Hochschule für Angewandte Wissenschaften Hamburg
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PARENTERAL ARTEMISININ BASED THERAPY VERSUS PARENTERAL QUININE IN THE TREATMENT OF SEVERE MALARIA: A COMPREHENSIVE LITERATURE REVIEW

SUBMITTED TO THE DEPARTMENT OF HEALTH SCIENCES FOR THE AWARD OF A MASTER OF PUBLIC HEALTH DEGREE

MASTER THESIS (MPH)

10/23/2014

By

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DECLARATION OF HONOUR

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HAMBURG, the 23rd of October, 2014 KENNETH ANEHBI ASANG

DEDICATION

This piece of work is dedicated to God Almighty and to all the lives lost to malaria.

ACKNOWLEDGEMENT

My heartfelt appreciation goes to Professor Dr. Ralf Reintjes who has not just been a supervisor but a mentor and Dr. Amena Ahmad for her relentless support even in the most difficult moments.

I express my gratitude to the entire HAW Hamburg staff for the tools there have equipped me with for the long journey of preventing disease and making populations healthy.

Finally, to my family and friends for their emotional and financial support.

This will not have been possible without you All!

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ABSTRACT

BACKGROUND

Prompt effective treatment is central in preventing death in severe malaria. Several studies have compared different artemisinin derivatives to quinine in the treatment of severe malaria. Recently, there have been reports of delayed hemolysis after parenteral artesunate use in the treatment of severe malaria. This review seeks to answer the research question: parenteral artemisinin derivatives versus parenteral quinine which is better, in efficacy and adverse events for the treatment of severe malaria?

METHODS

All relevant studies on the efficacy and/or adverse events of artemisinin derivatives in the treatment of severe malaria were included in this review. Data bases searched were: MEDLINE, the Cochrane Library, EMBASE and Google.

RESULTS

31 studies were included (15,174 participants). Artemisinin derivatives had lower mortality compared to quinine. Artemisinin derivatives had similar duration of hospital stay compared to quinine. Artemisinin derivatives resolved coma faster, cleared parasites faster and cleared fever faster than quinine. More cases of hypoglycemia, hearing disturbances, visual disturbances, prolongation of QTc interval, hepatotoxicity and acute renal failure were reported in quinine than in the artemisinin derivatives. More cases of delayed haemolysis were reported in the artemisinin derivatives, specifically artesunate, compared to quinine.

CONCLUSION

Artemisinin derivatives have more efficacy and less adverse events compared to quinine. There is a need for pharmocavigilance after parenteral artesunate use for 4 weeks.

CHAPTER ONE

BACKGROUND

Malaria for decades remains a global public health problem. It is caused by a protozoan transmitted by the female anopheles mosquitoes. It is endemic in more than 100 countries (Hess et al., 2010) , with over 40% of the world´s population being at risk of infection (Efferth and Kaina, 2010). Nearly 250 million malaria cases and 1million malaria deaths are reported annually worldwide (Hess et al., 2010).

125 million international travelers visit malaria endemic areas annually (Hess et al., 2010), with this huge international migration to and from malaria endemic areas, malaria is no longer a public health problem just to malaria endemic regions especially Africa where over 85% of malaria related mortality occurs in children (I. Hendriksen et al., 2013), but also in the UK where annually over 1500 imported cases reported (Eder et al., 2012), the US with about 1,500 imported cases are reported annually (Hess et al., 2010), 562 imported cases reported in Germany in 2011, and generally approximately 5000 imported cases reported to the WHO European region with about 25 deaths (Rolling et al., 2013).

Uncomplicated malaria progresses rapidly within few hours to severe malaria, if ineffective medicines are given or treatment is delayed. Severe malaria usually manifests with one or more of the following: coma (cerebral malaria), metabolic acidosis, severe anemia, hypoglycemia, acute renal failure, or acute pulmonary oedema (World Health Organization, 2010a). Severe malaria is a medical emergency which if left untreated results in 100% mortality (Byakika-Kibwika et al., 2012). Prompt effective treatment is central in preventing death in severe malaria (World Health Organization, 2010a). Antimalarial chemotherapy therefore remains the mainstay of patient management (Kremsner et al., 2012).

Quinine was the mainstay for the treatment of severe malaria since the introduction of Cinchoma Bark to European medicine in the 1630s (Dondorp et al., 2005), then came the deployment of parenteral chloroquine, due to its safety and more effectiveness in the 1950s. It later lost its place of pride back to parenteral Quinine due to reported resistance in South East Asia that spread to Africa at the end of the 1970s, allowing quinine once more to resume its primary role in the treatment of severe malaria (Dondorp et al., 2010). However, quinine has several adverse effects (including cardiotoxicity, hypotension,

hypoglycemia and cinchonism), and has a narrow therapeutic range (Zoller et al., 2011). In addition, there is limited evidence that the efficacy of quinine in severe malaria maybe declining (Sinclair et al., 2012).

The primacy of Quinine in the treatment of severe malaria, has been challenged by the introduction of artemisinin derivatives. Over a thousand years before the curative powers of cinchoma bark were known to European explorers, qinghao (sweet wormwood), was in use in China as a herbal remedy for fever. It was not until 1970 that Chinese scientists identified the active antimalarial ingredient, qinghaosu (extract of qinghao) or artemisinins (Artemether-Quinine Meta-analysis Study Group, 2001). Today, artemisinins are considered the most important antimalarial agents worldwide due to their potency, tolerability, limited resistance in malaria parasites and rapid antiparasytic activity and symptom resolution. (Hess et al., 2010). Compared to quinine, they have been shown to have a broader spectrum of activity and the most rapidly acting of all antimalarial drugs in terms of parasite clearance (Artemether-Quinine Meta-analysis Study Group, 2001), and reach peak concentrations faster. This is of crucial importance as majority of severe malaria deaths occur within 24 to 48 hours following hospital admission (Sinclair et al., 2012).

Several studies have been carried out comparing quinine and different artemisinin derivatives (such as artemether, arteether, and sodium artesunate). Artesunate which is water soluble and can be given both intramuscular and intravenous injections, is the most studied of the artemisinin derivatives and has been shown to reliably reach peak concentration within an hour due to rapid and reliable absorption (Sinclair et al., 2012). Artemether and arteether are both lipid soluble. Due to the slow and erratic nature of these two compounds, studies have found them not to demonstrate any superiority in mortality over quinine (except in areas where quinine resistance have been reported), but have been demonstrated as satisfactory alternatives to quinine therapy as they present little adverse events compared to quinine (PrayGod et al., 2008; Tran et al., 1996a; Artemether-Quinine Meta-analysis Study Group, 2001).

Following the highly powered evidence from the multi-centered studies of the –QUAMATs in South East Asia and Africa, where artesunate compared to quinine in treating severe malaria had an absolute reduction in mortality of 34.7% in Asia (Dondorp et al., 2005) and a relative reduction of 22.5%, with no serious drug related adverse events (Dondorp et al.,

2010), the World Health organization recommended intravenous artesunate as the first line treatment of severe malaria (2010). Artesunate has superior anti-malaria properties to quinine and artemether. Its efficacy demonstrated by rapid parasite clearance and fever clearance is enhanced by its rapid hydrolysis to its active metabolite dihydroartemisinin (Byakika-Kibwika et al., 2012). Little is known about drug-drug interactions with intravenous artesunate, but its short half- life of less than 2 hours, makes this less of a significant concern (Hess et al., 2010).

Though data on human toxicity is limited, evidence and surveillance data suggest that artemisinins are safe to use in adults and children (Hess et al., 2010).

Despite these overwhelming evidences, regarding the superiority of artemisinin derivatives particularly intravenous artesunate over quinine in treating severe malaria, artesunate considered the most favourable in treating severe malaria among the artemisinin derivatives, has not been certified under the Good Manufacturing Practice in Europe and America (Kreeftmeijer-Vegter et al., 2012). However, artesunate is made available from the CDC under the investigational new drug (IND) protocol, which is produced by the U.S. Army Medical Materiel Development Activity in the US (Briggs and Arguin, 2013). However, there have been recent reports regarding adverse events including delayed hemolysis of artemisinins particularly IV artesunate. This could be extremely dangerous not just to non-immune patients in non-endemic regions with developed health systems but even more so to endemic regions where the health care system are still fragile and most patients are still in hard-to-reach and resource limited settings.

Looking at these recent concerns, there emerged a need to carry out a comprehensive review on the efficacy and adverse events of artemisinin derivatives and comparing it to that of quinine in the treatment of severe malaria. This study therefore seeks to answer the research question: parenteral artemisinin derivatives versus parenteral quinine which is better, in efficacy and adverse events for the treatment of severe malaria?

OBJECTIVES

- To assess the efficacy of parenteral artemisinin derivatives versus parenteral quinine in treating severe malaria.
- To determine the adverse events of parenteral artemisinin derivatives versus parenteral quinine in the treatment of severe malaria.

CHAPTER TWO

METHODS

A comprehensive literature search was carried for this review.

SEARCH STRATEGY

Data bases

The data bases searched were: MEDLINE, EMBASE, and COCHRANE CENTRAL (published in the Cochrane library). The google search engine was equally used to identify relevant documents and literature.

Search terms

The following search terms were used, `severe malaria´, `parenteral artemisinins´, `parenteral quinine´, `severe malaria and parenteral artemisinins´, and `severe malaria and parenteral quinine´.

Two searches were conducted. The first search used the following combination: severe malaria AND parenteral artemisinins, and the second search used: Severe malaria AND parenteral quinine. The limits used are articles in English and French and articles from 1990 till May 19, 2014 week 20. To retrieve recent publications that had not been indexed yet, no MeSH terms were used. Table 1 shows the search strategy in Medline and Embase and their respective results.

Table 1: Search strategy (Medline and Embase) and results

Search Terms	**Combination AND**	**Results in Medline**	**Results in Embase**	**Total**
Severe Malaria	Parenteral Artemisinins	**66**	**2**	**68**
Severe Malaria	Parenteral quinine	**88**	**30**	**118**
Total		**154**	**32**	**186**

The Cochrane data base was searched through the Cochrane library using the search terms `Severe malaria AND parenteral artemisinins AND Parenteral quinine´, and **1** articles was found.

SELECTION CRITERIA

For relevant literature extraction, the following selection criteria were used:

Inclusion criteria

- Articles focused on the effects of parenteral artemisinins in the treatment of severe malaria.
- Articles focused on the effects of parenteral quinine in the treatment of severe malaria
- Articles comparing the effects of a parenteral artemisinin derivative with parenteral quinine in the treatment of severe malaria.
- Articles from 1990 to May 19, 2014 week 20 focused on the effects of parenteral artemisinins and/or parenteral quinine in the treatment of severe malaria.
- English and French articles.

Exclusion criteria

- Articles focused on acute malaria
- Articles in which other routes of drug administration than the parenteral route are used.
- Any articles involving drugs other than artemisinins and/or quinine.
- Articles older than 1990.

