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Evaluation of Efficacy and Safety of Artemisinin Derivatives for Treatment of Severe Malaria: A Meta-Analysis Approach

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ABSTRACT

Despite progress in antimalarial management and intensive care, the prevalence of malaria is growing and the mortality rate is very high. Yet even with timely treatment of quinine in maximum doses, the death in patients of severe malaria is very high. The successive synthesis of artemether and artesunate has supplied highly successful substitutes to quinine. This systematic review and meta-analysis approach provides a comparative outcome analysis of Artemisinin derivatives (intervention) and other antimalarials (comparison) in the paediatric and adult population. From the year 1985 to the year 2015, studies were recognized using database searches, citation searches of selected articles. The electronic databases searched engines: Pubmed, Web of Science, Global Health, Medline & Cochrane review of Journals up to April 2015. We selected published randomized controlled clinical trials information comparing artemisinin derivatives and quinine for the management of severe malaria in adult and paediatric population as per WHO malaria treatment guideline, any gender, age group less than or greater than 15 years who were diagnosed with severe malaria. The primary outcome was efficacy in terms of parasite clearance time (PCT), Parasite clearance at D7 and D28 and fever clearance time (FCT). The secondary outcome was the mortality and adverse events. We measured 95% confidence interval by the using of REVMAN software version 5.3 for meta-analysis and summarized the collected data on the basis of characteristics of inclusion criteria of articles. We included total 33 RCTs, enrolling 8396 paediatric and adult patients who were suffering from severe malaria. Artemisinin and its derivatives showed mean parasite clearance time (PCT) (MD -8.50 hours, 95% CI -9.41 to -7.60) and mean fever clearance time (FCT) (MD -9.51 hours, 95% CI -11.22 to -7.81) $P<0.00001$ statistically significant as compared to quinine therapy. Artemisinin and its derivatives showed a statistically significant clearance of parasites when compared to quinine at Day 7 (OR 0.41, 95% CI 0.21, 0.81, random effect model, $P=0.01$). Overall artemisinin derivatives has shown more parasite clearance at D28 than quinine group (Odds ratio 0.54, 95% CI 0.23, 1.29, random effect model, $P=0.17$). We evaluated secondary outcomes mortality which showed artemisinin or its derivatives a statistically significant mortality reduction as compared to quinine. (Odds Ratio 0.77, 95% CI 0.67 to 0.89; 27 trials, 8396 participants) $P=0.0002$ and also showed a statistically significant reduction in the adverse events as compared with quinine (RR0.73, 95% CI 0.62 to 0.87) $P=0.003$. An overall positive result was found with artemisinin derivatives across all evaluated outcomes.

Keywords: Artesunate, Arteether, Artemether, Antimalarial, Children, Adult, Severe Malaria.

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INTRODUCTION

Malaria is one of the major health concerns in most of the tropical countries. [1] It constitutes a medical crisis as it can quickly lead to complications and death without timely and suitable management. Malaria is caused by protozoa of the genus Plasmodium and humans can be affected by one or more of the following species: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Despite progress in antimalarial management and intensive care, the prevalence of malaria is increasing, and the mortality rate is very high. [2] WHO report shows that, in 2015 there were approximately 212 million new malaria cases throughout the world and the estimated deaths due to malaria were about 429 000. The number of Artemisinin based combination therapy treatment courses obtained from manufacturers raised from 187 million in 2010 to 393 million in 2013, globally. [3]

The drug suggested for the management of severe malaria in South America, Africa, and most of Asia is quinine. Yet even with timely treatment of quinine in maximum doses, the death in patients of severe malaria is very high. An important feature of severe malaria is cerebral malaria, has a treated death rate of around 15–20%. Due to different vital organ failure, the death rates can increase by more than 30%. The rediscovery artemisinin in China in 1972 and the successive synthesis of artemether and artesunate have supplied highly successful substitutes to quinine. [4]

There are four formulations of artemisinin: artesunate, arteether, dihydroartemisinin and artemether. [2] The artemisinin derivatives are quick acting with the clearance of parasites from the blood occurring within 48 h in most cases and effective of all the other antimalarial drugs. They can be administered once in a day and are safer to administer than quinine. [4] These drugs if used early help in preventing clinical deterioration and have specific benefits over quinine drugs in the management of severe malaria. [5]

In patients with severe malaria, pilot randomised comparison results of IV artesunate and quinine in Thailand showed that death rate in the quinine treated group was 22% and in the artesunate group was 12%. The major pharmacodynamic contrast between quinine and artesunate is the much wider stage specificity of action of the artemisinin derivatives. [4] The main aim of management for malaria patients is to reduce the mortality and the development of its complications. The clinical response rate and parasites clearance can provide significant comparative data between alternative therapies. [5] The artemisinin derivatives have confirmed their effectiveness in the management of malaria, including severe, cerebral malaria and multi-resistant malaria. They earn a significant place in the treatment of malaria due to their efficacy, lack of major adverse effects and low costs of manufacturing and distribution. [1] We conducted this meta-analysis to get stronger evidence on treatment outcomes of malaria in adult and children population. This systematic review and meta-analysis approach sharing the comparative outcome analysis of Artemisinin derivatives (intervention) and other antimalarial such as quinine, chloroquine (comparison) in the paediatric and adult population. Clinical outcome in various aspects such as mortality, FCT, PCT, parasite clearance at D7, parasite clearance at D28 and adverse events were evaluated.

MATERIALS AND METHODS

Types of studies

Study searched; randomized clinical trials (RCT) of treatment comparator, abstracts or full article, review article.

Types of participants

Children and adults with complicated malaria disease as defined by the WHO, Study subjects will belong to any gender, any country, with confirmed malaria infection through RDT or by blood slide test/ microscopy age less than and more than 15 years. Pregnant or lactating women, uncomplicated malaria patients were excluded.

Types of Interventions

RCT or study was selected in which the route of administration was intramuscular, intravenous route of administration or both, rectal and followed by oral antimalarial treatment as applicable. We excluded trials with any other routes of administration than described above.

Outcomes

Primary outcome was to evaluate the clinical characteristic of malaria symptoms; Fever Clearance Time (FCT), Parasite clearance time (PCT in hours), Parasite clearance at D7 and D28. The secondary outcome was to evaluate morality and adverse effects due to severe malaria during the treatment.

Studies inclusion and search methodology

From the year 1985 to the year 2015, studies were recognized using database searches, citation searches of selected articles. The electronic databases searched engines: Pubmed, Web of Science, Global Health, Medline & Cochrane review of Journals. In this meta-analysis, individual study is provided with a coding consisting of name of the investigator, initial three alphabet of Country code where the study was conducted, the study year published in the respective

journal. Keywords were used for searching in the database; Antimalarial Drug, Quinine, Drug Resistance, Efficacy, Safety, and Tolerability, Malaria, Artemisinin, Dihydroartemisinin, Artesunate, Artemether, Arteether, severe malaria, complicated malaria, paediatrics and children.

