] and Olumese(1999)[36] studies. In the Murphy (1996)[32] study the per protocol analysis showed that compared to artemether, quinine had lower mortality but the difference was not significant. An intention to treat analysis showed that quinine had significantly lower mortality than artemether. In the Olumese(1999)[36] study it was shown that artemether had lower mortality than quinine but the difference was not significant. In this trial it was implicated that there was no loss to follow up in artemether group but there was about 9% loss to follow up in quinine group. Assuming that all those who were excluded from analysis died during the trial, there is a possibility that an intention to treat analysis would have revealed that compared to quinine, artemether had significantly lower mortality. As it is

with the Murphy (1996)[32] study the effect of intention to treat analysis on Olumese(1999)[36] study would not be to change the direction of treatment effect but rather to increase the size of treatment effect in the original direction. Therefore though attrition bias might have been introduced in the two trials, it is unlikely that the availability of intention to treat findings would have changed the overall summary estimate for the primary outcome. However it is difficult to predict the influence of this bias on summary estimates for secondary outcomes.

Findings from the funnel plot suggest that there was publication bias. It is likely that the absence of unpublished trials and trials in languages other than English, which are likely to have negative results, may have contributed to the asymmetry of the funnel plot.[50] Literature suggests that the asymmetry of the funnel plot could also result from many other things including: poor methodological quality of smaller studies, true heterogeneity, and chance.[50] The review has shown that most of the small studies (e.g. Walker(1993)[31], Ojuawo(1998)[35], Huda(2003)[40], and Mohanty(2004)[41]) had poor methodology, but since it is not evident that they had larger treatment effects their contribution to the asymmetry of the funnel may have been small. Though heterogeneity was not detected in the primary outcome, the analysis of secondary outcomes (parasite clearance time, fever clearance time and 28th day cure rate) showed there was heterogeneity among included trials. Therefore is likely that true heterogeneity might have contributed to the asymmetry of the plot. Whether this observation in the graph occurred by chance, is difficult to say with certainty, as there was no statistical test accompanying the graph.

4.2.2 Potential bias in the review process

Because of the short duration in which this review was to be conducted it was not practical to exhaustively search for publications in grey literature, journals (through hand searching) and correspondence with authors for clarification, additional or missing data. As a result no data from conference presentations and unpublished trials was found and included in the review. This deficiency may have introduced some bias. An attempt was made to avoid database bias by making sure that potential articles were searched in all major electronic databases. Selection and quality assessment biases were minimised by ensuring that two independent individuals carried out study selection and methodological quality assessment.

4.2.3 Agreements and disagreements with other studies or reviews

The findings of this review are somehow similar to those of the other two previous reviews of published randomised trials.[44,45] The first review was on artemether versus quinine[44] and the second on artemisinin derivatives versus standard drugs for the treatment of severe malaria,[45] both involved adults and children. In the first review it was shown that compared to quinine, artemether was neither superior nor inferior in reducing mortality from severe malaria and the second review showed that though artemisinin derivatives seemed to have lower mortality when all trials were pooled together, when only those with adequate concealment were considered there seemed to be no difference between the two drug groups. Unlike the first review the second one included many artemisinin products and therefore was much similar to this review. The difference in findings between this and the second review is due to the fact that this review included children only. Unlike adults most deaths in children with severe malaria occur within 24 hours and therefore drugs like artemisinin derivatives may not have

enough time to act before children die.[8,46] This may explain why unlike the second review the summary estimate from all trials in this review did not favour artemisinin derivatives.

Like this review one previous review[45] had shown that between the two drug groups there was either no difference or the evidence was inconclusive in fever clearance time, coma resolution time, incidence of neurological sequelae and 28th day cure rate. Similar to this review data from previous review[45] indicated that parasite clearance time tended to be shorter in many included trials in the artemisinin derivatives group compared to the quinine group.

4.2.4 Conclusion on strength of evidence

Evidence for the primary outcome is fairly strong since; most trials were of high quality (thus bias which was introduced despite measures to prevent it did not affect it), effect measures were similar across the trials, and other previous review seem to have findings that are some how similar to this one. However evidence for secondary outcomes need to be taken cautiously as biases that were in original studies may have had more influence on these outcomes than in the primary outcome.