From searching Medline, Embase and Cochrane data bases a total of **187** articles were found. First a selection based on title was made and **63** articles were excluded, because they did not meet the inclusion criteria. Secondly, a selection based on abstract was made and **64** articles were excluded, because they did not meet the inclusion criteria. Thirdly, articles were excluded based on dates of publication (before 1990), and **16** articles were excluded. Finally article that appeared more than once, were considered just once. In Medline, **35** articles were selected, among which **14 articles** were found in both search groups (that is, severe malaria AND parenteral artemisinins and severe malaria AND parenteral quinine), resulting in **21 final articles** from Medline.

The **1** article found in Cochrane was already among the selected articles in Medline, hence was considered just once.

12 articles were selected from Embase, out of which **12** were among the selected articles in Medline. Hence, no additional article was considered from Embase.

Reference lists

The reference list of all selected articles was checked and **10** relevant articles were selected based on the relevance to the inclusion criteria.

Therefore, a total of **31** articles were considered for this study.

DATA EXTRACTION

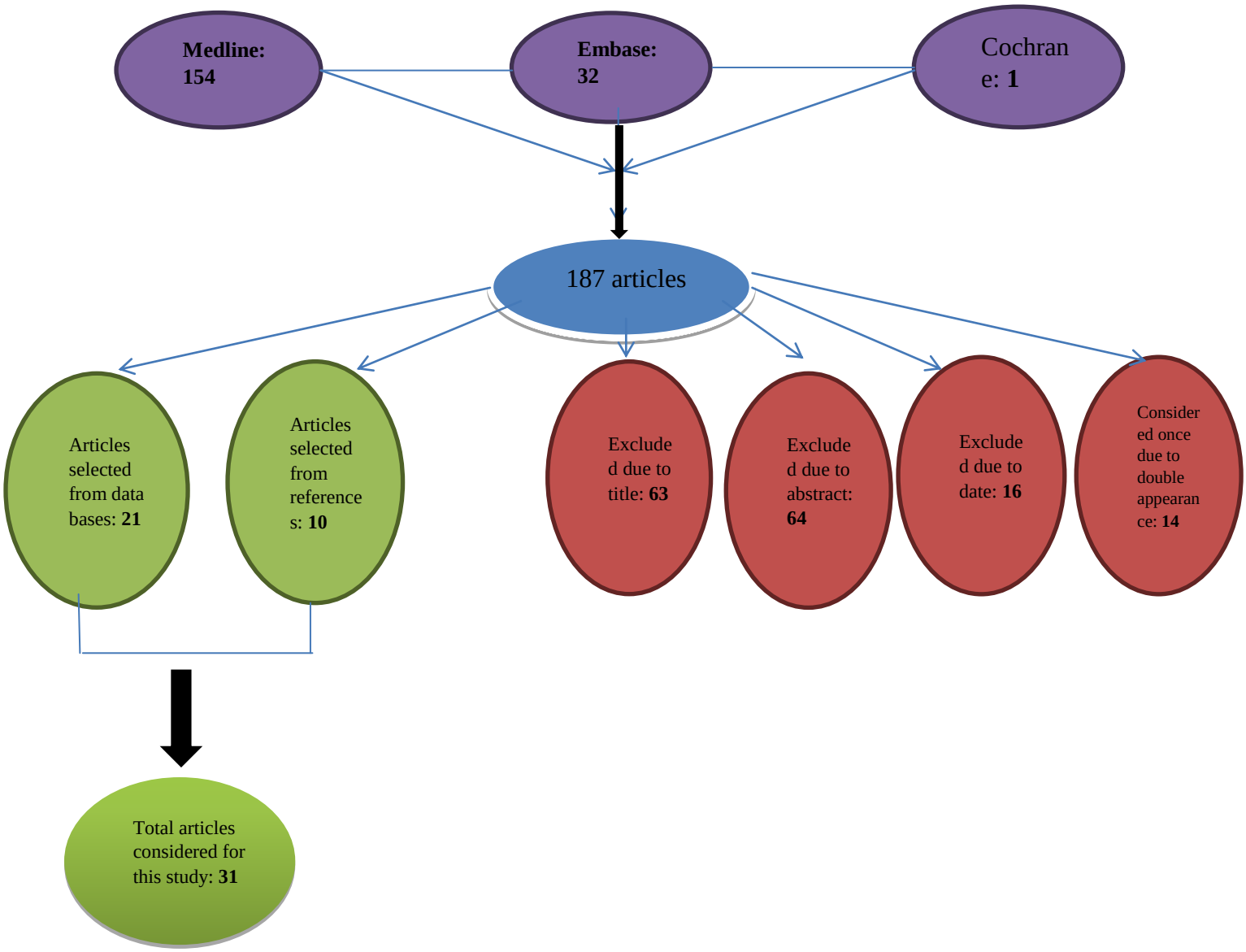
Data was extracted using an excel spreadsheet. The aim was to extract data on the study characteristics (the study authors, region where the study was carried out, date of publication, number of participants, target group, study design, drug used and duration of treatment), the efficacy (mortality rate, duration of hospital stay, coma resolution time, parasite clearance time and fever clearance time) and the number of patients reporting the following adverse events in each study; hypoglycemia, delayed hemolysis, hearing disturbances, visual disturbances, hepatotoxicity, acute renal failure and prolongation of QTc interval (>500ms) (See appendix Ia and Ib).

ASSESSMENT OF RISK OF BIAS IN THE RANDOMIZED CONTROLLED TRIALS

An assessment was carried out to investigate whether adequate steps had been taken to reduce the risk of bias in the randomized controlled trials included in this study. This was done in the following five domains: random sequence allocation, allocation concealment, blinding, loss of follow up and reporting bias.

These judgments were categorized as `yes´ (low risk bias, that is, if a clear description of how the above domains were carried out) and `no´ (high risk of bias, if was not described) and `unclear´ where my judgments were unclear. (See appendix II).

Figure 1: Selection procedure of included articles



CHAPTER 3

RESULTS

DESCRIPTION OF STUDIES

31 studies met the inclusion criteria, and were included for this review. These studies enrolled a total of 27,182 participants. However, since this was a comprehensive literature review, there were some studies that were reported more than once, that is, some reviews reported trials that were already part of the study and some studies were sub-sets of larger trials (Adam et al., 2002; Rolling et al., 2012; Kreeftmeijer-Vegter et al., 2012; Zoller et al., 2011; Caramello et al., 2012; Dondorp et al., 2010; Dondorp et al., 2005; Hendriksen et al., 2013a). Also, there were studies that were reported in more than one review, that is, Cao et al., 1997 in Sinclair et al., 2012; Hien et al., 1996 in Artemether-Quinine Meta-analysis Study Group, 2001; Danis et al., 1996 in Ambroise-Thomas, 1997). All these were considered just once, resulting in a reduction of 12,008 participants. Therefore these results are based on 15,174 participants. Three studies (Fargier et al., 1999 and Ambroise-Thomas, 1997 and Artemether-Quinine Meta-analysis Study Group, 2001) did not differentiate the number of children from adults in their report, making it difficult to get the precise number of children and adults included in this study.

These studies were reported from Africa, Asia, Europe and North America, with majority (44%) of the studies reported from Africa. (See Table 2)

Table 2: **Number of studies carried out in different regions**

Region	Number	Percentage
Africa	13	42%
Asia	8	26%
Africa and Asia	3	10%
Europe	6	19%
North America	1	3%
Total	**31**	100%

Participants

Study participants reported in the studies included a neonate, children and adults. 1 study reported on neonates (1 neonate), 10 studies reported on children, 12 studies reported on adults and 8 studies reported on both adults and children. (See table 3)

Table 3: **Number of studies with different age group participants**		
Target group	**Number**	**Percentage**
Neonates	1	3%
Children	10	32%
Adults	12	39%
Adults and children	8	26%
Total	31	100%

Study treatments

15 studies compared artemisinin derivatives to quinine (1 of them compared artemether, artesunate, and arteether to quinine, 6 of them compared artesunate to quinine, 1 of them compared both artemether and artesunate to quinine and 6 of them compared artemether to quinine (See Table 4).

Table 4: **Summary of Main results from studies that compared artemisinin derivatives to quinine**
Mortality: artemisinin derivatives had lesser mortality rates than quinine (9 out 10 studies: 90.0% and 1 study did not find any difference between both).
Parasite clearance time: 9 out of the 10 studies (90%) found that artemisinin derivatives cleared parasites faster and 1 study did not find any difference between both.
Fever clearance time: 9 studies reported FCT. *4* studies found artemisinins with shorter fever clearance time than quinine, 2 studies found quinine shorter FCT and 3 found both comparable.
Coma resolution time: 10 studies reported on this. **2** studies found artemisinin derivatives with shorter CRT than quinine, **4** studies found quinine with shorter CRT than artemisinin derivatives, 4 studies found no difference between both groups.
Duration of hospital stay: 5 studies reported on this. **2** studies found artemisinin derivatives to have shorter hospital stay, while **1** found hospital stay longer in artemisinin derivatives than in quinine and **2** studies found both similar
Adverse events: 1 study did not report adverse events, **1** study did not record any adverse events. Overall more adverse events were associated to quinine: Hypoglycemia (7 studies), hearing disturbances, visual impairment, QTc interval prolongation, Acute Renal Failure, Neurological sequelae in general (7 studies), reticulocyte drop, haemoglobin drop, local reactions, tinnitus 2, abdominal pain and nausea, blurred vision, and vertigo were reported while, in artemisinin derivatives: delayed hemolysis (1 study), neurological sequelae in general (7 studies); reticulocyte drop, hemoglobin drop, local reactions. Abdominal pain and nausea hypoglycemia, pain at injection site, reduction in number of leucocytes and reticulocytes in artemether were reported.

* See Appendix IV for the study details (study, target group, treatment and main results)

11 studies focused solely on artesunate and 6 studies focused on quinine. The dosages of these interventions varied between studies. The duration of artemisinin derivative treatment ranged from 1,5 days to 7 days, while quinine ranged from 2 to 7 days. (See table 5: Baseline characteristics of studies). Although standardized clinical definitions for severe malaria exist, the entry criteria were not consistent across studies.

Assessment of risk of bias in the randomized controlled trials

This review included studies with varied study designs including randomized controlled trials, cohort studies, case series, case reports, meta-analysis, systematic reviews and literature reviews. Majority, 10 of the 32 studies (34%) were randomized controlled trials.