Data extraction and management

We extracted complete data from the included RCT articles and collected in the datasheet as per predefined outcomes for meta-analysis. The primary measure of effectiveness was parasite clearance at D7, D28, Parasite clearance time (hours) and fever clearance time (hours) and secondary measure mortality and adverse effects. (Fig 1: Flow Chart for Identification and inclusion of studies).

Data Synthesis

Analysis of data was performed through Review Manager (updated software version Revman 5.3) pooling data where appropriate. Standard methods of Meta-analysis, e.g., Peto-Mantel-Haenszel method to test for differences in odds ratio or relative risk in terms of above-mentioned outcomes was used for this study. The mean difference was calculated for data of FCT, PCT and Parasite clearance is compared on day 7 and day 28. We included total thirty- seven RCT to evaluate for our outcome analysis.

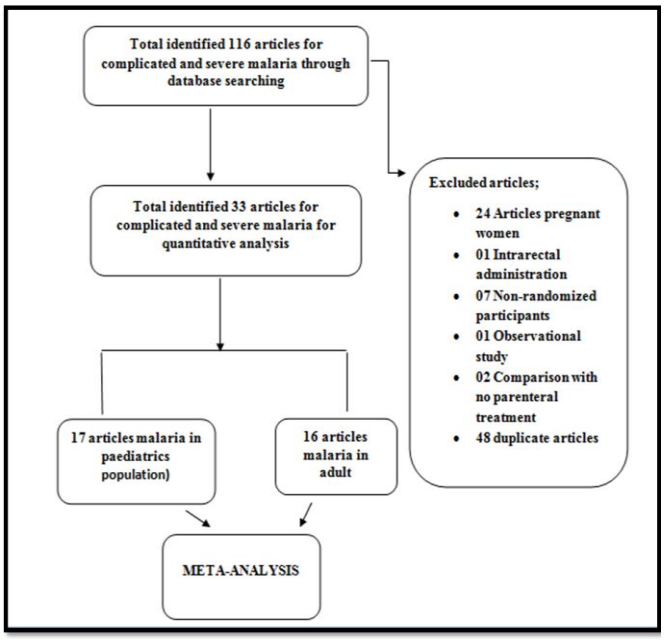

Fig. 1: Flow Chart for Identification and inclusion of studies

RESULTS

All collected and evaluated thirty-three RCT studies (8396 participants) showed comparative outcome in artemisinin derivatives and other antimalarials paediatric and adult patients. We included RCT studies given mainly three intervention artemisinin derivatives: arteether, artemether and artesunate; artesunate (ninestudies; ArjenAQUAMATAFR2010 [6], BirkuETH1999 [7], HienVIE1991 [8], HienVIE1992 [9], LooareesuwanTHA1997 [10], MohantyIND2004 [11], PhuongVIE1997 [12], ThweMYA1996 [13], VinhVIE1992 [14]), Artemether (twenty-two studies; AdamAFR2002 [15], AguwaNIG2010 [16], BunnangTHI1992 [17], DanisAFR1996 [18], HienVIE1996 [19], HudaIND2003 [20], KarbwangTHI1992 [21], KarbwangTHI1994 [22], KarbwangTHI1995 [23], MintaMLI2005 [24], MurphyKEN1996 [25], OjuawoNIG1998 [26], OlumeseNIG1999 [27], OsonugaNIG2009 [28], PhuVIE2010 [29], SattiSUD2002 [30], SeatonPNG1998 [31], TaylorMAL1998 [32], VanhensbroekGAM1996 [33], WalkerNIG1993 [34], WhiteGAM1992 [35], WinMYA1992 [36]) and arteether (two studies; MoyouCAM2001 [37], ThumaZAM2000 [38]). These RCT conducted in various countries; Africa (4 studies), Nigeria (5 studies), Thailand (5 studies), India (2 studies), Sudan (01 studies), Malawi (1 study), Mali (1 study), Gambia (2 studies), Cameroon (1 study), Kenya (1 study), Vietnam (6 studies) and Zambia (1 study), Myanmar (2 studies), Papua New Guinea (1 study) detail showed in table 1.

Dose and frequency

Included RCT studies showed variability in dose of artesunate derivatives and quinine as per WHO malaria guideline, ArjenAQUAMATAFR2010 [6]; Artesunate was given either intramuscularly (i.m.) or intravenously (i.v.) initial dose 2.4 mg per kg at the period of admission at twelve hours of span following once in a day until patient was conscious to take oral antimalarial drug though Quinine was given 20 mg per kg initial dose in 5% of dextrose thrice a day until patient was responsive to take oral antimalarial drug. In case of intramuscular administration, similar doses were given as in intravenous though quinine was diluted in normal saline and given into the anterior thigh of patients. BirkuETH1999 [7]; Artesunate was given intramuscularly 4250 mg (Initial dose 750 mg following 500 mg at twelfth hour, then 500 mg every day from day 2 to day 7) Quinine was administered intravenously 20 mg/kg over four hour followed by 10 mg/kg at 8 hour interval , till patient was responsive to take oral therapy.

HienVIE1991 [8]; (Artesunate i.m + MQ10 vs Artesunate i.v + MQ10) Artesunate was given 2 mg/kg at the initial dose followed by 1 mg/kg at 12^{th} and 24^{th} hour, then every day till the patient was conscious to take oral drugs + MQ 500 mg. HienVIE1992 [9]; (Artemisinin suppositories + Mefloquine 10 vs Artesunate i.v + MQ10 vs Quinine i.v) Artemisinin suppositories (600 mg initially, 4 hour, 400 mg at 24 hour, 32 hour, 48 hour and 56 hour) + MQ 500 mg Artesunate intravenously (60 mg initially and 4 h, 60 mg at 24 hour and 48 hour) + MQ 500 mg (single dose, sequential) Quinine 500 mg, 8 hours interval for 14 days. LooareesuwanTHA1997 [10]; (Artesunate suppositories 1200 + MQ25 vs Artesunate suppositories 1600 + MQ25) Artesunate 1200: 200 mg initially, 12 h followed by 24 h, 36 h, 48 h and 60 h + MQ1250 mg (sequential, 750 mg at 72 h & 500 mgat 84 h), Artesunate1600: 200 mg initially, followed by 4 h, 8 h, 12 h, 24 h, 36 h, 48 h and 60 h + MQ1250 (as previous).