4.3 Overall completeness and applicability of evidence

4.3.1 Location

Nine of the eleven studies included in this review came from Africa (Sub-Saharan Africa) and the rest from India (Asia). The domination of African studies is perhaps appropriate as most of the mortality resulting from severe malaria in children occur in sub-Saharan Africa.[2] This would make it easier for health workers and policy makers on the continent to feel at ease in applying the findings to their localities. However, the absence of many studies from South-

east Asia is of concern. This region has an established record of multi-drug resistance falciparum malaria.[1] Following the emergence of drug resistance there has been wide scale use of artemisinin derivatives for treating malaria in this region[1] as such the availability of many studies from this region would have helped to apply the findings to this region. The absence of studies from Latin America also makes it difficult to infer the findings to this region.

All articles did not report on malaria transmission intensities in localities in which studies were conducted. Reporting on transmission intensities would have made it easier to apply the findings to those areas with similar transmission intensities to areas where included trials were conducted. In addition, although articles did not report on the resistance levels of quinine in localities where studies were conducted, empirical evidence has suggested that multidrug (including quinine) resistance falciparum malaria is much more wide spread in Asia than in Africa.[1] Therefore the artemisinin derivatives might appear to be more efficacious in Asia than in Africa. In exploring heterogeneity by subgroup analysis it was found that parasite clearance time was shorter in Asian studies than in African studies. However since parasite clearance time is of secondary importance in severe malaria, it can not be suggested that compared to quinine, the artemisinin derivatives are more useful in treating severe malaria in children in Asia but not in Africa.

4.3.2 Population

The review included studies which involved children aged 0 to 14 years. However judging from the mean age and standard deviation of studies included it appears that children aged 10 to 14 years were not well represented (Table 3.2). Therefore applying the findings to this population group based on this review may be questioned.

4.3.3 Product and Regimen

Different artemisinin derivatives were used in the included studies. Since they were manufactured in different countries and perhaps under different manufacturing conditions it can not be taken for granted that they had the same potency and are comparable to those currently on the market. It is of importance to note that most of the evidence came from trials of artemether versus quinine. There were eight artemether studies, two arteether studies, and one artesunate study. Surely one would be more confident to apply these findings to settings where artemether is in common use than in areas where artesunate is used widely.

4.4 Benefits and Risks

From this review we can say that the data available suggest that artemisinin derivatives are as good as quinine in preventing mortality from childhood severe malaria. However data arising from randomised trials included in this review are not adequate to compare safety profile of artemisinin derivatives versus quinine for treating severe malaria in children.

4.5 Conclusions

Implications for practice

1. Parenteral artemisinin derivatives are as good as quinine in treating severe malaria in children and not superior to quinine with regard to mortality outcome.
2. Parenteral artemisinin derivatives may have a marginal benefit over quinine in parasite clearance time in children with severe malaria.
3. Parenteral artemisinin derivatives are not conclusively better over quinine in coma resolution time in children with severe malaria.

4. Parenteral artemisinin derivatives are not better or worse when compared to quinine regarding fever clearance time in children with severe malaria.
5. There is no difference in the incidence of neurological sequelae among the two study groups.
6. 28th day cure rates among the two study groups are the same.
7. The data available on the incidence of adverse effects between the two groups is not adequate to make any meaningful inference.

Implications for research

1. In the light of the fact that there were no studies included from South East Asia and Latin America, trials on artemisinin derivatives versus quinine in children are needed in these regions in order to improve the applicability of findings of future reviews.
2. Most of the studies included in this review involved artemether versus quinine. There is a need to do more work on the other two derivatives i.e. artesunate and arteether to compare their efficacy versus to quinine in treating severe malaria in children.
3. Further research is needed to clarify the potential advantages of artemisinin derivatives over quinine in parasite clearance and coma resolution times and their potential for reduction of severe malaria mortality in childhood.
4. The review lacked adequate data on adverse effects of the artemisinin derivatives compared to quinine. Therefore there is a need to ensure future artemisinin derivatives trials are designed to identify and report adverse effects.
5. In all future trials there is a need to ensure; definitions, ascertainment and reporting of outcomes are standardised across the trials.

5. APPENDICES

APPENDIX A

***Trial eligibility form**

Study ID: _____ Date_____ Extractor (initials): _____
Journal: _____ Year published: _____
Year conducted_____
Trial name: _____

(1) DESIGN
(a) Described as randomised?

YES	NO	UNCLEAR

If NO Exclude. If YES go to question 2.