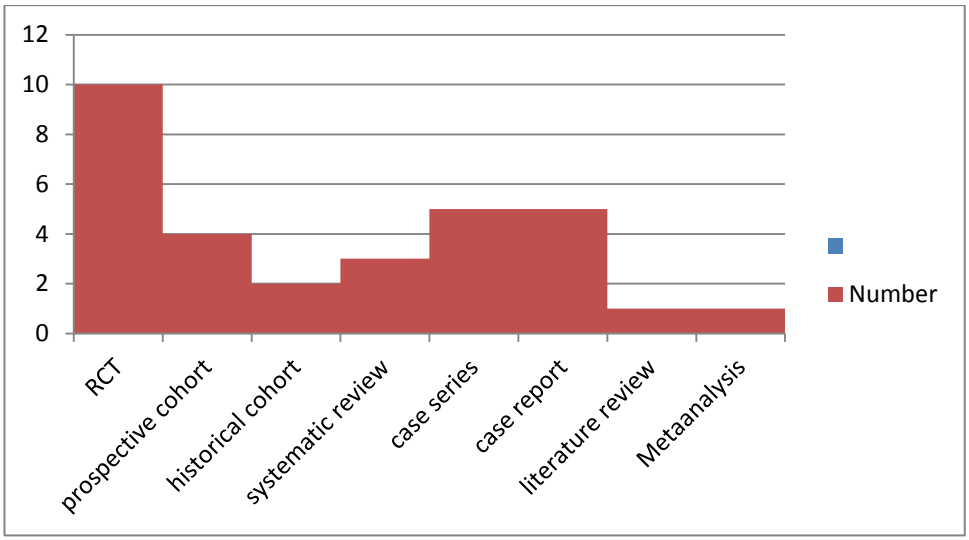


Figure 2: Number of the different study designs

An assessment of the risk of bias in the randomized controlled trials was done based; random sequence allocation, allocation concealment, blinding, loss of follow up, and reporting bias.

Random sequence Allocation

The methods used in generation of allocation sequence in the 11 trials in this study was done in 8 trials (Dondorp et al., 2010; Hendriksen et al., 2013a; Tran et al., 1996; van Hensbroek et al., 1996; Dondorp et al., 2005; Eltahir et al., 2010; Hendriksen et al., 2013b; Kremsner et al., 2012), and were not clear in the remaining trials (Adam et al., 2002 and Fargier et al., 1999). 8 trials did allocation concealment (Dondorp et al., 2010; Hendriksen et al., 2013a; Tran et al., 1996; van Hensbroek et al., 1996a; Dondorp et al., 2005; Eltahir et al., 2010; Hendriksen et al., 2013b; Kremsner et al., 2012, and were not clear in the remaining 2 trials (Adam et al., 2002 and Fargier et al., 1999).

Table 5: **Baseline Characteristics of studies**						
Studies	***Region***	***Year of study Publication***	***Number of participants***	***Target group***	***Study Design***	***Duration of treatment (days)***
PrayGod et al., 2008	Asia and Africa	2008	1524	children (0 to16 years)	systematic review	4,5
(Rolling et al., 2013)	Europe (Germany)	2013	36	adults 18 years and above	Hospital- based Retrospective study	5
(Rolling et al., 2012)	Europe (Germany)	2012	3	Adults 19 years and above	Case series	2
(Kremsner et al., 2012)	Africa	2012	197	children (6 months to 10 years)	A randomized double-blind controlled trial	2,5
(Dondorp et al., 2010)	Africa	2010	5425	children less than 15 years	A randomized open labelled trial	Not specified
Krudsood et al., 2003	Asia (Thailand)	2003	803	adults 15 years and above	prospective cohort study	5 and 3 respectively
(Lubell et al., 2011)	Africa	2011	2300	children less than 15 years	A randomized open labelled trial	Not specified
Prashanth et al., 2012	Asia (India)	2012	1	preterm neonate (borne at 30 weeks gestation)	case report	6
Davis et al., 2001	Asia (Vietnam)	2001	30	Adults	prospective cohort study	Not specified

(Byakika-Kibwika et al., 2012)	Africa (Uganda)	2012	14	adults 18 years and above	prospective cohort study	Not specified
(Hendriksen et al., 2013a)	Africa (Tanzania)	2013	70	children aged 7 months to 11 years	A randomised controlled trial	Not specified
(Tran et al., 1996)	Asia (Vietnam)	1996	560	adults 15 years and above	A randomized double blind controlled trial	3,4
(van Hensbroek et al., 1996a)	Africa (Gambia)	1996	576	children 1 to 9 years	A randomized unblinded controlled trial	4
(Zoller et al., 2011)	Europe (Germany, Denmark, Sweden, and Norway)	2011	25	1 child and 24 adults	case series	4
Briggs et al., 2013 CDC Report	North America (USA)	2013	19	adults and children	Literature Review	Not specified
(Dondorp et al., 2005)	Asia (South East Asia)	2005	1461	adults and children	open labelled RCT	Not specified
(Kreeftmeijer-Vegter et al., 2012)	Europe (Netherlands and Belgium)	2012	55	adults and children	case series	2

(Caramello et al., 2012)	Europe (Italy)	2012	1	Adult	case report	1,5
(Artemether-Quinine Meta-analysis Study Group, 2001)	Africa	2001	1919	adults and children	Meta-analysis of trials	Not specified
(Eltahir et al., 2010)	africa (Sudan)	2010	66	Children	open labelled RCT	Not specified
(Adam et al., 2002)	africa (Sudan)	2002	41	Children	open RCT	4
(Eder et al., 2012)	Europe (UK)	2012	167	adults 16 year and above	case series	2,7
(Chaudhari et al., 2013)	North America (USA)	2013	1	Adult	case presentation	7
(Sinclair et al., 2012)	Asia and Africa	2012	7429	adults (1664)and children (5765)	systematic review (8 studies, 6 in Asia and 2 in Africa)	Not specified
(Fargier et al., 1999)	Africa (Cameroon)	1999	90	children and adults above 6 years.	open RCT	5
(Ambroise-Thomas, 1997)	Africa and Asia	1997	3024	adults and children	systematic review	5

(Ogetii et al., 2010)	Africa (Kenya)	2010	1237	children 0 to 12 years	Retrospective cohort	Not specified
(Nwosu, 2012)	Africa (Nigeria)	2012	2	adults 20 years and above	case series	Not specified
(Hendriksen et al., 2013b)	Africa (Tanzania)	2013	75	children aged 4 months to 8 years	A randomized open-label trial	Not specified
(Gunawan et al., 2007)	Asia (Indonesia)	2007	1	Adults	Case report	2
(van Hensbroek et al., 1996b)	Africa (Gambia)	1996	29	children less than 2 years (20cases) and 2 years to 10 yrs (9 control)	prospective cohort	Not specified
(Looareesuwan et al., 1990)	Asia (Thailand)	1990	1	Adult	case report	3,2

Blinding

In 8 trials, the procedure was described as open (Dondorp et al., 2010; Hendriksen et al., 2013a; van Hensbroek et al., 1996; Dondorp et al., 2005; Eltahir et al., 2010; Hendriksen et al., 2013b; Adam et al., 2002 and Fargier et al., 1999), while in the remaining 2 trials, both participants and investigators were not aware of the treatment allocation, that is, double blinded (Tran et al., 1996; Kremsner et al., 2012).

Loss of follow-up

In 8 trials there was no report of loss of follow up (Dondorp et al., 2010; Hendriksen et al., 2013a; Tran et al., 1996 ; Dondorp et al., 2005; Eltahir et al., 2010; Fargier et al., 1999 ; Hendriksen et al., 2013b). In 1 trial, the loss of follow-up was less than 10% (van Hensbroek et al., 1996a), while 2 trials had a loss to follow-up of over 15% (Kremsner et al., 2012 and Adam et al., 2002).

Selective reporting

No evidence of selective reporting was detected.

5 trials described how the sample size required to detect statistical significant differences in outcomes among treatment groups was achieved (Dondorp et al., 2010; Dondorp et al., 2005; Tran et al., 1996; van Hensbroek et al., 1996a; Kremsner et al., 2012). 5 trials had small sample size (Hendriksen et al., 2013a; Eltahir et al., 2010; Adam et al., 2002; Fargier et al., 1999; Hendriksen et al., 2013b). 2 trials were sub-studies of the AQUAMAT (Hendriksen et al., 2013a; Hendriksen et al., 2013b) (See Appendix II).

EFFICACY

In this review; mortality rate, parasite clearance time, fever clearance time, coma recovery time, and duration of hospital stay were used as outcome measures to assess the efficacy of artemisinin derivatives and quinine (See Table 6).

Mortality

Mortality was reported by 28 studies. One review reported a reduced risk of mortality with artesunate treatment in adults (RR 0.61 95% CI0.50 to0.75; 1664 participants, and in children (RR 0.76 95% CI 0.65 to0.90; 5765 participants) (Sinclair et al., 2012). Another review comparing artemisinin derivatives to quinine found no difference in mortality (RR 0.90 95% CI: 0.73 to 1.12; 1,524 participants) (PrayGod et al., 2008). 20 studies reported artemisinin derivatives mortality rate: 10 studies reported 0% mortality rate in 307 adults and children in Africa, Asia and Europe; 9 studies reported a mortality rate ranging from 1.1% to 15%. 1 artemether study in Gambia (Africa), reported a mortality rate of 20.5% in 288 participants.

16 studies reported quinine mortality rate: 3 studies reported 0% mortality rate in 49 adults and children in Africa and Asia; 10 studies reported a mortality rate from 3.5% to 17.3%. 2 studies reported a mortality rate of 21.5% (in Gambia, Africa in 288 participants) and 22% (in Asia in 731 participants), and 1 study in Thailand (Asia) reported a 100% mortality rate in 1 participant.

2 did not report mortality (Rolling et al., 2013 and Melissa Briggs et al., 2013).

Table 6: **Drug efficacy as presented in the different studies**

Characteristics					**Efficacy**				
Study	***Region***	***number of participants***	***drug used***	***Number of participants in each drug group***	***Mortality (%; RR)***	***duration of hospital stay (days)***	***Coma recovery time (days; WMD)***	***Fever clearance time (days; WMD)***	***Parasite clearance time (days; WMD)***
PrayGod et al., 2008	Asia and Africa	1524 children	*artesunate, artemether and ß artemotil*	not specified	RR=0.90 95% CI: 0.73, 1.12	Not reported	WMD= -4.61, 95%CI:-7.21,-2.00	WMD= -2.58, 95%CI: -9.53, 4.38	WMD= -3.82, 95%CI: -8.73, 1.10
			Quinine	not specified	RR=0.90 95% CI: 0.73, 1.12	Not reported	WMD= -4.61, 95%CI:-7.21,-2.00	WMD= -2.58, 95%CI: -9.53, 4.38	WMD= -3.82, 95%CI: -8.73, 1.10
(Rolling et al., 2013)	Europe (Germany)	36 adults	*artesunate*	5	not reported	11 (median)	not reported	not reported	not reported
			Quinine	31	not reported	19 (median)	not reported	not reported	not reported
(Rolling et al., 2012)	Europe (Germany)	3 adults	*artesunate*	3	0%	18 (mean)	all fully conscious	Not reported	120 (mean)
(Kremsner et al., 2012)	Africa	197 children	*artesunate*	197	1.1%	Not reported	Not reported	12 (median)	36 (median)