Table 1: Characteristics of included trials

S. No	Trial	Country	Study population	Inclusion	N Artemisinin derivatives/ Other Antimalarial	ROA	Outcome
1	ArjenAQUAMATAFR2010	Africa Multicentre	<15 Yrs	PS +CF of severe malaria	2712/2713	A=i.m./I.V.Q=I.M.	Mortality
2	BirkuETH1999	Africa	>15 years	PS +CF of severe malaria	32/33	A=I.M., Q=I.V	Mortality, Parasite clearance at D7 and D28
3	HienVIE1991	Vietnam	>15 years	PS +CF of severe malaria	18/30	A=I.M/I.V	Mortality
4	HienVIE1992	Vietnam	>15 years	PS +CF of severe malaria	31/30	A=I.V/pr, Q=I.V	Mortality
5	LooareesuwanTHA1997	Thailand	>15 years	PS + CF of severe malaria	63/63	A=pr MQ=PO	Mortality, FCT, PCT, AE
6	MohantyIND2004	India	Paediatric, Age; NS	PS + CF of severe malaria	40/40	A=I.V, Q=I.M	FCT, Mortality, PCT
7	PhuongVIE1997	Vietnam	<15 Yrs	PS + CF of severe malaria	37/35	A=I.M., Q=I.V.	FCT, Mortality, PCT, Parasite clearance at D7
8	ThweMYA1996	Myanmar	>15 years	PS + CF of severe malaria	54/54	A=pr	Mortality, FCT, PCT
9	VinhVIE1992	Vietnam	>15 years	PS + CF of severe malaria	A=175	A=i.m/i.v/pr	Mortality, PCT, FCT
10	AdamAFR2002	Africa Multicentre	Paediatric, Age; NS	PS + CF of severe malaria	20/21	A=I.M., Q=I.V.	FCT, Mortality, AE, PCT
11	AguwaNIG2010	Nigeria	<12 Yrs	PS + CF of severe malaria	44/46	A=I.M., Q=I.V./I.M.	Mortality
12	BunnangTHI1992	Thailand	>15 years	PS + CF of severe malaria	A=106	A=I.M	FCT, PCT
13	DanisAFR1996	Africa	>15 years	PS + CF of severe malaria	133/135	A=I.M Q=I.V	Mortality, FCT, PCT
14	HudaIND2003	India	<14 Yrs	PS + CF of severe malaria	23/23	A=I.M., Q=I.V.	Mortality, FCT, PCT
15	HienVIE1996	Vietnam	>15 years	PS + CF of severe malaria	284/276	A=I.M Q-I.M	Mortality, AE, Parasite clearance at D7
16	KarbwangTHI1992	Thailand	>15 years	PS + CF of severe malaria	14/12	A=I.M Q=I.V	FCT, PCT, Mortality, parasite clearance at D7
17	KarbwangTHI1994	Thailand	>15 years	PS + CF of severe malaria	28	A=I.M	Parasite clearance at D7
18	KarbwangTHI1995	Thialand	>15 years	PS + CF of severe malaria	50/52	A=I.M Q=I.V	PCT, FCT, AE, Mortality
19	MintaMLI2005	Mali	<15 Yrs	PS + CF of severe malaria	33/34	A=I.M., Q=I.V.	AE, FCT, Mortality, PCT
20	MurphyKEN1996	Kenya	<12 Yrs	PS + CF of severe malaria	89/71	A=I.M., Q=I.V.	AE, FCT, Mortality, PCT
21	OjuawoNIG1998	Nigeria	<6 Yrs	PS + CF of severe malaria	18/19	A=I.M., Q=I.V.	Mortality, FCT,
22	OlumeseNIG1999	Nigeria	<5 Yrs	PS +CF of severe malaria	54/49	A=I.M., Q=I.V.	Mortality, Parasite clearance at D7, Parasite clearance at D28, FCT, PCT
23	OsonugaNIG2009	Nigeria	<12 Yrs	PS + CF of severe malaria	16/16	A=I.M., Q=I.V.	Mortality, PCT
24	PhuVIE2010	Vietnam	>15 years	PS +CF of severe malaria	370	A=I.M	Death, PCT, FCT, AE
25	SattiSUD2002	Sudan	<15 Yrs	PS + CF of severe malaria	38/39	A=I.M., Q=I.V.	Mortality, FCT, PCT
26	SeatonPNG1998	Papua New Guinea	>15 years	PS + CF of severe malaria	15/18	A=I.M Q=I.V	Mortality, Parasite clearance at D28
27	TaylorMAL1998	Malawi	Paediatric,	PS + CF of	83/81	A=I.M., Q=I.V.	Mortality,

			Age; NS	severe malaria			Parasite clearance at D7, Parasite clearance at D28, FCT, PCT
28	VanhensbroekGAM1996	Gambia	<10 Yrs	PS + CF of severe malaria	288/288	A=I.M., Q=I.V.	AE, Mortality
29	WalkerNIG1993	Nigeria	<5 Yrs	PS + CF of severe malaria	25/29	A=I.M., Q=I.V.	Mortality, FCT, PCT
30	WhiteGAM1992	Gambia	>15 years	PS + CF of severe malaria	21/22	A=I.M, CLQ=I.M	Mortality
31	WinMYA1992	Myanmar	>15 years	PS + CF of severe malaria	NS	A=I.M/I.V Q=I.V	Parasite clearance at D28, Mortality
32	MoyouCAM2001	Cameroon	<10 Yrs	PS + CF of severe malaria	51/51	A=I.M., Q=I.V.	Mortality, FCT, PCT
33	ThumaZAM2000	Zambia	<10 Yrs	PS + CF of severe malaria	48/44	A=I.M., Q=I.V.	Mortality, FCT, PCT

A = Artemisinin derivative, AE = adverse events, CF = clinical features, CRT = coma resolution time, FCT = fever clearance time, im = intramuscular, iv = intravenous, N = number of participants, NS = not specified, PCT = parasite clearance time, PS = peripheral smear showing asexual forms of Plasmodium