(2) PARTICIPANTS
(a) Were participants aged between 0 to 14 years?

YES	NO	UNCLEAR

(b) Did the participants have confirmed falciparum severe malaria? (*NB Confirmed by blood slide)*

YES	NO	UNCLEAR

If NO to (a) or (b) Exclude.

(3) INTERVENTIONS
(a) Was one group given artemisinin derivative (artesunate, artemether, artemotil or β-arteether) as treatment?

YES	NO	UNCLEAR

(b) Did another group receive quinine and the same care?

YES	NO	UNCLEAR

If NO to (a) or (b) then Exclude

(4) FINAL DECISION

YES(If all Yes)	NO(If any No or any Unclear)

*****Adapted from: Cochrane collaboration 2003.[48]

APPENDIX B

***Data extraction form**

Study ID: _____ Assessor (initials): _____
Journal: _____ Year published: _____
Year conducted:_____
Trial name: _____
Name of artemisinin derivative used:_____ Type of severe malaria:_____

PARTICIPANTS
Average age: _____
Median age: _____ Age range: _____
Gender: _____ Sample size:_____ Ethnicity:_____
Country:_____ Continent/Subcontinent: _____

Transmission level (High/low/unclear): _____
Quinine resistance level (High/low/unclear):_____

INCLUSION CRITERIA	EXCLUSION CRITERIA

Were intervention and control groups comparable at baseline? Yes No Unclear

METHODS

Randomisation method: _____

Generation of allocation sequence Adequate Inadequate Unclear
Concealment of allocation sequence Adequate Inadequate Unclear

Blinding

Participant blinded	Yes	No	Unclear
Provider blinded	Yes	No	Unclear
Outcome assessor blinded	Yes	No	Unclear

Patients

Assessed for eligibility: (Yes , No or Unclear)……

No of patients randomised	Group 1 (artemisinin derivative)	Group 2(quinine)

INTERVENTIONS

Group	Drug	Total dose(mg/kg)	Total duration(days)
Artemisinin derivative			
Quinine			

Timing of dose

Group	Day1 dosing	Day 2 dosing	Day 3 dosing	Day 4 dosing	Day 5 dosing	Day 6 dosing	Day 7 dosing
Artemisinin derivative							
Quinine							

OUTCOMES

Maximum duration of surveillance: _____

Time-points at which follow up is reported:_____

RESULTS

1. Mortality rate

Groups	No of pts treated	No confirmed death at the end of follow up	%age of death	p-value
Artemisinin derivative				
Quinine				

2. Parasite clearance time

Group	Sample size	Mean	Std	95%CI	Median	Iqr	p-value
Artemisinin derivative							
Quinine							

3. Fever clearance time

Group	Sample size	Mean	Std	95%CI	Median	Iqr	p-value
Artemisinin derivative							
Quinine							

4. Coma resolution time

Group	Sample size	Mean	Std	95%CI	Median	Iqr	p-value
Artemisinin derivative							
Quinine							

6. Serious adverse effects reported

Adverse effect	Frequency Artemisinin derivative	Frequency in quinine	Total Frequency	%age in artemisinin derivative	%age in quinine

P-value if any: No

Source of data:

Investigators contacted for more information: Yes No

Name and address of contacted person…….....
……
……
……
Data: Available……Requested……..Obtained…….

Remarks……
……

*Adapted from: Cochrane collaboration 2003[48]

APPENDIX C

***Methodological quality assessment form**

Study ID: _____ Date_____ Extractor (initials): _____
Journal: _____ Year published: _____
Trial name: _____

1. GENERATION OF RANDOM ALLOCATION NUMBER

ADEQUATE	INADEQUATE	UNCLEAR

2. ALLOCATION CONCEALMENT

ADEQUATE	INADEQUATE	UNCLEAR

3. BLINDING

OPEN	SINGLE	DOUBLE	UNCLEAR

4. LOSS TO FOLLOW UP

ADEQUATE (≤20%) Indicate actual %age below	INADEQUATE(>20%) Indicate actual %age below	UNCLEAR

If any of the categories above is unclear indicate action taken:
……
……
……
……

*****Adapted from: Cochrane collaboration 2003.[48]

***Criteria for assessing methodological quality of trials.**

1. Generation of allocation sequence

Adequate if: Random numbers are generated by computer, table of random numbers, drawing of lots or envelopes, tossing of coin, shuffling cards or throwing of dice.