(Dondorp et al., 2010)	Africa	5425 children	*artesunate*	2712	8.1%	3 (median)	20 (median)	Not reported	not reported
			Quinine	2713	10.2%	3 median	18 (median)	not reported	not reported
Krudsood et al., 2003	Asia (Thailand)	803 adults	*artesunate*	517	2%	28 (median)	69.6 (median)	80 (mean)	56 (mean)
			artemether	204	2%	28 (median)	74.4 (median)	108 (mean)	62 (mean)
			Quinine	82	5%	28 (median)	76,8 (median)	107 (mean)	92 (mean)
Prashanth et al., 2012	Asia (India)	1 neonate	*artesunate*	1	0%	21	Not reported	Not reported	168
Davis et al., 2001	Asia (Vietnam)	30 adults	*artesunate*	30	0%	3-21 (range)	72 hours (median)	34, 36, 32 respectively (median)	not specified
(Byakika-Kibwika et al., 2012)	Africa (Uganda)	14 adults	*artesunate*	14	0%	Not reported	Not reported	Not reported	17 (median)
(Hendriksen et al., 2013a)	Africa (Tanzania)	70 children	*artesunate*	70	13%	not specified	Not reported	Not reported	not reported

(Tran et al., 1996)	Asia (Vietnam)	560 adults	*artemether*	284	13%	12 (median)	66 (median)	127 (median)	72 (median)
			Quinine	276	17%	10 (median)	48 (median)	90 (median)	90 (median)
(van Hensbroek et al., 1996a)	Africa (Gambia)	576 children	*artemether*	288	20.5 %	Not reported	26 (median)	30 (median)	48 (median)
			Quinine	288	21.5 %	not reported	20 (median)	33 (median)	60 (median)
(Zoller et al., 2011)	Europe (Germany, Denmark, Sweden, and Norway)	25 (1 child and 24 adults	*artesunate*	25	0%	not specified	Not reported	Not reported	81.2 (mean)
Briggs et al., 2013 CDC Report	North America (USA)	19 (18 adults and 1 child)	*artesunate*	19	not reported	Not reported	Not reported	Not reported	120 (mean)
(Dondorp et al., 2005)	Asia (South East Asia)	1461 (202 children and 1259 adults	*artesunate*	730	15%	5 (median)	Not reported	Not reported	not reported
			Quinine	731	22%	5 (median)	not reported	not reported	not reported
(Kreeftmeijer-Vegter et al., 2012)	Europe (Netherlands and Belgium)	55 (52 adults and 3 children)	*artesunate*	55	3.6%	4,5 (median)	Not reported	Not reported	29,5 (mean 99% PCT)

(Caramello et al., 2012)	Europe (Italy)	1 adult	*artesunate*	1	0%	18	not reported	Not reported	96
(Artemether-Quinine Meta-analysis Study Group, 2001)	Africa	1919 (adults and children)	*artemether*	961	14%	not specified	24 (median)	42 (median)	20 (median)
			Quinine	958	17%	not specified	23 (median)	48 (median)	32 (median)
(Eltahir et al., 2010)	africa (Sudan)	66 children	*artesunate*	33	3%	not specified	8,1 (mean)	16,2h mean	19,7 (mean)
			Quinine	33	6%	not specified	9,1 (mean)	18,2 (mean)	20,8 (mean)
(Adam et al., 2002)	africa (Sudan)	41 children	*artemether*	21	0%	not specified	12,5 (mean)	30,5 (mean)	16 (mean)
			Quinine	20	5%	not specified	20,2 (mean)	18 (mean)	22,4h (mean)
(Eder et al., 2012)	Europe (UK)	167 adults	*artesunate*	24	0%	3,5 (median)	Not reported	18 (mean)	65 (mean)
			Quinine	143	3.5%	5 (median)	not reported	54 (mean)	85 (mean)
(Chaudhari et al., 2013)	India (Asia)	1 adult	*artesunate*	1	0%	not specified	Not reported	Not reported	168

(Sinclair et al., 2012)	Asia and Africa	7429 (1664 adults and 5765 children).	*artesunate*	3720	adults:RR=0.61(0.50,0.75). Children RR=0.76 (0.65,0.90) favouring AS	not specified	not specified	Not specified	WMD= -9.77h (95% CI -18.11 to -1.44) favouring AS
			Quinine	3709	adults: RR=0.61 (0.50,0.75). children RR=0.76 (0.65,0.90) favouring AS	Not specified	Not specified	Not specified	WMD= -9.77h (95% CI -18.11 to -1.44) favouring AS
(Fargier et al., 1999)	Africa (Cameroon)	90 children and adults	*artemether*	44	0%	not specified	31,2 (mean)	28,1 (mean)	34,6 (mean)
			Quinine	46	0%	not specified	30 (mean)	39,5 (mean)	42,4 (mean)
(Ambroise-Thomas, 1997)	Africa and Asia	3024 adults and children	*artemether*	not specified	not specified	not specified	not specified	Not specified	not specified
			Quinine	not specified	not specified	Not specified	not specified	Not specified	not specified
(Ogetii et al., 2010)	Africa (Kenya)	1237 children	*Quinine*	1237	10.5%	not reported	not reported	not reported	not reported

(Nwosu, 2012)	Africa (Nigeria)	2 adults	*Quinine*	2	0%	not reported	not reported	not reported	not reported
(Hendriksen et al., 2013b)	Africa (Tanzania)	75 children	*Quinine*	75	17.3%	not reported	not reported	not reported	not reported
(Gunawan et al., 2007)	Asia (Indonesia)	1 adult	*Quinine*	1	0%	7	Not reported	not reported	not reported
(van Hensbroek et al., 1996b)	Africa (Gambia)	29 children	*Quinine*	29	13.8%	not reported	not reported	168	168
(Looareesuwan et al., 1990)	Asia (Thailand)	1 adult	*Quinine*	1	100%	3,2	did not regain consciousness	22	parasite not cleared

Duration of hospital stay (days)

Duration of hospital stay refers to the period from the admission of the patient till discharge from the hospital.

The 6 out of the 7 studies reported median duration of hospital stay. It ranged between 3 days to 12 days in 3810 adults and children who received an artemisinin derivative in Africa, Europe and Asia. The 28 days median duration of hospital stay was reported by Krudsood et al. (2003) in Thailand in 721 participants. 2 studies reported the mean duration of hospital stay in artemisinin derivatives in 4 adults in Europe, which ranged from 18 days to 21 days. Prashanth et al. (2012), from India reported the 21 day hospital stay in 1 preterm neonate. An 18 day duration was reported in 1 adult in Italy (Caramello et al., 2012), and Rolling et al. (2012) in Germany also reported a mean duration of 18 days in 3 adults.

The reported median duration of hospital stay in quinine recipients ranged from, 3 to 19 days in 3894 in adults and children in Europe, Africa and Asia, in 5 out of 6 studies. The fifth study reported a 28 days median duration of hospital stay in 82 participants in Thailand (Krudsood et al., 2003). A 3.2 days (in Thailand) and 7 days (in Indonesia) duration of hospital stay were reported in a single patient each by Looareesuwan et al. (1990) and Gunawan et al. (2007) respectively. 1 study reported the range 3 to 21 days (Davis et al., 2001).

Coma resolution time (CRT in hours)

This is time taken for the unconscious individual to regain full consciousness (Glasgow coma scale=15 for adults or Blantyre coma scale=5 for children).

4 studies reported a median coma recovery time between 20 to 66 hours in 4245 adults and children in Africa and Asia receiving an artemisinin derivative. Krudsood et al. (2003) in Thailand reported a median CRT of 69.6 hours in artesunate (517 adults) and 74.4 hours in artemether (204 adults). Davis et al. (2001), reported a median CRT of 72 hours in 30 adults receiving artesunate. 3 studies reported a mean CRT (Range: 8.1 to 31.2 hours) in 98 adults and children in Asia and Africa: 66 children receiving artesunate in Sudan, had a mean CRT 8.1 hours (Eltahir et al., 2010).

4 of 5 studies reported median CRT ranging between 18 to 48 hours in 4235 children and adults in Africa and Asia who received quinine. The 5th study reported median CRT of 76.8

hours in 82 Thailand adults (Krudsood et al., 2003). The mean CRT (range 9.1 to 30 hours) was reported in 3 studies in 99 children and adults in Africa.

1 systematic review (1524 children) reported artemisinin derivatives to resolve coma faster than quinine weighted mean difference (WMD = -4.61, 95% CI: -7.21 to -2.00, fixed effect Model) (PrayGod et al., 2008).

Fever clearance time (FCT in hours)

It is the time taken for body temperature to drop below 38 degrees Celsius and maintained for 24 hours.

The median FCT ranged from 12 to 34 hours in 3 studies of 515 adults and children in Africa and Asia who received artemisinin derivatives. A meta-analysis reported median FCT of 42 hours in 961 adults and children in Africa who received artemether (Artemether-Quinine Meta-analysis Study Group, 2001) and a 127 hours median FCT was also reported in randomized double blinded study in 284 adults in Vietnam receiving artemether (Tran et al., 1996). Mean FCT (range: 16.2 hours to 30.5 hours) was reported in 4 studies. Krudsood et al. (2003), reported mean FCT of 80 hours in 517 adults in Thailand receiving artesunate and 108 hours in 204 Thailand adults receiving artemether.

3 studies reported the median FCT (range: 33 to 90 hours) in 1522 adults and children in Africa and Asia who received quinine: Tran et al. (1996), in a randomized controlled trial reported 90 hours median FCT in 276 Vietnamese adults receiving quinine. The mean FCT was reported by 5 studies (range: 18 to 54 hours). A mean FCT of 107 hours was reported in Thailand in 82 adults receiving quinine (Krudsood et al., 2003) and 168 hours mean FCT was reported in 29 Gambian children (van Hensbroek et al., 1996b).

1 systematic review did not find any statistically significant difference between the artemisinin derivatives and quinine in the FCT (WMD = -2.58, 95%CI: -9.53 to 4.38, random effect model reported) (PrayGod et al., 2008).

Parasite clearance time 100% (PCT 100% in hours)

This is the time taken for the patient to become aparasitaemic (free of the parasites in blood). 5 studies reported the median PCT (range: 17 to 72 hours) in artemisinin derivatives 1744 adults and children in Africa and Asia. 7 studies reported a mean PCT (range: 16 to 96 hours) in artemisinin derivatives in 869 adults and children in Europe, Africa and Asia. 2 studies reported a mean PCT of 120 hours each. One was a CDC report 19 delayed

hemolysis cases reported in Europe (Melissa Briggs, and Arguin, 2013) and the other was a case series of 3 adults in Germany (Rolling et al., 2012). A case of an adult was reported in whom parasites were cleared in 168 hours in India (Chaudhari et al., 2013)

3 studies involving 1522 adults and children in Africa and Asia reported the median PCT in quinine ranging from 32 to 90 hours. Mean PCT in quinine was reported 5 studies involving 324 adults and children, ranging from 20.8 to 92 hours. 1 cohort study reported 168 hours mean PCT in 29 Gambian children receiving quinine.