MohantyIND2004 [11]; first group of patients received quinine 20 mg/kg as initial dose by the following of 10 mg per kg at every eight hours of span until the patient was responsive to take oral antimalarial though the second group of patients were given artesunate 2.4 mg per kg iv following 1.2 mg per kg at every six hrs of interval by the following of once daily for next 5 days. PhuongVIE1997 [12]; At the time of initial dose artemisinin therapy was administered 40 mg following of 20 mg at every specified period of interval as per WHO guideline with 750 mg mefloquine or Artesunate 3 mg per kg at time of starting dose by the following of 2 mg per kg at every 12 hours of span with 750 mg of mefloquine though Quinine was given 20 mg per kg by the following of 10 mg per kg at every 8 hours till 7 days. ThweMYA1996 [13]; (Artesunate suppositories 800 mg + MQ25 vs Artesunate suppositories 1200 mg + MQ25) Artesunate 800 mg (200 mg was given initially , 12 h, then at 24 h and at 36 h) + MQ 1250 mg (sequential, 750 mg at 48 h, then 500 mg at 60 h) Artesunate 1200 mg (200 mg at starting dose, then at 12 h followed by 24 h, 36 h, 48 h and 60 h) + MQ 1250 mg (sequential, 750 mg at 72 h, 500 mg at 84 h). VinhVIE1992 [14]; (Artemisinin suppositories vs Artemether i.m vs Aretsunate i.m vs Artesunate i.v) Artemisinin suppositories 2800 mg (1200 mg initially, 400 mg at 4 h, at 24 h, at 48 h and 72 h) Artemether 500 mg (200 mg initially, 100 mg at 24 h and at 48 h and 72 h) Artesunate 300 mg (120 mg initially, then 60 mg at 24 h, 48 h and 72 h). AdamAFR2002 [15]; loading dose of intramuscular artemether was administered 3.2 mg per kg at the time of admission following 1.6 mg/kg/day up to 4 days though loading dose of intravenous quinine was given 20 mg per kg in 5% of dextrose solution by the following of 10 mg per kg of quinine in 5% dextrose solution infused up to four hours for specified period of interval i.e. every eight hours for three days by the following oral quinine up to seven days. AguwaNIG2010 [16]; starting dose of intramuscular artemether was administered 3.2 mg per kg at the time of admission following 1.6 mg /kg/day for 2 days through IV or IM quinine was given 20 mg per kg at the period of admission as starting dose by the following of 10 mg per kg at every specified time of interval i.e. eight hours. BunnangTHI1992 [17]; (Artemether i.m 480 vs Artemether i.m 600) Artemether 480: 160 mg on was given intramuscularly on first day, 80 mg on days 2 to 5. Artemether 600: 200 mg was given intramuscularly on day 1, then 100 mg on day 2 to day 5. DanisAFR1996 [18]; Artemether was given intramuscularly vs Quinine was given intravenously) Artemether: < 50 kg, 9.6 mg/kg (1.6 mg/kg initially, 12th h, day 2 to day 5; > 50 kg, 480 mg (80 mg initially, 12 h, days 2 to 5). Quinine: 20 mg/kg, then 10 mg/kg at every 8 h, per oral from day 3 to day 7. HienVIE1996 [19]; Artemether and quinine both were given intramuscularly. Artemether was administered 4 mg/kg followed by 2 mg/kg at every 8 h interval whereas quinine was given 20 mg/kg, then 10 mg/kg at every 8hour interval. HudaIND2003 [20]; Loading dose of intramuscular artemether was 1.6 mg per kg twice daily at the time of admission by the following of 1.6 mg/kg/day for 5 days though starting dose of quinine was 20 mg per kg by the following of 10 mg per kg at specified time of intervals i.e. eight hours until patient was responsive to take oral antimalarial. MintaMLI2005 [21]; initial dose of intramuscular artemether was given 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg once for four days though initial dose of intravenous quinine was given 20 mg per kg at the time of admission by the following of 10 mg/kg at every specified time of intervals i.e. eight hours followed by oral antimalarial therapy until patient was responsive to take oral antimalarial. KarbwangTHI1992 [22]; Artemether was given intramuscular lyand quinine was given intravenously, Artemether was given 160 mg on first day , 80 mg on day 2 to 7, whereas quinine was given 20 mg/kg on first day, 10 mg/kg at every 8 h till day 7. KarbwangTHI1994 [23]; Artemether 640 and 700 mg was given intramuscularly. Artemether 640 was given 160 mg on first day, 80 mg on day 2 to day 72 and

Artemether 700 mg was given 300 mg first day, 100 mg on day 2 to day 5. KarbwangTHI1995 [24]; Artemether was given intramuscularly 160 mg on first day, 80 mg on day 2 to 72 and quinine was given intravenously 20 mg/kg on first day, 10 mg/kg every 8 hour till day 7. MurphyKEN1996 [25]; starting dose of intramuscular artemether was 3.2 mg per kg by the following of 1.6 mg per kg once daily up to 3 doses by the following of sulfadoxine-pyrimethamine though starting dose of intravenous quinine was 20 mg per kg administered up to four hours by the following of 10 mg per kg at every specified period of intervals i.e. eight hours followed by oral antimalarial therapy until patient was responsive to take oral antimalarial by the following of sulfadoxine-pyrimethamine. OjuawoNIG1998 [26]; starting dose of intramuscular artemether was 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg at every 12 hours of span by the following of 1.6 mg per kg once daily for 48 hours though starting dose of intravenous quinine was 10 mg per kg administered up to two hours following of 10 mg per kg at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy until patient was responsive to take oral antimalarial for seven days. OlumeseNIG1999 [27]; starting dose of intramuscular artemether was 3.2 mg per kg at the time of admission by the following of 1.6 mg/kg/day for 4 days though starting dose of intravenous quinine given 20 mg per kg administered up to four hours by the following of 10 mg per kg administered up to two hours at every specified time of intervals i.e. eight hours followed by oral antimalarial therapy until patient was responsive to take oral antimalarial for seven days or twenty-one day's administration. OsonugaNIG2009 [28]; starting dose of intramuscular artemether was 1.6 mg per kg twice daily at the time of admission by the following of 1.6 mg /kg/day up to four days though starting dose of intravenous quinine was 10 mg per kg administered up to four hours following of 10 mg per kg at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy until patient was responsive to take oral antimalarial for seven days. PhuVIE2010 [29]; Intramuscular artemether 3.2 mg/kg loading dose was given followed by 1.6 mg/kg/ day for 2 days. Intramuscular artesunate 2.4 mg/kg loading dose on admission, followed by 1.2 mg/kg/day for 2 days, followed by 2 mg/kg of oral artesunate for seven days. SattiSUD2002 [30]; loading dose of intramuscular artemether was 1.6 mg per kg twice daily following of 1.6 mg per kg per day up to four days though starting dose of intravenous quinine was given 10 mg per kg at every specified time of intervals i.e. eight hours followed by oral antimalarial therapy until patient was responsive to take oral antimalarial. SeatonPNG1998 [31]; Artemether intramuscularly was given 9.6 mg/kg (3.2 mg/kg followed by 1.6 mg/kg daily on days 2 to 5) whereas Quinine was given intravenously 20 mg/kg then 10 mg/kg every 8 h for 7 days; then orally after 48 hour if well tolerated. TaylorMAL1998 [32]; starting dose of intramuscular artemether was 3.2 mg per kg at the period of admission following of 1.6 mg per kg per day up to three doses by the following of oral sulfadoxine-pyrimethamine when patients are able to take oral antimalarial though starting dose of intravenous quinine was 20 mg per kg administered up to four hours by the following of 10 mg per kg administered up to two hours at every specified time of intervals i.e. eight hours followed by oral antimalarial therapy following oral sulfadoxine-pyrimethamine.