Inadequate if: Random numbers are generated using case record number, date of birth, day or year of admission.

Unclear if: No explanation is given on how random numbers were generated.

2. Allocation concealment

Adequate if: If participants and investigators enrolling participants can not predict assignment. This occurs if the coding of the drug containers were done by independent centre or if envelopes which contain randomisation assignment codes are sequentially numbered opaque and opened only after all participant details have been written on the particular envelope.

Inadequate if: If participants and investigators enrolling participants can predict assignment. This is associated with inadequate allocation sequence generation, open allocation schedule, alternation in assignment and unsealed & non opaque envelopes.

Unclear if: No explanation is given on how random allocation concealment was done.

3. Blinding

Open if: Both Investigators and participants know interventions to which participants are assigned to

Single if: Investigators or participants know interventions to which participants are assigned to

Double blind if: Investigators and participants do not know interventions to which participants are assigned to

Unclear if: No explanation is given on how blinding was done

4. Loss to follow up

Adequate If: ≤20% of the participants enrolled are not followed-up to the end points or study completion or are excluded from analysis.

Inadequate if: >20% of the participants are not followed-up to the end points or study completion or are excluded from analysis.

Unclear if: Explanation is not given, especially when it seems that there was loss to follow-up or exclusion from analysis.

*****Adapted from: Cochrane collaboration 2003.[48]

APPENDIX D

Characteristics of included trials

Study name	**Walker(1993)[31]**
Study article	Walker O, Salako LA, Omukhodion SI, Sowunmi A. An open randomized comparative study of intramuscular artemether and intravenous quinine in cerebral malaria in children. *Trans Roy Soc Trop Med Hyg*1993;87:564-56
Country& year conducted	Nigeria,1991-94
Methods	Trial design: randomised controlled trial Generation of allocation sequence: Unclear Allocation concealment: Unclear Blinding: Open Loss to follow up: None (Adequate)
Participants	54 male and female children aged 1-5 years with cerebral malaria All 54 were evaluated(25 Artemether and 29 Quinine) Inclusion criteria: Cerebral malaria Exclusion criteria: Not stated
Interventions	(1)Artemether(i/m) for 5 days(3.2 mg/kg in the first day, then 1.6mg/kg during next 4 days (2)Quinine(i/v) for 7 days(20mg/kg loading dose, followed by 10mg/kg 8 hourly thereafter).This was changed to oral dose when child was able to swallow.
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5)neurological sequelae (6) 28^{th} day cure rate (7) adverse effects(cardiac signs)

Study name	**Murphy(1996)[32]**
Study article	Murphy S, English M, Waruiru C, Mwangi I, Amukoye E, Crawley J et al. An open randomized trial of artemether versus quinine in the treatment of cerebral malaria in African children. *Trans Roy Soc Trop Med Hyg* 1996;90:298-301
Country& year conducted	Kenya,1992-94
Methods	Trial design: randomised controlled trial Generation of allocation sequence: random number table(Adequate) Allocation concealment: Sealed envelopes open sequentially(Adequate) Blinding: Open Loss to follow up: 20%,40 children excluded from analysis(Adequate)
Participants	200 male and female children aged 2-12 years with cerebral malaria 160 were evaluated (89 Artemether and 71 Quinine), 40 excluded from analysis for various reasons. Inclusion criteria: Comatose children with asexual forms of *P.falciparum* Exclusion criteria: Evidence of pre -existing neurological deficit, head injury and history of recent treatment with antimalarial drugs other than chloroquine.
Interventions	(1)Artemether(i/m) for a minimum of 3 days(3.2 mg/kg first day, then 1.6mg/kg for the next 2 days (2)Quinine (i/v) for a maximum of 7 days (20mg/kg loading dose, followed by 10mg/kg 8 hourly thereafter). *Once patient was conscious and parasites were cleared, patients in both groups were given oral or i/m sulfadoxine-pyrimethamine (pyrimethamine 1.25/kg, sulfadoxine 25mg/kg), this happened after at least three doses of intervention drugs had been administered.*
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5)neurological sequelae (6) adverse effects

