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

Jeetu Gangil1*, Bhaswat S. Chakraborty2

1Department of Pharmacology, KB Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwavidyalaya, Near GH6, Pujya Mota Cir, Sector 23, Gandhinagar- 382023, Gujarat, India
2Institute of Pharmacy, Nirma University, S-G Highway, Ahmedabad- 382481, Gujarat, India

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. 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. 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.

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 artsunate have supplied highly successful substitutes to quinine.

There are four formulations of artemisinin: artesunate, arteether, dihydroartemisinin and artemether. The artemisinin derivatives are quick acting with the characteristic of malaria symptoms; Fever Clearance Time (FCT), Parasite clearance time (PC T), and adult population. Clinical outcome in various 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, Artemether, 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.

**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], HienVIE1992 [19], HudalIND2003 [20], KarbwangTHI1992 [21], KarbwangTHI1995 [22], KarbwangTHI1995 [23], MintaMLI2005 [24], MurphyKEN1996 [25], OjuawoNIG1998 [26], OlumeseNIG1999 [27], OsonugaNIG2009 [28], PhuVIE2010 [29], SattiSUD2002 [30], SeatonPNG1998 [31], TaylorMAL1992 [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), Marijuana (2 studies), Papua New Guinea (1 study) detail showed in table 1.

**Dose and frequency**
Included RCT studies showed variability in dose of artemisinin 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 12th and 24th 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 (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 Antimalarials | ROA                          | Outcome                                      |
|-------|---------------|--------------|------------------|-----------|-----------------------------------------------|------------------------------|----------------------------------------------|
| 1     | ArjenAQUAMATAFR2010 | Africa Multicentre | <15 Yrs          | PS + CF of severe malaria | 2/12/2/13 | 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/L.I.V                                | Mortality                         |
| 4     | HienVIE1992   | Vietnam      | >15 years        | PS + CF of severe malaria | 31/30      | A=I.V/pr, Q=I.V                            | Mortality                         |
| 5     | LooareesawanTHA1997 | Thailand    | >15 years        | PS + CF of severe malaria | 63/63      | A=pr MQ=PO                                 | Mortality, FCT, PCT, AE, FCT, Mortality, PCT, FCT |
| 6     | MohantyIND2004 | India        | Paediatric, Age; NS | PS + CF of severe malaria | 40/40      | A=I.V, Q=I.M                              | Mortality, PCT, Parasite clearance at D7 |
| 7     | PhuongVIE1997 | Vietnam      | <15 Yrs          | PS + CF of severe malaria | 37/35      | A=I.M., Q=I.V                              | Mortality                         |
| 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                    |
| 10    | AdamAFR2002   | Africa Multicentre | Paediatric, Age; NS | PS + CF of severe malaria | 20/21      | A=I.M., Q=I.V                             | 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                              |
| 13    | DanisAFR1996  | Africa       | >15 years        | PS + CF of severe malaria | 133/135    | A=I.M Q=I.V                              | Mortality, FCT                    |
| 14    | HudaIND2003   | India        | <14 Yrs          | PS + CF of severe malaria | 23/23      | A=I.M., Q=I.V                            | Mortality, 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                              | Mortality, parasite clearance at D7 |
| 17    | KarbwangTHI1994 | Thailand     | >15 years        | PS + CF of severe malaria | 28         | A=I.M                                     | Parasite clearance at D7, PCT, FCT, AE, Mortality |
| 18    | KarbwangTHI1995 | Thailand     | >15 years        | PS + CF of severe malaria | 50/52      | A=I.M Q=I.V                              | Mortality, PCT, AE, Mortality     |
| 19    | MintaML2005   | Mali         | <15 Yrs          | PS + CF of severe malaria | 33/34      | A=I.M., Q=I.V                            | Mortality, PCT, AE, FCT          |
| 20    | MurphyKEN1996  | Kenya        | <12 Yrs          | PS + CF of severe malaria | 89/71      | A=I.M., Q=I.V                            | Mortality, PCT                    |
| 21    | OjuawoNIG1998 | Nigeria      | <6 Yrs           | PS + CF of severe malaria | 18/19      | A=I.M., Q=I.V                            | Mortality, PCT                    |
| 22    | OlumeseNIG1999 | Nigeria      | <5 Yrs           | PS + CF of severe malaria | 54/49      | A=I.M., Q=I.V                             | Mortality, Parasite clearance at D7 |
| 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, Mortality |
| 25    | SattiSUD2002  | Sudan        | <15 Yrs          | PS + CF of severe malaria | 38/39      | A=I.M., Q=I.V                            | Mortality, PCT, Parasite clearance at D28 |
| 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 severe malaria | 83/81      | A=I.M., Q=I.V                            | Mortality                         |
MohanthyIND2004 [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 artemunate 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 5 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 Artesunate 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/kday 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. HudalIND2003 [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 intramuscularly and 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 arteether 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 arteether was 3.2 mg per kg at the time of admission by the following of 1.6 mg per kg per day for 4 days 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 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. OlumesesiNIG1999 [27]; starting dose of intramuscular arteether 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 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 until patient was responsive to take oral antimalarial for seven days or twenty-one day's administration. OsonugaNIG2009 [28]; starting dose of intramuscular arteether 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 arteether 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 arteether 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 arteether was 3.2 mg per kg at the period of admission following of 1.6 mg/kg 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 arteether 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 arteether 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 Artesether 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. MiosoCAM2001 [37]; Arteether was administered intramuscularly 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 arteether 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).
Parasite clearance at D28
Parasite clearance at 28th day was reported in 5 RCT studies (488 participants) to evaluate parasite clearance time in paediatric and adult patients at D28. Failures were observed in the quinine group in the artemesunate 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 artemesunate 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 artemesunate 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.
### Evaluation of Efficacy and Safety of Artemisinin Derivatives for Treatment