VanhensbroekGAM1996 [33]; starting dose of intramuscular artemether was 3.2 mg per kg at the time of admission by the following of daily doses of 1.6 mg per kg for three days though starting dose of intravenous quinine was given 20 mg per kg by the following of 10 mg per kg at every 12 hours of interval and switched to oral antimalarial when the patient is conscious, quinine for five days by the following of oral dose of 1.25 mg/kg pyrimethamine and 25 mg/kg sulfadoxine. WalkerNIG1993 [34]; starting dose of intramuscular artemether was 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg for four days though initial dose of intravenous quinine was 20 mg per kg administered up to four hrs at the time of admission by the following of 10 mg per kg at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy. WhiteGAM1992 [35]; Artemether was administered intramuscularly 4 mg/kg on first day, 2 mg/kg daily whereas i.m chloroquine was given 3.5 mg/kg at every 6 hour interval. WinMYA1992 [36]; Intramuscular Artemether 600 mg (200 mg, followed by 100 mg at 12 h, then at 24 h, 36 h and 48 h) + MQ 1000 mg at 48 h (sequential, single dose). Artesunate i.v 240 mg (120 mg was given initially, then 60 mg at 12 h, then at 24 h and 48 h) + MQ 1000 mg. Quinine i.v was given 600 mg at every 8 h up to 10 days + Tc (250 mg at 48 h later every 6 h for next 7 days. MoyouCAM2001 [37]; Arteether was administered intramuscular 3.2 mg per kg at the time of admission by the following of 1.6 mg/kg/day up to four days though Quinine 20 mg/kg was administered intravenously starting dose up to 4 hrs by the following of 10 mg per kg at every 8 hours up to six days by the following of oral quinine 10 mg per kg at every specified time of intervals i.e. eight hrs followed by oral antimalarial therapy and recrudescent cases were treated with sulfadoxine-pyrimethamine in this RCT. ThumaZAM2000 [38]; intramuscular artemotil was administered as starting dose of 3.2 mg per kg by the following of daily doses of 1.6 mg per kg though i.v quinine was given 20 mg per kg initial dose in 5% dextrose solution by the following of 10 mg per kg in 5% dextrose solution given at every specified time of intervals i.e. eight hrs followed by oral antimalarial quinine therapy continued for of 7 days.

Primary Outcomes

Parasite clearance time

We performed a meta-analysis of fourteen RCT (1074 participants) to evaluate mean parasite clearance time

in paediatric and adult patients (figure 2) and it was observed 8.5 hours less with artemisinin derivatives (MD -8.50 hours, 95% CI -9.41 to -7.60). Forest plot shows the statistical difference and significant improvement with artemisinin derivatives compared to other antimalarials (*P*<0.00001).

Parasite clearance at D7

We performed a meta-analysis of seven RCT (1129 participants) to evaluate parasite clearance time in paediatric and adult patients at D7 (figure 3). Artemisinin and its derivatives showed a statistically significant clearance of parasites when compared to quinine. (OR 0.41, 95% CI 0.21, 0.81, random effect model, *P*=0.01).