Study name	**Van Hensbroek(1996)[33]**
Study article	Van Hensbroek MB, Onyiorah E, Jaffar S, Schneider G, Palmer A, Frenkel J et al. A trial of artemether or quinine in children with cerebral malaria. *N Engl J Med* 1996;335(2):69-75
Country& year conducted	Gambia,1992-94
Methods	Trial design: randomised controlled trial Generation of allocation sequence: Adequate Allocation concealment: Sealed envelopes opened after admission procedures were completed(Adequate) Blinding: Open-label, (microscopists blinded) Loss to follow up: 0.5 % (Adequate),.3 excluded from final analysis.
Participants	579 male and female children, aged 1-9 years 576 were evaluated(288 Artemether and 288 Quinine) Inclusion criteria: Unconscious children 1-9 years,blantyre coma scale of 2 or less and identification of asexual forms of *P.falciparum* Exclusion criteria: Children with diseases other than cerebral malaria, children who regained consciousness after correction of hypoglycemia, convulsing children who recovered one hour after admission, children treated with quinine before admission and children treated with artemether before admission(None was treated with artemether before admission)
Interventions	(1)Artemether(i/m) for 4 days(3.2 mg/kg first day, then 1.6mg/kg in the next 3 days (2)Quinine(i/m) for 5 days(20mg/kg loading dose, followed by 10mg/kg 12 hourly thereafter).This was changed to oral dose when child was able to swallow. *Because of the observation that recrudescence of parasitaemia at one month after treatment was common in both groups, in the second and third years, a dose of 1.25mg of pyrimethamine/kg and 25mg sulfadoxine/kg were given orally after consciousness was regained, and parasite and fever were cleared.*
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5)neurological sequelae (6) 28th day cure rate (7) adverse effects

Study name	**Taylor(1998)**[34]
Study article	Taylor TE, Wills BA, Courval JM, Molyneux ME. Intramuscular artemether vs intravenous quinine: an open, randomized trial in Malawian children with cerebral malaria. *Trop Med Int Health* 1998;3(1):3-8
Country& year conducted	Malawi,1992-94
Methods	Trial design: randomised controlled trial Generation of allocation sequence: Computer generated random numbers(Adequate) Allocation concealment: sealed envelopes opened after admission procedures were completed(Adequate) Blinding: Open-label, (microscopists blinded) Loss to follow up: 10.4 % (Adequate).19 excluded from final analysis.
Participants	183 male and female children(Age range not specified), analysis showed mean age was 2.7 years with s.d of 1.9 for ART and 3.2 years with s.d of 1.9 in Q 164 were evaluated(83 Artemether and 81 Quinine) Inclusion criteria: Children with asexual forms of *P. falciparum*, Blantyre coma score of ≤2 with no other cause of fever or altered conscious. Exclusion criteria: Excluded if within one hour blantyre coma score was >2, CSF or blood culture examination was abnormal and parasitaemia failed to decrease within 24hours after the start of treatment.
Interventions	(1)Artemether(i/m) for 5 days(3.2 mg/kg first day, then 1.6mg/kg in the next 4 days (2)Quinine(i/v) for 7 days(20mg/kg loading dose, followed by 10mg/kg 8 hourly thereafter).This was changed to oral dose when child was able to swallow if the patient had already received at least three intravenous doses of quinine. *In both groups when the patient was fully conscious and if parasitaemia had been cleared a dose of sulphadoxine-pyrimethamine was administered (1.25mg/kg pyrimethamine and 25mg/kg sulphadoxine)*.
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5)neurological sequelae (6) adverse effects (7) 28th day cure rate

Study name	**Ojuawo (1998)**[35]
Study article	Ojuawo A, Adegboye AR, Oyewalo O. Clinical response and parasite clearance in childhood cerebral malaria: A comparison between intramuscular artemether and intravenous quinine. *East Afr Med J* 1998;75(8):450-452
Country& year conducted	Nigeria, year not yet established
Methods	Trial design: randomised controlled trial Generation of allocation sequence: Unclear Allocation concealment: Unclear Blinding: Unclear(Though context preclude blinding) Loss to follow up: None (Adequate)
Participants	37 male and female children with cerebral malaria, analysis showed mean age was 3.7 years with s.d of 1.7 for ART and 4.1 years with s.d of 1.9 in Q All 37 were evaluated(18 Artemether and 19 Quinine) Inclusion criteria: Children with arousable coma, children who had asexual forms of *P.falciparum* and children with no other causes of coma Exclusion criteria: Not stated
Interventions	(1)Artemether(i/m) for 3 days(3.2 mg/kg starting dose then 1.6mg/kg 12 hours later on first day, then 1.6mg/kg in the next 2 days (2)Quinine (i/v) for 7 days(10mg/kg initial dose, followed by 10mg/kg 8 hourly thereafter).This was changed to oral dose when child was able to swallow.
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5)neurological sequelae