1 systematic review involving 1524 children in Asia and Africa did not find a statistically significant difference in PCT between artemisinin derivatives and quinine (WMD = -3.82, 95%CI: -8.73 to 1.10, random effect model) (PrayGod et al., 2008), while another systematic review between artesunate and quinine, found that artesunate cleared parasites faster. (Mean Difference -9.77h 95% CI -18.11 to -1.44, 419 patients) (Sinclair et al., 2012). 1 study involving 55 adults and children receiving artesunate in Europe reported a mean 99% PCT of 29.5 hours (Kreeftmeijer-Vegter et al., 2012). In 1 case report involving an adult in Thailand, who received quinine, parasites were not cleared (Looareesuwan et al., 1990).

ADVERSE EVENTS

Hypoglycemia, delayed hemolysis, hearing disturbances, visual disturbances, hepatotoxicity, prolongation of QTc-interval (>500ms), and acute renal failure were used to assess adverse events in both artemisinin derivatives and quinine.

Table 7: **Total number of cases per adverse event in each drug group.**

	Hypoglycaemia (cases)	***delayed haemolysis(cases)***	***Hearing disturbances (cases)***	***Visual Disturbances (cases)***	***Hepatotoxicity (cases)***	***Prolongation of QTc interval (cases)***	***acute renal failure (cases)***
Artemisinin derivatives	216	23	4	1	22	39	149
Quinine	478	2	36	5	28	69	166

**See Appendix V for detailed case distribution across different studies*

Hypoglycemia

6 studies reported a total of 111 cases (range: 1 to 31 cases) of hypoglycemia in adults and children receiving artemisinin out of 5147 adults and children. 48 cases were reported out

of 2712 children receiving artesunate in a large multicenter randomized controlled trial in Africa (Dondorp et al., 2010) and 57 cases were reported out of 961 children receiving artemether and adults in a meta-analysis in Africa (Artemether-Quinine Meta-analysis Study Group, 2001).

10 studies reported a total of 273 cases (range: 1 to 69 cases) of hypoglycemia in adults and children receiving quinine out of 6264 adults and children. 1 randomized controlled trial reported 75 cases of hypoglycemia receiving quinine out of 2713 children in Africa (Dondorp et al., 2010) and 1 cohort study in Kenya reported 130 cases of hypoglycemia receiving quinine out of 1237 children receiving quinine (Ogetii et al., 2010).

Delayed hemolysis

The definition for delayed hemolysis varied across studies.

7 studies reported 23 cases (range: 1 to 7 cases) of delayed hemolysis out of a total of 115 adults and children receiving artesunate. All these cases were reported from Europe. There was 1 hospital based retrospective study, 4 case series, 1 literature review and 1 case report.

2 cases of delayed hemolysis was reported in adults who received both intravenous quinine and intrarectal artesunate, but there was no case among the adults that received exclusively intravenous quinine (Rolling et al., 2013).

Hearing disturbances

4 hearing disturbances cases were reported in 2 studies (Kreeftmeijer-Vegter et al., 2012 and Hendriksen et al., 2013a) out of 125 adults and children receiving artesunate in Europe and Tanzania respectively.

36 cases of hearing disturbances in 4 studies were reported in adults and children receiving quinine out of a total of 111 adults and children in Sudan, Cameroon, Indonesia and Germany.

Visual disturbances

1 case of visual disturbance was reported in 1 study out of a total of 70 Tanzanian children receiving artesunate (Hendriksen et al., 2013a)

5 cases of visual disturbances were reported in 4 studies (range: 1 to 2) in Africa and Europe out of a total of 1037 adults and children receiving quinine.

Hepatotoxicity

22 cases of hepatotoxicity were reported in Africa in 961 children and adults receiving artemether (Artemether-Quinine Meta-analysis Study Group, 2001)

28 cases were reported in 2 studies (Artemether-Quinine Meta-analysis Study Group, 2001 and Rolling et al., 2013), out of a total of 989 adults and children in Africa and Europe

Prolongation of QTc interval (>500ms)

1 study reported 38 cases of QTc interval prolongation out of 284 Vietnamese adults receiving artemether (Tran et al., 1996) and another study reported 1 case of QTc prolongation out of 55 adults and children receiving artesunate in Europe (Kreeftmeijer-Vegter et al., 2012)

5 studies reported 9 cases QTc prolongation out of 3086 adults and children receiving quinine. 60 cases were reported in Vietnam adults out of 276 adults receiving quinine (Tran et al., 1996).

Acute renal failure

4 studies reported 88 cases of acute renal failure out of 369 adults and children in Europe and Asia artemisinin derivatives. 1 randomized controlled trial reported 60 cases out of 730 adults and children receiving artesunate in Asia (Dondorp et al., 2005)

4 studies reported 90 cases of acute renal failure out of 1266 adults and children in Europe, Africa and Asia receiving quinine. 1 randomized controlled trial reported 76 out of 731 adults and children receiving quinine in Asia (Dondorp et al., 2005)

Other adverse events

Also, 3 studies reported black water fever (Dondorp et al., 2010; Tran et al., 1996 and Dondorp et al., 2005) in artemisinin compared to 4 studies that reported this in quinine (PrayGod et al., 2008; Dondorp et al., 2010; Tran et al., 1996 and (Dondorp et al., 2005). 3 studies (Ambroise-Thomas, 1997; Fargier et al., 1999 and van Hensbroek et al., 1996a), these were all in artemether studies, reported pain at injection site compared to 4 studies (PrayGod et al., 2008; van Hensbroek et al., 1996a van Hensbroek et al., 1996b; and Ambroise-Thomas, 1997)that reported pain at injection in quinine.

Vomiting, nausea, headaches, weakness, diarrhea, cough, anorexia, aphasia, mild urticarial rash, pyuria, Gastro-intestinal bleeding, convulsions, abdominal pain, pneumonia, respiratory failure, rash and temporal decrease in reticulocyte and leucocyte count were reported in artemisinin derivatives while vomiting nausea, headache, weakness, aphasia,

diarrhea, cough, pneumonia, rigors, anorexia, dizziness, bloating, gastro-intestinal bleeding, pyuria, abscess formation, urticarial rash, convulsions, abdominal pain, and acne were reported in quinine.

CHAPTER 4

DISCUSSION AND CONCLUSION

This comprehensive literature review included studies from Africa, Asia, Europe and North America and suggests that artemisinin derivatives have more efficacy and fewer adverse events compared to quinine in the treatment of severe malaria. Artemisinin derivatives were associated with less mortality compared to quinine in both adults and children irrespective of geographical location. The artemisinin derivatives cleared parasites faster, had shorter coma recovery time and cleared fever faster than quinine. Both artemisinin derivatives and quinine had similar duration of hospital stay.

Quinine was the only option of parenteral therapy in the treatment of severe malaria, not until recently when the artemisinin derivatives were found to possess better antimalarial properties. Quinine has a growing resistance in endemic countries such as Sudan, narrow therapeutic window and is prone to toxic events (Hendriksen et al., 2013b). Artemisinins are thought to interfere with malaria parasites ability to metabolize human hemoglobin and kills parasites rapidly within few hours and reduce cytoadherence ("Artemisinins in malaria treatment in the UK," 2010). A unique feature of the artemisinins is the ability to kill parasites at several stages of their development, including gametocytes involved in transmission of malaria from person to person (Hess et al., 2010). These advantages help artemisinin derivatives not only to reducing death from severe malaria by preventing multi-organ failure, but also by limiting the possibility of malaria transmission.

Artesunate as shown in this study has better efficacy compared to the other artemisinin derivatives (artemether and arteether), which are both (artemether and arteether), available as intramuscular oil preparations. The pharmacodynamics properties of the latter are affected by their pharmacokinetic properties. Artemether is prone to erratic and partial absorption and arteether to low peak concentrations and slow absorption (Sinclair et al., 2012).

Artesunate is available as an intravenous and intramuscular water soluble preparation that reaches peak concentrations reliably within 1 hour of administration (Sinclair et al., 2012), accounting for the most likely explanation for the much larger reduction in mortality with artesunate than artemether.

The SEAQUAMAT (artesunate had absolute reduction in mortality of 34·7% (95% CI18·5–47·6%; p=0·0002), compared to quinine) and AQUAMAT (relative reduction in

mortality of 22·5% (95% CI 8·1–36·9%) favouring artesunate; corresponding to an overall number needed to treat of 41 to prevent 1 death) trials have been instrumental in pushing recommendations for artesunate to be first line treatment of severe malaria in adults and children. Following these strong evidences, WHO updated its recommendations for the treatment of severe malaria, recommending artesunate as the first line treatment (2010).

Despite this recommendation, availability of artesunate is limited and quinine is still widely used. There are concerns that the artesunate produced by Guilin Pharmaceutical Company (the same products that were used in the –QUAMATs), is not being manufactured under conditions of full Good Manufacturing Practice (GMP). In 2010, Guilin Pharmaceutical Company received a pre-qualification by WHO. Nevertheless, this is not the same as GMP certification in both the EU and US. Despite the fact that artesunate is not licensed in Europe, it has been made available within few compassionate use programs, through few import companies such as, ACE pharmaceuticals BV in Netherlands or Indis Pharma, UK or could be ordered directly from the manufacturer Guilin Pharmaceutical Corporation in China.

There are several pharmaceutical initiatives that aim for production under full GMP conditions (such as, Sigma Tau, Italy), but it is still unclear when GMP-conform intravenous artesunate will become available in Europe. While in the U.S. artesunate is made available from CDC under an investigational New Drug (IND) protocol produced by the U.S. Army Medical Materiel Development Activity.

Recently, there have been reported cases of late-onset (delayed) hemolysis in severe malaria patients who received artesunate. All of these cases have been reported in Europe with none reported outside of Europe. This review identified 23 reported cases treated with intravenous artesunate and 2 cases treated with intravenous quinine and intrarectal artesunate. These patients were all hyperparasitaemic.

Malaria remains a rare disease in Europe. The studies that reported the delayed hemolysis cases were all challenged by small sample sizes, were retrospective and were case presentations and case series, making it difficult to assess whether exposure to artesunate was the sole cause of the delayed hemolysis observed. The aetiology of the delayed hemolysis remains unknown.

Artesunate generally has been deployed in hyperparasitaemic and more severely ill malaria patients because they have been shown to possess stronger antiparasitic activity and reduce

mortality. Hyperparasitaemia has been implicated as a risk factor for delayed hemolysis, therefore parasite densities might be a confounder (Rolling et al., 2013). The fact that mainly hyperparasiteamic patients develop hemolysis may point to a mechanism called `pitting´, which simply refers to a reduced lifespan of once-infected red blood cells (`pitted´red blood cells), after the blood stage parasites have been extracted during splenic passage. These `pitted´ red blood cells have a mean lifespan of about 180 hours and with a total removal of `pitted 'erythrocytes' after 28 days (Rolling et al., 2013). Hyperparasitaemic patients could point to more pitted red blood cells, which could result to more delayed hemolysis observed.