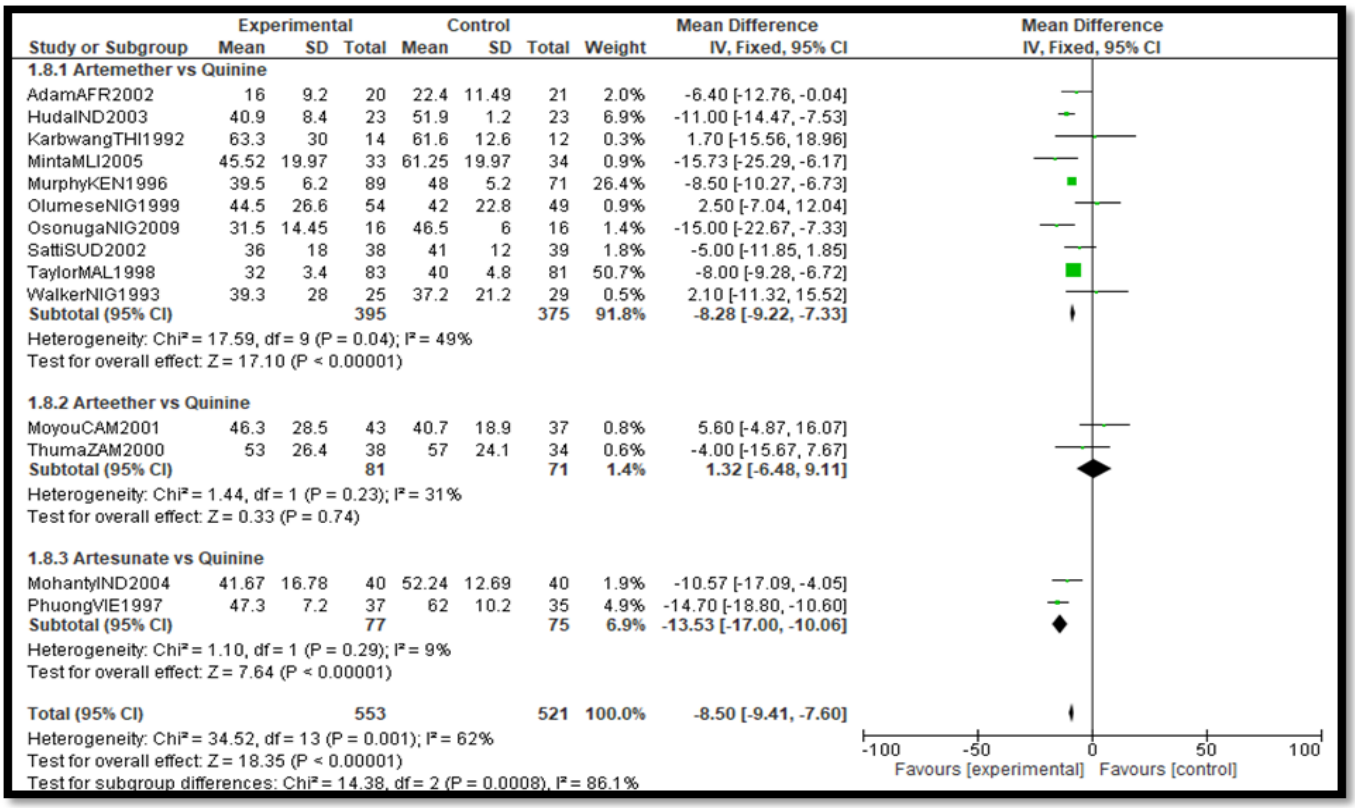

Fig. 2: Forest Plot Parasite Clearance time

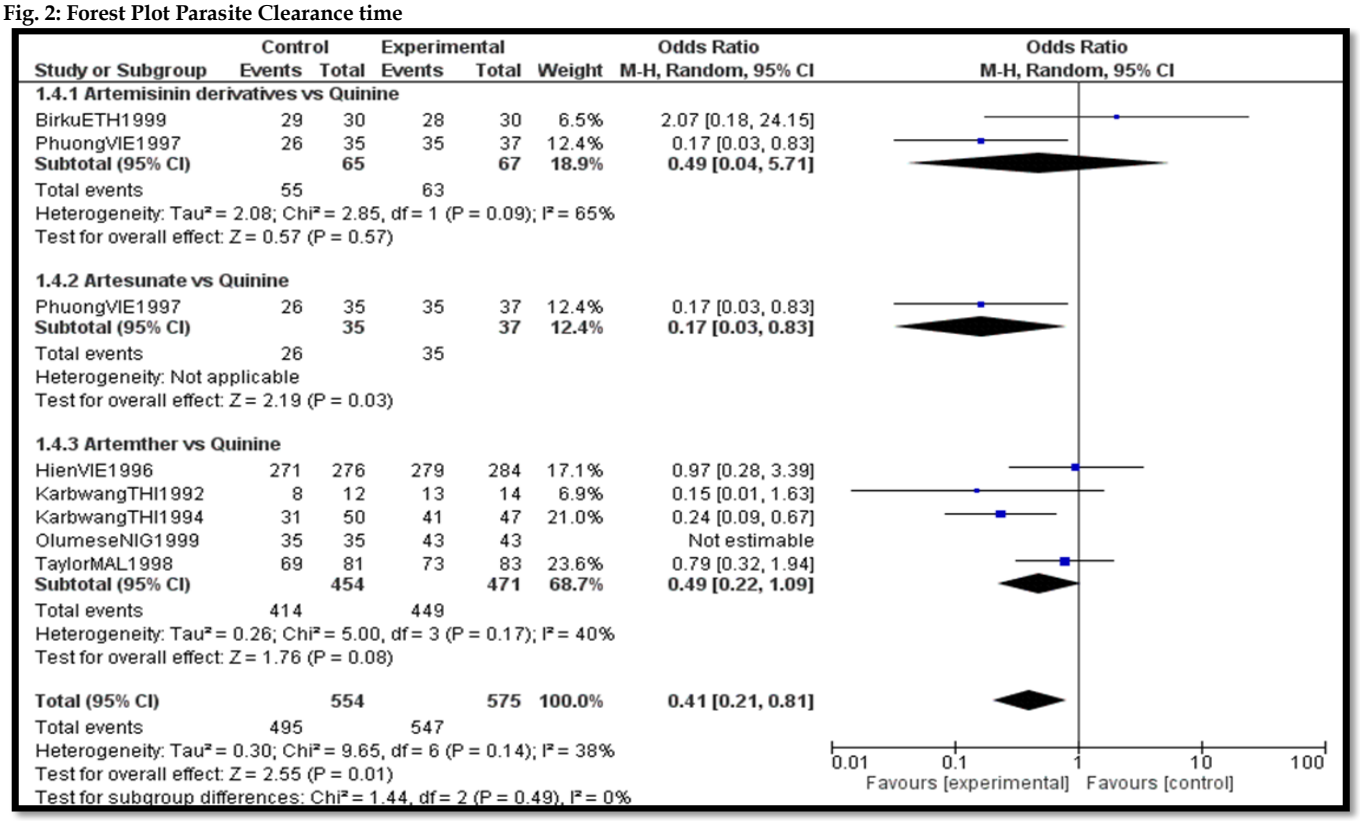

Fig. 3: Forest Plot Parasite Clearance at D7

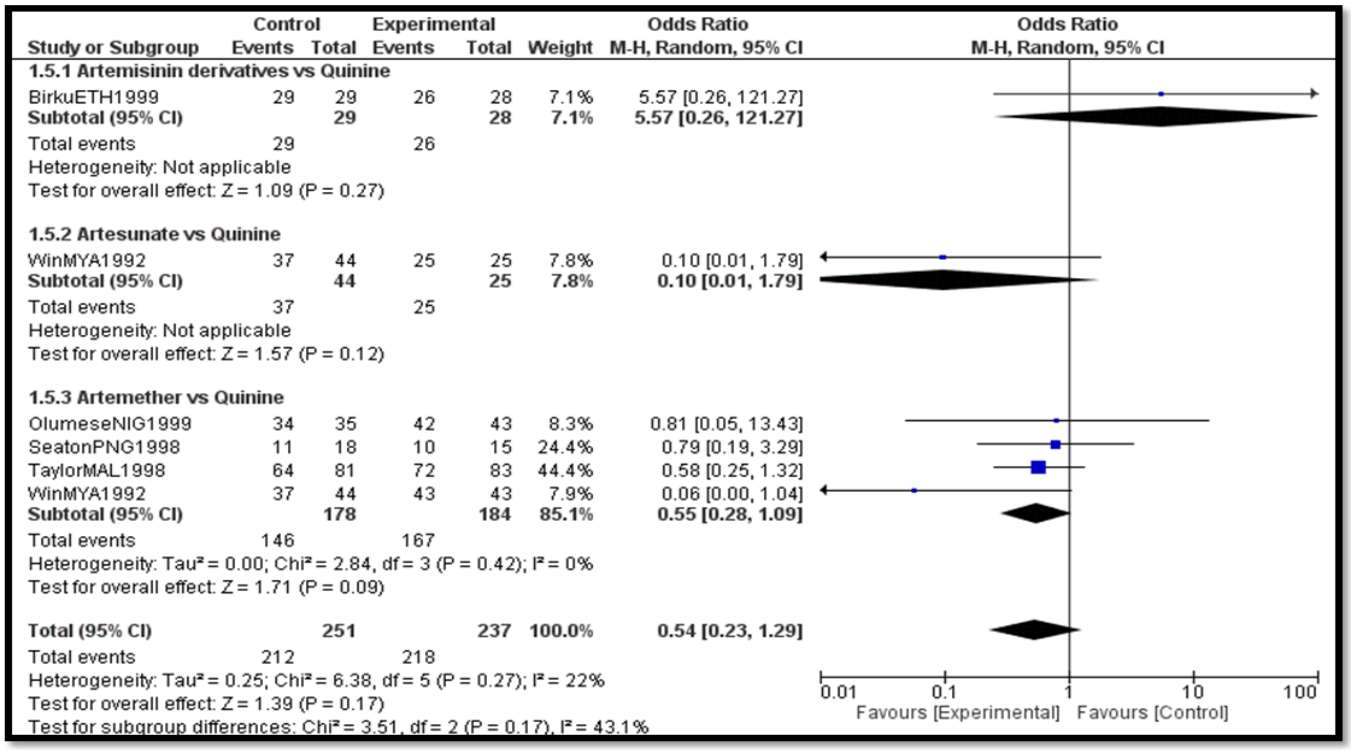

Fig. 4: Forest Plot Parasite Clearance at D28

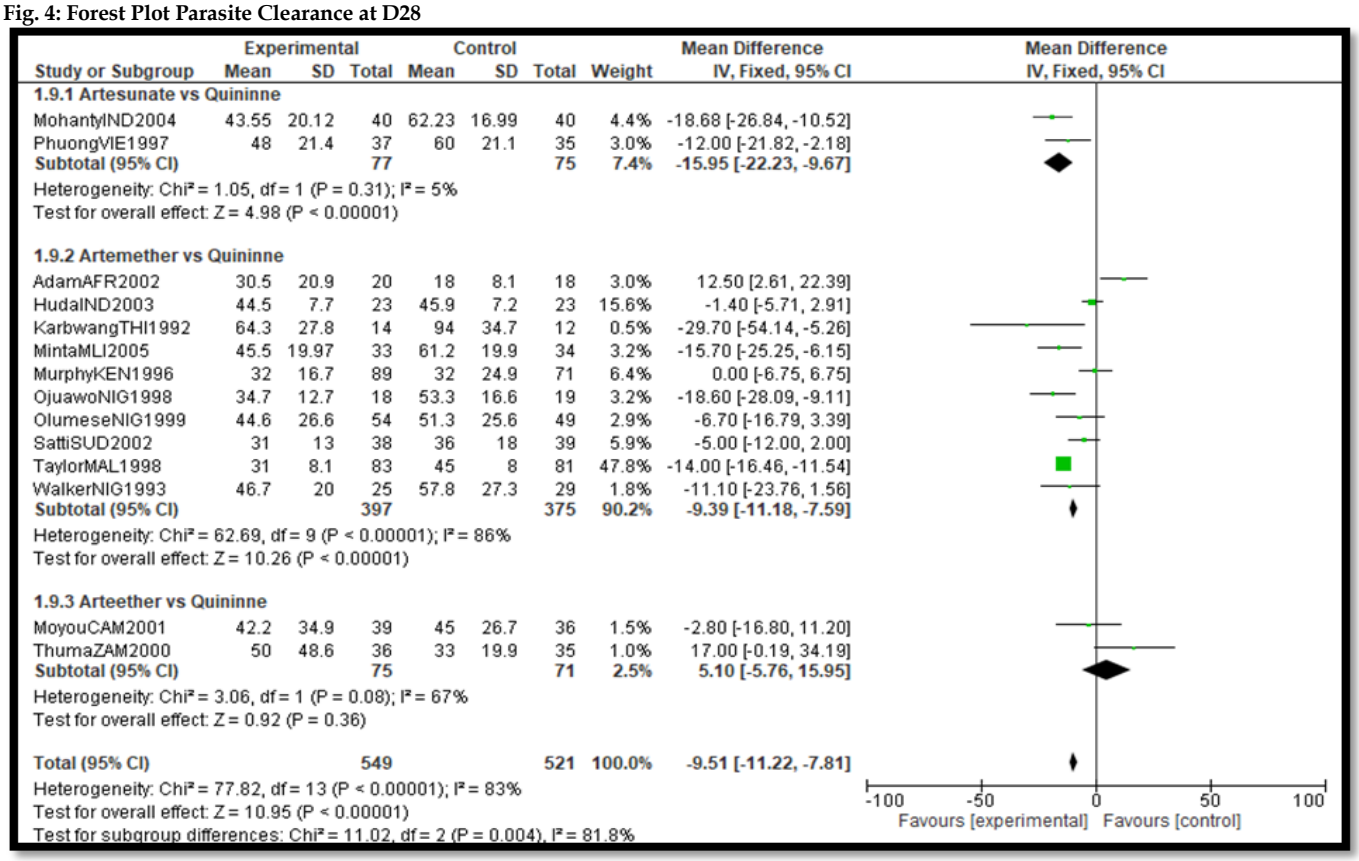

Fig. 5: Forest Plot Fever Clearance Time

Parasite clearance at D28

Parasite clearance at 28th day was reported in 5RCT studies (488 participants) to evaluate parasite clearance time in paediatric and adult patients at D28. Failures were observed in the quinine group in the artesunate study that reported this outcome. Overall artemisinin derivatives have shown 1. 84 times more parasite clearance at D28 than quinine group (Odds ratio 0.54, 95% CI 0.23, 1.29, random effect model, *P*=0.17) (Figure 4).

Fever Clearance Time

Total fourteen RCT studies reported mean FCT with a statistically significant reduction of about nine hrs with artesunate derivatives overall (MD -9.51 hours, 95% CI -11.22 to -7.81; fourteen trials, 1070 participants, *P*<0.00001 (Figure 5).

Secondary Outcomes

Mortality

We evaluated total twenty-five clinical trials for mortality outcomes in Artemisinin derivatives compared with quinine. Forest plot meta-analysis (figure 6) confirmed that artemisinin or its derivatives showed a statistically significant mortality reduction as compared with quinine. There was an overall difference (OR 0.77, 95% CI 0.67 to 0.89; 27 trials, 8396 participants) *P*=0.0002 shown in all-cause mortality in artesunate derivatives as compared with quinine.

Adverse Events

We evaluated seven trials (5582 participants) for the adverse events outcome in the artemisinin derivatives compared with quinine. Forest plot meta-analysis (figure 7) confirmed that artemisinin or its derivatives showed a statistically significant reduction in the adverse events as compared with quinine. There was an overall difference (RR 0.73, 95% CI 0.62 to 0.87) *P*=0.003 which is shown in adverse events of artesunate derivatives as compared with quinine.