#### Table: Comparison of Adverse Events

| Study or Subgroup | Experimental Events | Control Events | Total | Weight | Risk Ratio M-H Fixed, 95% CI |
|-------------------|---------------------|----------------|-------|--------|-----------------------------|
| QT Prolongation   |                     |                |       |        |                             |
| M. (255)          | 0                   | 33             | 1     | 34     | 0.8 | 0.34 (0.01, 6.13) |
| M. (219)          | 20                  | 82             | 5     | 80     | 1.9 | 3.90 (0.64, 24.89) |
| Subtotal (95% CI) | 22                  | 87             | 6     | 93     | 2.4 | 3.10 (0.13, 7.19) |

- Heterogeneity: $Chi^2 = 2.09$, df = 1 ($P = 0.15$); $I^2 = 92$
- Test for overall effect: $Z = 2.03$ ($P = 0.009$)

| Skin reaction |                     |                |       |        |                             |
| Vannenbroek/GAM1996 | 2                   | 288            | 17    | 288    | 1.8 | 0.12 (0.02, 0.50) |
| Subtotal (95% CI) | 2                   | 288            | 17    | 288    | 1.8 | 0.12 (0.02, 0.50) |

- Heterogeneity: Not applicable
- Test for overall effect: $Z = 2.03$ ($P = 0.004$)

| Abcess |                     |                |       |        |                             |
| Vannenbroek/GAM1996 | 2                   | 288            | 17    | 288    | 1.8 | 0.12 (0.02, 0.50) |
| Subtotal (95% CI) | 2                   | 288            | 17    | 288    | 1.8 | 0.12 (0.02, 0.50) |

- Heterogeneity: Not applicable
- Test for overall effect: $Z = 2.03$ ($P = 0.004$)

| Urticarial Rash |                     |                |       |        |                             |
| Vannenbroek/GAM1996 | 0                   | 288            | 17    | 288    | 1.8 | 0.12 (0.02, 0.50) |
| Subtotal (95% CI) | 0                   | 288            | 17    | 288    | 1.8 | 0.12 (0.02, 0.50) |

- Heterogeneity: Not applicable
- Test for overall effect: $Z = 2.03$ ($P = 0.004$)

### Forest Plot Adverse Events

**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. [11] In conclusion, this meta-analysis showed stronger evidence for artemisinin and its derivatives on treatment outcomes of severe malaria population.

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