Study name	**Olumese(1999)[36]**
Study article	Olumese PE, Bjorkman A, Gbadegesin RA, Adeyemo AA, Walker O. Comparative efficacy of intramuscular artemether and intravenous quinine in Nigerian children with cerebral malaria. *Acta Trop* 1999;*73:231-236*
Country& year conducted	Nigeria,1994-96
Methods	Trial design: randomised controlled trial Generation of allocation sequence: computer generated random numbers(Adequate) Allocation concealment: Sealed envelopes opened sequentially(Adequate) Blinding: Unclear(Though context would preclude any blinding) Loss to follow up: 4.7%(Adequate), 5 excluded (did not meet inclusion criteria)
Participants	108 male and female children aged 6m-5 years 103 were evaluated(54 Artemether and 49 Quinine) Inclusion criteria: Cerebral malaria, children with asexual forms of *P.falciparum*, an arousable coma lasting more than 30 minutes(with or without convulsions) Exclusion criteria: Abnormal CSF and Low blood glucose responding to glucose infusion.
Interventions	(1)Artemether(i/m) for 5 days(3.2 mg/kg first day, then 1.6mg/kg in the next 4 days (2)Quinine(i/v) for 7 days(20mg/kg loading dose, followed by 10mg/kg 8 hourly thereafter).This was changed to oral dose when child was able to swallow.
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5)neurological sequelae (6) 28th day cure rate

Study name	**Thuma(2000)**[37]
Study article	Thuma PE, Bhat GJ, Mabeza GF, Osborne C, Biemba G, Shakankale GM et al. A Randomized controlled trial of artemotil(β-arteether) in Zambian children with cerebral malaria. *Am J Trop Med Hyg* 2000;62(4):524-29
Country& year conducted	Zambia,1996-97
Methods	Trial design: randomised controlled trial Generation of allocation sequence: computer generated block randomisation(Adequate) Allocation concealment: sealed coded envelope(Adequate) Blinding: Unclear(Though the context would preclude blinding) Loss to follow up: 3.2% 3 excluded, they died after randomisation but before treatment (Adequate)
Participants	95 male and female children aged 0-10 years with cerebral malaria 92 were evaluated(48 arteether and 44 Quinine) Inclusion criteria: Unconscious children 0-10 years,blantyre coma scale of 2 or less, identification of asexual forms of *P.falciparum*, children with no other cause of coma i.e. normal CSF and normoglycemic and 30 minutes should have passed since last convulsion. Exclusion criteria: Prior history of any chronic illness, chemical intoxication from traditional medicine and black water fever(frank hemoglobinuria)
Interventions	(1)Arteether (artemotil)(i/m) for 5 days(3.2 mg/kg first day, then 1.6mg/kg in the next 4 days (2)Quinine(i/v) for 7 days(20mg/kg loading dose, followed by 10mg/kg 8 hourly thereafter).This was changed to oral dose when child was able to swallow.
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5)neurological sequelae (5) adverse effects

Study name	**Moyou-somo(2001)[38]**
Study article	Moyou-somo R, Tietche F, Ondoa M, Kouemeni L.E, Ekoe T, Mbonda E et al. Clinical trial of β-arteether versus quinine for the treatment of cerebral malaria in children in Yaounde, Cameroon. *Am J Trop Med Hyg* 2001;64(5,6):229-232
Country& year conducted	Cameroon,1995-97
Methods	Trial design: randomised controlled trial Generation of allocation sequence: Computer generated random numbers(Adequate) Allocation concealment: Sealed coded envelopes(adequate) Blinding: Unclear(Though the study context would preclude blinding) Loss to follow up: 3.7%(Adequate)
Participants	106 male and female children aged 0-10 years with cerebral malaria 102 were evaluated(51 β-Arteether and 51 Quinine) Inclusion criteria: Unconscious children 0-10 years, Blantyre coma scale of 2 or less, identification of asexual forms of *P.falciparum* and children with no other causes of coma. Exclusion criteria: Prior history of any chronic illness e.g. renal and liver diseases, frank AIDS, epilepsy and cardiovascular accident, chemical intoxication from traditional medicine ,black water fever(frank hemoglobinuria),children taking cardioactive drugs, children with history of black water fever and children were withdrawn incase of positive blood culture or CSF
Interventions	(1)Arteether(i/m) for 5 days(3.2 mg/kg first day, then 1.6mg/kg in the next 4 days (2)Quinine(i/v) for 7 days(20mg/kg loading dose, followed by 10mg/kg 8 hourly thereafter).This was changed to oral dose when child was able to swallow. Recrudescent cases were treated with sulfadoxine-pyrimethamine.
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5)neurological sequelae (6)adverse effects (7) 28th day cure rate