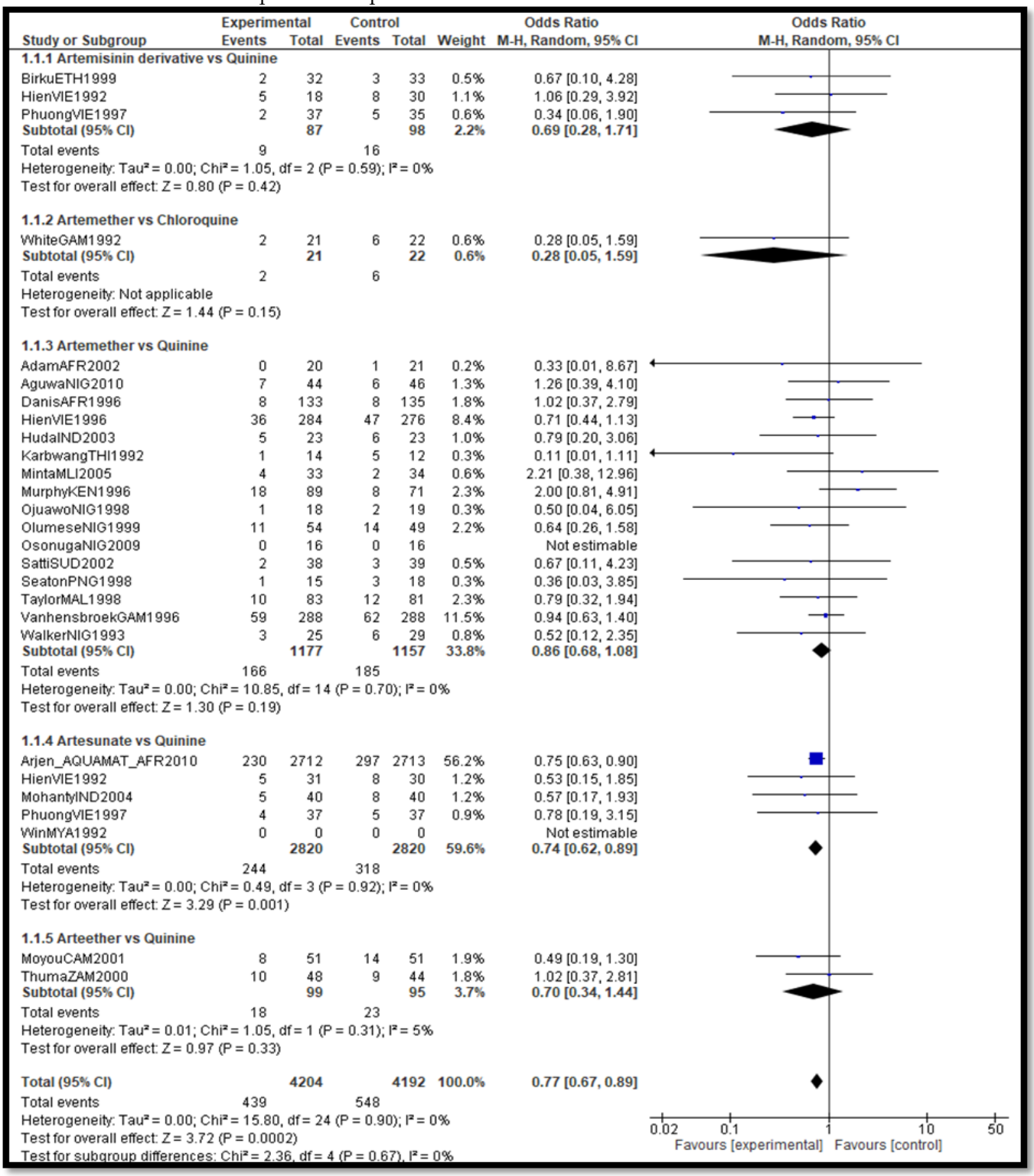

Fig. 6: Forest Plot Mortality

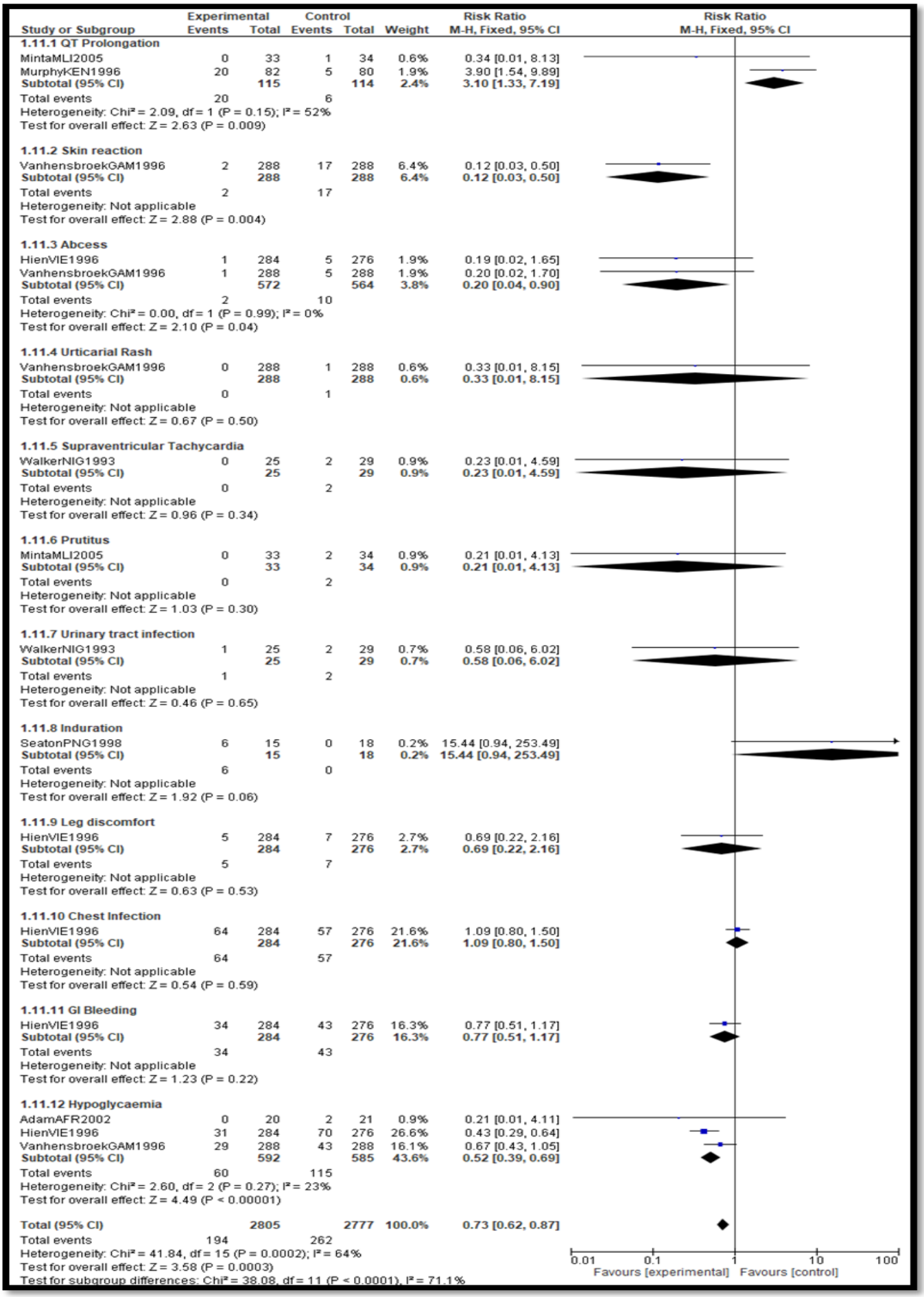

Fig. 7: Forest Plot Adverse Events

DISCUSSION

Malaria is one of the most prevalent diseases which have affects millions of people and around 40% of the population in the world are at risk for this infection. The prevalence of death from *Plasmodium falciparum* is higher in the developing countries. [39] This systematic review and meta-analysis is done in the continuation of our research work of which was evaluated for efficacy and safety of antimalarial drug regimen in paediatric population. [40] Approach sharing the comparative outcome analysis of Artemisinin derivatives (intervention) and other antimalarials (comparison) in the paediatric and adult population. Clinical outcomes such as mortality, FCT, PCT, parasite clearance at D7, parasite clearance at D28 and adverse events were evaluated. This meta-analysis showed benefit with artemisinin drugs in comparison with quinine in management of severe malaria.

The most important outcome is the meta-analysis of mortality confirms that patients with artemisinin derivatives have a better survival chance than patients treated with quinine. We observed artemisinin, or its derivatives showed a statistically significant mortality reduction as compared to quinine (Odds ratio 0.77, 95% CI 0.67 to 0.89; 27 trials, 8396 participants) P=0.0002. Evaluation of fever clearance time of fourteen RCT studies reported mean FCT with a statistically significant reduction of nine hrs with artesunate derivatives overall (MD -9.51 hours, 95% CI -11.22 to -7.81; fourteen trials, 1070 participants) P<0.00001. Studies conducted by Phuong *et al* (1997) showed PCT were significantly faster in artemisinin derivatives treated patients compared to those who received quinine (P<0.0001). [12]

Artemisinin derivatives also shorten the parasite clearance time by around 8.5 hours when compared to quinine. We evaluated seven trials (5582 participants) for the adverse events outcome in the artemisinin derivatives compared with quinine. Forest plot meta-analysis confirmed that artemisinin or its derivatives showed a statistically significant reduction in the adverse events as compared to quinine (RR 0.73, 95% CI 0.62 to 0.87) P=0.003. An overall comparable effect was found with artemisinin derivatives across all evaluated outcomes.

Since artemisinin and its derivatives have showed better outcomes, they earn a significant place in the treatment of malaria due to their efficacy and lack of major adverse effects. [1] In conclusion, this meta-analysis showed stronger evidence for artemisinin and it derivatives on treatment outcomes of severe malaria population.

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