However, it can be argued that not all hyperparasitaemic patients develop delayed hemolysis. Artesunate however has been associated with suppressive effects on erythropoiesis (Kreeftmeijer-Vegter et al., 2012). In 2010, 39 patients were treated with intravenous artesunate through the CDC IND protocol and thus far no case of delayed hemolysis has been reported, which fuels further the concerns of a possible contamination in the imported artesunate which does not meet GMP. The observed effects (delayed hemolysis) might well be due to the disease course than due to artesunate.

It will be important for standardized pharmacovigilance for at least 4 weeks for all patients receiving intravenous artesunate in both the endemic and non-endemic countries, so that standardized data can be available. This foreseeably is going to be challenging in the malaria endemic countries, due to their underdeveloped health systems.

More cases of hypoglycemia, hearing disturbances, visual disturbances, prolongation of QTc interval, hepatotoxicity and acute renal were more frequently reported in the quinine recipients than in the artemisinin derivative recipients.

Hypoglycemia is a well-known adverse event associated to quinine, but the aetiology is incompletely understood and could be multifactorial. Hyperinsulinaemia due to quinine therapy has been well advanced as an iatrogenic cause and is well established in adults (Ogetii et al., 2010).

69 quinine cases of QTc interval prolongation (>500ms) were reported. van Hensbroek et al., (1996b) also found lengthening of the QRS interval within the first 4 hours of commencing treatment in Africa children less than 2 years of age. Quinine if given rapidly intravenously could result to hypotension and it also prolongs ventricular repolarization (Tran et al., 1996).

Overall adverse events with the artemisinin derivatives were mild and were less common than with Quinine.

Economic commentary

Populations in the most resource-constrained settings are the most affected by malaria. Malaria and poverty have been seen to affect each other in a vicious cycle. Malaria results to poverty and poverty results to malaria. This makes cost a fundamental factor that needs to be taken into consideration in antimalarial treatment policy and practices by policy makers. The World Health Organization takes these into account in its malaria treatment recommendations (2010).

The primary goal of severe malaria treatment is first to prevent death, then consequently to reverse the course of the disease to bring the individual back to health as soon as possible, with as little side effects possible. High efficacy therapy is fundamental but also has to help frail health systems to sustain its routine use.

Lubell et al. (2011), explored the cost-effectiveness of parenteral artesunate for the treatment of severe malaria in children and its potential impact on hospital budget and found that artesunate showed an incremental cost per DALY averted and an incremental cost per death averted of US$ 3.8 and US$ 123 respectively compared to quinine. They found artesunate as highly cost effective and an affordable alternative to quinine for treating children with severe malaria with very negligible budgetary implications to the health systems. This similar to the findings of Eder et al. (2012) who found less need for intensive care, cessation of blood glucose monitoring and reduced hospital stay in the patients that received artesunate, thereby reducing cost, both to the hospital and the individual, and the need for manpower. This study however found similar duration of hospital stay between the artemisinin group and the quinine group, which could be due to the diverse nature of the health systems from which the results were gotten.

Quinine is cheaper to purchase but more expensive to administer in severe malaria, as it is given as slow infusion three times daily requiring constant monitoring and many more supplies and more manpower, whereas the artemisinin derivatives are expensive to purchase but cheaper and easier to administer, as they are administered either as an artesunate intravenous bolus once daily or an artemether intramuscular injection once daily requiring lesser supplies and fewer manpower.

This study has some limitations:

- Only articles in French and English were included. There could be possible relevant articles in different languages that were not included.
- The precise number of adults and children could not be identified due to the failure of some reviews to specify this. This resulted in a generalization of the efficacy and adverse events between both treatment groups to adults and children.
- Most studies left out some outcome measures, which could have affected the overall results

CONCLUSION

Despite the reported cases of delayed hemolysis in artesunate, the evidence is still inconclusive and should not alter the preference of artesunate as the first line treatment of severe malaria.

The process of making available artesunate meeting current GMP should be expedited so that concerns regarding possible concerns of the contamination of the present available can be cleared. Also, there is an urgent need for a 4 week long pharmacovigilance of patients receiving artesunate for the treatment of severe malaria.

Despite the reported cases of delayed hemolysis, artemisinin derivatives still were showed to be safe with fewer adverse events compared to quinine. Artemisinin derivatives had a lesser mortality compared to quinine, cleared parasites faster, cleared fever faster and resolved coma faster compared to quinine.

Artemisinin derivatives have therefore been shown by this review to have a better efficacy compared to quinine and present fewer adverse events compared to quinine.

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APPENDIX

APPENDIX IA: ARTEMISININS OUTCOME MEASURES												
	Positive effects					**Negative effects**						
Studies	***Mortality rate(%)***	***Duration of hospital stay (days)***	***coma resolution time(h)***	***Fever clearance time(h)***	***Parasite clearance time 100 % (h)***	***Hypoglycaemia(number of cases)***	***delayed haemolysis(number of cases)***	***Hearing disturbances(number of cases)***	***Visual Disturbances(number of cases)***	***Hepatotoxicity(number of cases)***	***Prolongation of QTc-interval (>500ms)(number of cases)***	***Acute renal failure(number of cases)***
PrayGod et al., 2008	Risk Ratio=0.90 95% CI	Not reported	WMD= -4.61, 95% CI	WMD= -2.58, 95% CI	WMD= -3.82, 95% CI	0	0	not specified	not specied	0	not specified	0
(Rolling et al., 2013)	not mentioned	11 (median)	not mentioned	not mentioned	not mentioned	0	3	0	0	0	0	3
(Rolling et al., 2012)	0%	18 (mean)	all fully conscious	Not reported	120 (mean)	0	3	0	0	0	0	0

(Kremsner et al., 2012)	1.1%	Not reported	Not reported	12 (median)	36 (median)	0	0	0	0	0	0	0
(Dondorp et al., 2010)	8.1%	3 (median)	20 (median)	Not reported	not reported	48	not clear	not clear	not clear	0	0	0
Krudsood et al., 2003	2% each	28 (median)	69,6 and 74,4 respectively (median)	80 AT and 108 AM (mean)	56 and 62 respectively (Mean)	0	not clear	not specified	0	0	0	not clear
Prashanth et al., 2012	0%	21	Not reported	Not reported	168	0	0	0	0	0	0	0
Davis et al., 2001	0%	3-21 (range)	72 hours (median)	34, 36, 32 respectively (median)	not specified	0	0	0	0	0	0	0

(Byakika-Kibwika et al., 2012)	0%	Not reported	Not reported	Not reported	17 (median)	0	0	0	0	0	0	0
(Hendriksen et al., 2013a)	13%	not specified	Not reported	Not reported	not reported	8	0	1	1	0	0	0
(Tran et al., 1996)	13%	12 (median)	66 (median)	127 (median)	72 (median)	31	not clear	0	0	0	38	34
(van Hensbroek et al., 1996a)	20.5%	Not reported	26 (median)	30 (median)	48 (median)	29	not clear	not clear	not clear	0	0	0
(Zoller et al., 2011)	0%	not specified	Not reported	Not reported	81.2 (mean)	0	6	0	0	0	0	1
Briggs et al., 2013 CDC Report	not reported	Not reported	Not reported	Not reported	120 (mean)	0	2 (19 cases but 17 has been reported already in this review)	0	0	0	0	0

(Dondorp et al., 2005)	15%	5 (median)	Not reported	Not reported	not reported	19	not clear	0	0	0	0	60
(Kreeftmeijer-Vegter et al., 2012)	3.6% among severe malaria patients (55). But was not related to AS	4,5 (median)	Not reported	Not reported	29,5 (mean 99% PCT)	1	7	3	0	0	1	18
(Caramello et al., 2012)	0%	18	not reported	Not reported	96	0	1	0	0	0	0	0

(Artemether-Quinine Meta-analysis Study Group, 2001)	14%	not specified	24 (median)	42 (median)	20 (median)	57	not clear	not specified	0	22	0	33
(Eltahir et al., 2010)	3%	not specified	8,1 (mean)	16,2h mean	19,7 (mean)	0	0	0	0	0	0	0
(Adam et al., 2002)	0%	not specified	12,5 (mean)	30,5 (mean)	16 (mean)	0	0	0	0	0	0	0
(Eder et al., 2012)	0%	3,5 (median)	Not reported	18 (mean)	65 (mean)	0	1	0	0	0	0	0
(Chaudhari et al., 2013)	0%	not specified	Not reported	Not reported	168	0	0	0	0	0	0	0

(Sinclair et al., 2012)	RR= 0.61 adults and children RR= 0.76 favouring AS	not specified	not specified	Not specified	WMD= -9.77h (95% CI -18.11 to -1.44) favouring AS	23	0	not specified	0	0	0	0
(Fargier et al., 1999)	0%	not specified	31,2 (mean)	28,1 (mean)	34,6 (mean)	0	0	0	0	0	0	0
(Ambroise-Thomas, 1997)	not specified	not specified	not specified	Not specified	not specified	0	0	0	0	0	0	0

APPENDIX IB: QUININE OUTCOME MEASURES												
	Positive effects					**Negative effects**						
Studies	***Mortality***	***Duration of hospital stay (days)***	***coma resolution time (hours)***	***Fever clearance time (hours)***	***Parasite clearance time (100%)(h)***	***Hypoglycaemia(number of cases)***	***delayed haemolysis(number of cases)***	***Hearing disturbances(number of cases)***	***Visual Disturbances(number of cases)***	***Hepatotoxicity (number of cases)***	***Prolongation of QTc-interval (>500ms) (number of cases)***	***acute renal failure(number of cases)***
PrayGod et al., 2008	RR=0.90 95% CI	not reported	WMD = -4.61, 95%CI	WMD = -2.58, 95%CI	WMD = -3.82, 95%CI	not specified	0	not specified	not specified	0	not specified	0
(Rolling et al., 2013)	not reported	19 (median)	not reported	not reported	not reported	10	2 (intrarectal artesunate was added)	12	1	1	3	8
(Dondorp et al., 2010)	10.2%	3	18 (median)	not reported	not reported	75	not clear	not clear	not clear	0	0	0
Krudsood et al., 2003	5%	28 (median)	76,8 (median)	107 (mean)	92 (mean)	0	not clear	not specified	0	0	0	not clear
(Ogetii et al., 2010)	10.5%	not reported	not reported	not reported	not reported	130	0	0	0	0	0	0

(Nwosu, 2012)	0%	not reported	not reported	not reported	not reported	0	0	0	2	0	0	0
(Hendriksen et al., 2013b)	17.3%	not reported	not reported	not reported	not reported	11	0	0	0	0	0	0
(Gunawan et al., 2007)	0%	7	Not reported	not reported	not reported	0	0	1	0	0	1	0
(Tran et al., 1996)	17%	10 (median)	48 (median)	90 (median)	90 (median)	69	not clear	0	0	0	60	42
(van Hensbroek et al., 1996a)	21.5%	not reported	20 (median)	33 (median)	60 (median)	42	not clear	not clear	not clear	0	0	0
(Dondorp et al., 2005)	22%	5 (median)	not reported	not reported	not reported	6	not clear	0	0	0	0	76
(Artemether-Quinine Meta-analysis Study Group, 2001)	17%	not specified	23 (median)	48 (median)	32 (median)	64	not clear	not specified	1	27	0	39