Study name	**Adam(2002)[39]**
Study article	Adam I, Idris HM, Mohamed-Ali AA, A/Elbasit, Elbashir MI. Comparison of intramuscular artemether and intravenous quinine in the treatment of Sudanese children with severe falciparum malaria. *East Afr Med J* 2002;79(12):621-625
Country& year conducted	Sudan,2001-2002
Methods	Trial design: randomised controlled trial Generation of allocation sequence: Unclear Allocation concealment: Envelopes containing study group were open sequentially(Adequate) Blinding: Open Loss to follow up: None (Adequate)
Participants	41 male and female children with severe malaria, analysis showed mean age was 4.1 years with s.d of 2.5 for ART and 3.6 years with s.d of 3.2 in Q All 41were evaluated(20 Artemether and 21 Quinine) Inclusion criteria: cerebral malaria, repeated convulsions, severe anemia (hemoglobin less than 5mg/dl), hyper-pyrexia (temperature of 40 degrees or more) and hyper parasitaemia (more than 100,000 rings/µl or combinations of these criteria. Exclusion criteria: Not stated
Interventions	(1)Artemether(i/m) for 5 days(3.2 mg/kg first day, then 1.6mg/kg in the next 4 days (2)Quinine(i/v) for 7 days(20mg/kg loading dose, followed by 10mg/kg 8 hourly thereafter).This was changed to oral dose when child was able to swallow. Paracetamol was given to lower temperature
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5) adverse effects

Study name	**Huda(2003)**[40]
Study article	Huda SN, Shahab T, Ali SM, Afzal K, Khan HM. A comparative clinical trial of Artemether and quinine in children with severe malaria. *Indian Pediatr* 2003;40:939-945
Country& year conducted	India,2000-2001
Methods	Trial design: randomised controlled trial Generation of allocation sequence: Unclear Allocation concealment: Inadequate Blinding: Open Loss to follow up: None (Adequate)
Participants	46 male and female children aged 0-14 years with severe malaria All 46 were evaluated(23 Artemether and 23 Quinine) Inclusion criteria: Severe malaria and Asexual forms of Plasmodium falciparum demonstrated on peripheral smear. Exclusion criteria: History of having received artemether or quinine within 24 hours preceding admission and severe protein energy malnutrition or clinical/laboratory evidence of other significant illness not attributable to severe malaria.
Interventions	(1)Artemether(i/m) for 6 days(1.6 mg/kg twice a day on first day, then 1.6mg/kg in the next 5 days (2)Quinine(i/v) for 7 days(20mg/kg loading dose, followed by 10mg/kg 8 hourly thereafter).This was changed to oral dose when child was able to swallow.
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5) adverse effects

Study name	**Mohanty(2004)**[41]
Study article	Mohanty AK, Rath BK, Mohanty R, Samal AK, Mishra K. Randomized control trial of quinine and artesunate in complicated malaria. *Indian J Pediatr* 2004;71:291-295
Country& year conducted	India, 2000-2002
Methods	Trial design: randomised controlled trial Generation of allocation sequence: Inadequate Allocation concealment: Inadequate Blinding: single Loss to follow up: None (Adequate)
Participants	80 male and female children aged 2-14 years with complicated malaria All 80 were evaluated(40 Artesunate and 40 Quinine) Inclusion criteria: Complicated malaria Children who had in their peripheral blood asexual forms of *P.falciparum* Exclusion criteria: .Absence of asexual form of *Plasmodium falciparum,* renal failure due to other causes *and* hepatitis due to other causes
Interventions	(1)Artesunate(i/m) for 6 days(3.6 mg/kg first day, then 1.6mg/kg in the next 5 days (2)Quinine(i/v) for 7 days(20mg/kg loading dose, followed by 10mg/kg 8 hourly thereafter).This was changed to oral dose when child was able to swallow.
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5) 28th day cure rate (6) adverse effects