(Eltahir et al., 2010)	6%	not specified	9,1 (mean)	18,2 (mean)	20,8 (mean)	1	0	12	0	0	0	0
(Adam et al., 2002)	5%	not specified	20,2 (mean)	18 (mean)	22,4h (mean)	1	0	0	0	0	0	0
(Eder et al., 2012)	3.5 %	5 (median)	not reported	54 (mean)	85 (mean)	5	0	0	0	0	0	0
(van Hensbroek et al., 1996b)	13.8 %	not reported	not reported	168	168	0	0	0	0	0	3	0
(Looareesuwan et al., 1990)	100 %	3,2	did not regain consciousness	22	parasite not cleared	0	0	0	0	0	1	1
(Sinclair et al., 2012)	RR= 0.61 adults and children RR= 0.76 favouring	Not specified	Not specified	Not specified	WMD = -9.77h (95% CI -18.11 to -1.44) favouring AS	64	0	not specified	0	0	0	0

	AS											
(Fargier et al., 1999)	0%	not specified	30 (mean)	39,5 (mean)	42,4 (mean)	0	0	11	1	0	0	0
(Ambroise-Thomas, 1997)	not specified	not specified	Not specified	Not specified	not specified	0	0	0	0	0	1	0
(Lubell et al., 2011)	10.2 %	not reported	not reported	not reported	not reported	0	0	0	0	0	0	0

Appendix II: Assessment of risk of bias in the randomized controlled trials							
study	Participants	random sequence allocation (selection bias avoided)	allocation concealment (selection bias avoided)	Blinding	loss of follow up (attrition bias)	reporting bias	other bias

(Dondorp et al., 2010)	5425	yes	yes	no	no	no	no
(Lubell et al., 2011)	2300	yes	yes	no	no	no	no
(Hendriksen et al., 2013)	70	yes	yes	no	no	no	no
(Tran et al., 1996)	560	yes	yes	Yes (double blind trial)	no	no	no
(van Hensbroek et al., 1996a)	576	yes	yes	no	95% of the pateints were reexamined after 1 month and 92% after after 5 months for N. sequelae	no	no
(Dondorp et al., 2005)	1461	yes	yes	no	no	no	no
(Eltahir et al., 2010)	66	yes	yes	no	no	no	no
(Adam et al., 2002)	41	not clear	not clear	no	28.6% in the Q group but not repoted in the AM grp	no	no
(Fargier et al., 1999)	90	not clear	not clear	no	no	no	no

(Hendriksen et al., 2013)	75	yes	yes	no	no	no	no
(Kremsner et al., 2012)	197	yes	yes	Yes double blinding	24% in the 5 dose group and 18% in the 3 dose group	no	no

Appendix IV: Results from studies comparing artemisinin derivatives to quinine: Study, Target group, Interventions and Main results

study	*Target group*	*Intervention (drug, route and treatment duration)*	*Main results*
PrayGod et al., 2008	children (0 to16 years)	artemether (IM), artesunate (IM), artemotil/ß-arteether (IM) for 4.5 days. Quinine (IM and IV) for 3.5 days	artemisinin derivatives were not associated with a reduced **mortality** (RR=0.90, 95%CI:0.73 to 1.12). They didnot **clear parasites** faster than Quinine. They didnot **clear fever** faster than Quinine. They resolved **coma faster** than Quinine. No statistical difference between both groups in **Neurological sequelae**. Trials here were not designed to evaluate differences in adverse events.

(Rolling et al., 2013)	adults 18 years and above	IV artesunate was given in 4 doses. 2,4mg/kg (0h, 12h, 24h, 48h), followed by a full oral course for 5 days. IV Quinine: loading dose of 16.4mg of quinine base over 4hours. Followed by 8.2mg every 8 hours untill oral treatment is necessary/ 7days	Study aimed at assessing adverse events. **Duration of hospital stay** (median) 11 days for artesunate and 19 days for Quinine. 5/8 (63%) of patients, receiving IV artesunate with or without quinine developed **delayed hemolysis** compared to 0/8 (0%). No other **adverse event** for the artesunate group. For the quinine group, hypoglycemia (32%), hearing disturbances (38%), visual impairment (3%), QTc interval prolongation, acute renal failure (26%), aseptic eosinophilic pneumocitis (1 patient) and Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
(Dondorp et al., 2010)	children less than 15 years	IV artesunate: 2.4 mg/kg at 0h, 12h, 24h then once daily till oral medication. IV Quinine: 20mg/kg loading dose infusion, then10mg/kg infusion over 2-8 hrs 3 times daily till oral medication.	**Mortality**: 8.5% artesunate and 10.9% quinine. **Duration of hospital stay** (median) 3 days each in both groups. **Coma resolution time** (median): 20 hours artesunate and 18 hours quinine. **Severe neurological sequelae** was 2.3% overall (17/706 artesunate and 17/737 quinine). **No Severe adverse events** that could be attributed to drug toxicity. Blood transfusion was given to 55% each of patients in both groups.

Krudsood et al., 2003	adults 15 years and above	IV artesunate: 2.4 mg/kg loading dose, then 1.2 mg/kg 12 hourly until oral artesunate (50mg/tablet). Total of 600 mg in 5 days IM artemether (80 mg/ampoule) 3.2 mg/kg loading dose, then 1.6 mg/kg at 12, 24, 48, and 72 hours to provide a total dose of 480 mg for 3 days. Later substituted by oral artemether (50mg/cap) with same dose. IV Quinine 20g/kg over 4 hours, then 10mg/kg 8 hourly for 7 days	**Mortality**: artemisinin derivatives: 0 to 2 % was lesser than quinine 5%. Mean **parasite clearance time** was shorter in the artemisinin derivatives (53 to 62 hours), than quinine group (92hours). **Fever clearance time** for IM artemether and IV quinine were almost identical (107 to 108 hours) and that for IV artesunate (80 to 82 hours), were morethen 25 hours shorter than the others. **Coma recovery time** (median) was similar in all groups. 2.9 to 3.1 days in the artemisinin derivative group and 3.2 days in the quinine group. No major **adverse events** recorded in all groups.
(Lubell et al., 2011)	children less than 15 years	IV artesunate: 2.4 mg/kg at 0h, 12h, 24h then once daily till oral medication. IV Quinine: 20mg/kg loading dose infusion, then10mg/kg infusion over 2-8 hrs 3 times daily till oral medication.	**Mortality**: artesunate 8.5% while quinine 10.9%. No significant difference in the rate **neurological sequelae** between both groups. Mean cost for treating severe malaria patients: 63.5$ (US) Quinine and US$66.5 artesunate. Artesunate showed an incremental cost per DALY averted and incremental cost per death averted of US$3.8 and US$123 respectively. artesunate found to be highly cost effective affordable alternative to quinine for treating children with severe malaria

(Tran et al., 1996)	adults 15 years and above	IM artemether 4mg/kg. Followed by 2 mg/kg 8 hrly in 3.4 days IM Quinine. Loading dose of 20mg/kg, followed by 10mg/kg 8 hourly in 3.3 days	**Mortalit**y: artemether 13% and quinine 17% (Not significant). 4 **neurological sequelae** (3 artemether and 1 quinine). **Parasite clearance time** (Median): 72 hours artemether and 90 hours quinine. **Fever clearance time** (median): 127 hours artemether and 90 hours quinine. **Coma recovery time** (Median): 66 hours artemether and 48hours quinine. Artemether had **longer hospitalizations** than quinine. No significant difference in fall of hematocrit from base-line values. However, mean reticulocyte counts one week after treatment was significantly lower in artemether group (2.3% versus 5.6% range, 0.1 to 16.1 vs. 0.0 to 28).
(van Hensbroek et al., 1996a)	children 1 to 9 years	IM artemether 3.2mg/kg followed by daily doses of 1.6mg/kg in 4 days IM Quinine. Loading dose 20mg/kg followed by 10mg/kg bid in 5 days	**Mortality**: 20.5% artemether and 21.5 quinine. **Neurological sequelae**: 3.3% artemether and 5.3% quinine. **Coma recovery time** (median): 26 hours artemether and 20hours quinine. **Parasite clearance time** (median) : 48hours artemether and 60 hours quinine. Both groups were similar in fall of haemoglobin and need for blood transfusion in 7 days. **Local reactions**, abscess at injection site and urticarial rash was more common in the quinine group.
(Dondorp et al., 2005)	adults and children	IV artesunate. 2.4mg/kg at 0h, 12h, 24h, then daily, till oral medication. IV Quinine 20mg/kg loading dose infused over 4 h, then 10mg/kg infused over 2-8 h tid till the start of oral medication	**Mortality**: 15% artesunate versus 22% quinine. 7 **neurological sequelae** at discharge in artesunate and 3 in quinine. Significant excess of hypoglycemia in quinine group. **Duration of hospital stay** was similar for both groups.

(Artemether-Quinine Meta-analysis Study Group, 2001)	adults and children	Artemether: for BW <or= 50kg loading dose 3.2mg/kg, maintenance dose 1.6mg/kg. For BW >50kg 160mg maintenance dose 80mg. OR 4mg/kg loading dose and maintenance dose 2mg/kg Quinine dihydrochloride. Loading dose: 20mg/kg. Maintenance dose 10mg/kg	**Mortality**: 14% artemether and 17% quinine. **Neurological sequelae**: No significant difference between both groups. 10% in artemether group and 12% in quinine group. **Parasite clearance time** (median): artemether (20hours) **cleared parasites** more rapidly than quinine (32 hours). **coma clearance tim**e (median): No significant difference between both groups; 24hours artemether and 23hours quinine. **fever clearance time** (median): No difference in effect was found; 42hours artemether and 48 hours quinine.
(Eltahir et al., 2010)	children	*IV* artesunate 2.4 mg/kg body weight given at 0, 12, and 24 h, and then daily. intravenous quinine as 20 mg/kg loading dose infused over 4 h then 10 mg/kg infused over 2–4 h three times a day.	**Mortality**:3% artesunate and 6% quinine. **Fever clearance time** (mean): 16.2hours versus 18.2 hours. **Parasite clearance time** (mean): 19.7 hours versus 20.8 hours.**coma resolution time** (mean): No difference between both groups; 8.1 hours artesunate and 9.1 hours quinine. **Adverse events**: Quinine; tinnitus, abdominal pain and nausea and hypoglycemia and artesunate; abdominal pain and nausea.
(Adam et al., 2002)	children	IM artemether: loading dose 3.2mg/kg followed by 1.6mg/kg daily for 4 days. IV Quinine dihydrochloride: 20mg/kg given over 4h. Followed 8h later by 10mg/kg over 4h, then repeated 8hrly for 3 days	**coma resolution time** (mean): significantly shorter in artemether (12.5 hours) versus 20.0 hours quinine. **Fever clearance time** (mean): significantly shorter in quinine (18 hours) versus 30.5 hours artemether. **Parasite clearance time** (mean): shorter in artemether (16.0 hours) versus quinine (22.4 hours) with no significance. Hypoglycemia reported to the quinine group.