APPENDIX E

Characteristics of the excluded studies

Study name	**Taylor(1992)[58]**
Name of article	Taylor TE, Wills BA, Kazembe P, Chisale M, Wirima JJ, Esther YE et al. Rapid coma resolution with artemether in Malawian Children with cerebral malaria. *Lancet* 1993;341:661-62
Country and year conducted	Malawi, 1992(January-June)
Methods	Trial design: randomised controlled trial Generation of allocation sequence: Not stated, though a final article showed it was adequate. Allocation concealment: Not stated, though a final article showed it was adequate. Blinding: Unclear, (context preclude any blinding) Loss to follow up: None.(Adequate)
Participants	65 male and female children(Age range not specified) 65 were evaluated(28 Artemether and 37 Quinine) Inclusion criteria: Children with asexual forms of *Plasmodium falciparum*, Blantyre coma score of ≤2 with no other cause of fever or altered conscious. Exclusion criteria: Not stated
interventions	(1)Artemether(i/m) for 5 days(3.2 mg/kg first day, then 1.6mg/kg in the next 4 days (2)Quinine(i/v) for 7 days(20mg/kg loading dose, followed by 10mg/kg 8 hourly thereafter).This was changed to oral dose when child was able to swallow if the patient had already received at least three intravenous doses of quinine. *In both groups when the patient was fully conscious and if parasitaemia had been cleared a dose of sulphadoxine-pyrimethamine was administered (1.25mg/kg pyrimethamine and 25mg/kg sulphadoxine).The above doses and timing therefore needs to be interpreted in the light of this information.*
outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5)neurological sequelae
Reason for exclusion	This was an interim analysis of Taylor (1998)[34] study which is included in this review

Study name	**Salako (1994)[59]**
Name of article	Salako LA, Walker O, Sowunmi S, Omokhodion J, Adio R, Oduola AMJ. Artemether in moderately severe and cerebral malaria in Nigerian Children. *Trans Roy Soc Trop Med Hyg* 1994;88 Suppl 1:13-15
Country and year conducted	Nigeria, year not stated
Methods	Trial design: randomised controlled trial Generation of allocation sequence: Not stated Allocation concealment: Not stated Blinding: Unclear, (context preclude any blinding) Loss to follow up: None.(Adequate)
Participants	54 male and female children(1 to 5 years) 54 were evaluated(25 Artemether and 29 Quinine) Inclusion criteria: Unconscious children with asexual forms of *Plasmodium falciparum*, with no other cause of fever or coma Exclusion criteria: Not stated
Interventions	(1)Artemether(i/m) for 5 days(3.2 mg/kg first day, then 1.6mg/kg for next 4 days (2)Quinine(i/v) for 7 days(20mg/kg loading dose, followed by 10mg/kg 8 hourly thereafter).This was changed to oral dose when child was able to swallow
Outcomes	(1)mortality (2)parasite clearance time (3)fever clearance time (4)coma resolution time (5) parasite recrudescence rate
Reason for exclusion	Literature review revealed that this article was an interim analysis of another trial which was not randomised.(wrongly claimed as randomised)

Study name	**Satti (2000)[60]**
Name of article	Satti GM, Elhassan SH, Ibrahim SA. Efficacy of artemether versus quinine in the treatment of cerebral malaria. *J Egypt Soc Parasitol* 2000; 32(2): 611-23
Reason for exclusion	Only abstract of this article was retrieved despite efforts made to get a full article through Wits Health Science Library, the editor of the Journal and one author .

APPENDIX F

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 PrayGod

CLEARANCE CERTIFICATE	PROTOCOL NUMBER M040816
PROJECT	Efficacy of Artemisinin Derivatives in Treating Severe Malaria in Children: A Systematic Review & Meta Anaylis
INVESTIGATORS	Dr G PrayGod
DEPARTMENT	School of Public Health
DATE CONSIDERED	04.08.27
DECISION OF THE COMMITTEE*	Approved subject to completing the ethics form in full and submitting it

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 04.08.30 CHAIRPERSON .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr A de Frey

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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