(Eder et al., 2012)	adults 16 year and above	IV artesunate: 2.4 mg/kg body weight per dose 12 hourly x2 doses, then 24 hourly until scanty or no trophozoites were detected on thin films for 2.7 days. IV Quinine: 10mg/kg 8hrly until sufficiently recovered to tolerate oral regimen	**Mortality**: artesunate 0% and quinine 3.5%. **Median length of stay**: 3.5 days artesunate versus 5 days quinine. **Parasite clearance time** (median): significantly reduced in artesunate (65hours) versus quinine (85 hours). **Fever clearance time**: significantly shorter in artesunate (18 hours) versus quinine (54 hours). Hypoglycemia reported in quinine group.
(Sinclair et al., 2012)	adults (1664)and children (5765)	Dose varied between trials: artesunate: 2·4 mg/kg (IV or IM) on admission, at 12 h, at 24 h, and then once daily until starting oral therapy; 60 mg IV artesunate at admission, 4 h, 24 h and 48 h; 3 mg/kg IM AS on admission then 2 mg/kg IM at 12, 24, 48, and 72 h. IV AS 2.4 mg/kg on admission, 1.2 mg/kg at 12 h, and then 1.2 mg/kg every 24 h until able to swallow Dose varied between trials: quinine: 20 mg/kg IVorIM loading dose, then 10 mg/kg every 8 hours until starting oral therapy	**Mortality**: significant reduction by artesunate compared to quinine both children and adults. **Neurological sequelae** more common in those treated with artesunate than quinine at discharge but no longer statistically significant by day 28. artesunate associated with significant reduction in episodes of hypoglycemia.

(Fargier et al., 1999)	children and adults above 6 years.	IM Artemether 3.2mg/kg the first day, then 1.6mg/kg once daily for BW less than or equal to 50kg. For BW greater than 50kg 160mg in 2 IM inj, the first day and 80mg in one inj the 4 following days for 5 days IV Quinine dihydrochloride 16mg/kg for the first 4h, then 8mg/kg 8h for 3 days	Mean **parasite clearance time**: significant lesser 34.6hour artemether and 42.4 hour quinine. **Coma recovery time (mean)**: 31.2 hours artemether and 30 hours quinine. **Fever clearance time**: significantly less in artemether (28.1 hours) versus quinine (39.5 hours). More **adverse events** in the quinine group than artemether group. In quinine group; ringing ears, blurred vision and vertigo and acne and artemether; pain at injection site.
(Ambroise-Thomas, 1997)	adults and children	IM artemether: 2 ampoules of 80mg and 1 ampoule of 80mg/ day the following 4 days, for a total of 5 days in adults and 3.2mg/kg the first day and 1.6mg/kg/ day for the following 4 days for children for 5 days. IV quinine hydrochloride: 20mg/kg in 4 hours, then 10mg/kg every 8 hours for 7 days.	artemether **clears parasites** significantly faster than quinine. In terms of survival rates, **coma resolution time, neurological sequelae** and **fever clearance time**, both drugs have comparable results but in some cases artemther shows little superiority (but not statistically significant). **More local site injection**s with quinine than artemether. A few noted cases of temporary reduction in the number of reticulocytes and leucocytes in artemether. Artemether and quinine have roughly equivalent costs.

Table 4: Summary of Main results from studies that compared artemisinin derivatives to quinine
Mortality: artemisinin derivatives had lesser mortality rates than quinine (9 out 10 studies: 90.0% and 1 study didnot find any difference between both).
Parasite clearance time: 9 out of the 10 studies (90%) found that artemisinin derivatives cleared parasites faster and 1 study didnot find any difference between both.
Fever clearance time: 9 studies reported FCT. *4* studies found artemisinins with shorter fever clearance time than quinine, 2 studies found quinine shorter FCT and 3 found both comparable.

Coma resolution time: 10 studies reported on this. **2** studies found artemisinin derivatives with shorter CRT than quinine, **4** studies found quinine with shorter CRT than artemisinin derivatives, 4 studies found no difference between both groups.
Duration of hospital stay: 5 studies reported on this. **2** studies found artemisinin derivatives to have shorter hospital stay, while **1** found hospital stay longer in artemisinin derivatives than in quinine and **2** studies found both similar
Adverse events: 1 study did not report adverse events, **1** study did not record any adverse events. Overall more adverse events were associated to quinine: Hypoglycemia (7 studies), hearing disturbances, visual impairment, QTc interval prolongation, Acute Renal Failure, Neurological sequelae in general (7 studies), reticulocyte drop, haemoglobin drop, local reactions, tinnitus 2, abdominal pain and nausea, blurred vision, and vertigo were reported while, in artemisinin derivatives: delayed hemolysis (1 study), neurological sequelae in general (7 studies); reticulocyte drop, hemoglobin drop, local reactions. abdominal pain and nausea hypoglycemia, pain at injection site, reduction in number of leucocytes and reticulocytes in artemether were reported.

Appendix V: Case distribution of adverse events across studies

characteristics					**Adverse events**						
study	***Region***	***number of participants***	***drug used***	***Number of participants in each drug group***	***Hypoglycaemia (number of cases)***	***delayed haemolysis (number of cases)***	***Hearing disturbances(number of cases)***	***Visual Disturbances(number of cases)***	***Hepatotoxicity(number of cases)***	***Prolongation of QTc-interval (>500ms)(number of cases)***	***Acute renal failure(number of cases)***
PrayGod et al., 2008	Asia and Africa	1524 children	*artesunate, artemether and ß artemotil*	not specified	0	0	not specified	not specied	0	0	0

			Quinine	not specified	not specified	0	not specified	not specified	0	not specified	0
(Rolling et al., 2013)	Europe (Germany)	36 adults	*artesunate*	5	0	3	0	0	0	0	3
			quinine	31	10	2 (intrarectal artesunate was added)	12	1	1	3	8
(Rolling et al., 2012)	Europe (Germany)	3 adults	*artesunate*	3	0	3	0	0	0	0	0
(Kremsner et al., 2012)	Africa	197 children	*artesunate*	197	0	0	0	0	0	0	0
(Dondorp et al., 2010)	Africa	5425 children	*artesunate*	2712	48	not clear	not clear	not clear	Not reported	0	0
			quinine	2713	75	not clear	not clear	not clear	0	0	0
Krudsood et al., 2003	Asia (Thailand)	803 adults	*artesunate*	517	0	not clear	not specified	0	0	0	not clear
			artemether	204	0	not clear	not specified	0	0	0	not clear
			Quinine	82	0	not clear	not specified	0	0	0	not clear
Prashanth et al., 2012	Asia (India)	1 neonate	*artesunate*	1	0	0	0	0	0	0	0
Davis et al.,	Asia	30 adults	*artesuna*	30	0	0	0	0	0	0	0

2001	(Vietnam)		*te*								
(Byakika-Kibwika et al., 2012)	Africa (Uganda)	14 adults	*artesunate*	14	0	0	0	0	0	0	0
(Hendriksen et al., 2013a)	Africa (Tanzania)	70 children	*artesunate*	70	8	0	1	1	0	0	0
(Tran et al., 1996)	Asia (Vietnam)	560 adults	*artemether*	284	31	not clear	0	0	0	38	34
			quinine	276	69	not clear	0	0	0	60	42
(van Hensbroek et al., 1996a)	Africa (Gambia)	576 children	*artemether*	288	29	not clear	not clear	not clear	0	0	0
			quinine	288	42	not clear	not clear	not clear	0	0	0
(Zoller et al., 2011)	Europe (Germany, Denmark, Sweden, and Norway)	25 (1 child and 24 adults	*artesunate*	25	0	6	0	0	0	0	1
Briggs et al., 2013 CDC Report	North America (USA)	19 (18 adults and 1 child)	*artesunate*	19	0	2	0	0	0	0	0
(Dondorp et al., 2005)	Asia (South East Asia)	1461 (202 children and 1259	*artesunate*	730	19	not clear	Not reported	Not reported	Not reported	Not reported	60

		adults									
			quinine	731	6	not clear	0	0	0	0	76
(Kreeftmeijer-Vegter et al., 2012)	Europe (Netherlands and Belgium)	55 (52 adults and 3 children)	*artesunate*	55	1	7	3	0	0	1	18
(Caramello et al., 2012)	Europe (Italy)	1 adult	*artesunate*	1	0	1	0	0	0	0	0
(Artemether-Quinine Meta-analysis Study Group, 2001)	Africa	1919 (adults and children)	*artemether*	961	57	not clear	not specified	Not reported	22	Not reported	33
			Quinine	958	64	not clear	not specified	1	27	0	39
(Eltahir et al., 2010)	Africa (Sudan)	66 children	*artesunate*	33	0	0	0	0	0	0	0
			Quinine	33	1	0	12	0	0	0	0
(Adam et al., 2002)	Africa (Sudan)	41 children	*artemether*	21	0	0	0	0	0	0	0
			Quinine	20	1	0	0	0	0	0	0
(Eder et al., 2012)	Europe (UK)	167 adults	*artesunate*	24	0	1	0	0	0	0	0
			Quinine	143	5	0	0	0	0	0	0

(Chaudhari et al., 2013)	India (Asia)	1 adult	*artesunate*	1	0	0	0	0	0	0	0
(Sinclair et al., 2012)	Asia and Africa	7429 (1664 adults and 5765 children).	*artesunate*	3720	23	0	not specified	0	0	0	0
			Quinine	3709	64	0	not specified	0	0	0	0
(Fargier et al., 1999)	Africa (Cameroon)	90 children and adults	*artemether*	44	0	0	0	0	0	0	0
			quinine	46	0	0	11	1	0	0	0
(Ambroise-Thomas, 1997)	Africa and Asia	3024 adults and children	*artemether*	not specified	0	0	0	0	0	0	0
			quinine	not specified	0	0	0	0	0	1	0
(Ogetii et al., 2010)	Africa (Kenya)	1237 children	*quinine*	1237	130	0	0	0	0	0	0
(Nwosu, 2012)	Africa (Nigeria)	2 adults	*quinine*	2	0	0	0	2	0	0	0
(Hendriksen et al., 2013b)	Africa (Tanzania)	75 children	*quinine*	75	11	0	0	0	0	0	0
(Gunawan et al., 2007)	Asia (Indonesia)	1 adult	*quinine*	1	0	0	1	0	0	1	0

(van Hensbroek et al., 1996b)	Africa (Gambia)	29 children	*quinine*	29	0	0	0	0	0	3	0
(Looareesuwan et al., 1990)	Asia (Thailand)	1 adult	*quinine*	1	0	0	0	0	0	1	1