# Efficacy and Safety of Artemether-Lumefantrine for Treatment of Uncomplicated *P. Falciparum* malaria in Ethiopia: A Systematic Review and Meta-Analysis

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**Research**

**Keywords:** Efficacy, Artemether-lumefantrine, Plasmodium falciparum, Ethiopia

**Posted Date:** January 15th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-144492/v1

## Abstract

**Background**: Anti-malarial drug resistance, in particular resistance to *Plasmodium falciparum*, challenges the treatment and control of malaria. In Ethiopia, the first-line treatment of uncomplicated falciparum malaria has been changed from sulphadoxine-pyrimethamine (SP) to artemether-lumefantrine (AL) in 2004. To maximize efficacy of anti-malarial drugs and ensure adequate treatment outcomes; monitoring drug efficacy regularly is vital to establish rational malaria treatment guidelines. This systematic review and meta-analysis is performed to obtain an overall stronger evidence to guide management of uncomplicated falciparum malaria from the existing literature in Ethiopia after policy changes in 2004.

**Methods**: A systematic literature search was performed using the preferred reporting items for systematic review and meta-analysis (PRISMA) from published therapeutic efficacy studies conducted in Ethiopia from 2004 to 2020. The search was performed from Pubmed, Google Scholar and Clinical trial registry databases to identify literature. Two reviewers independently assessed study eligibility and extracted data. While computing the efficacy of AL, polymerase chain reaction (PCR)-corrected cure rate (adequate clinical and parasitological response, ACPR) at 28$^{th}$ day was considered as the primary endpoint. Meta-analysis was computed using OpenMeta-Analysis software to calculate the pooled ACPR. Statistical heterogeneity was evaluated with the Cochran chi-square test ($X^2$) test and inverse variance index ($I^2$). Publication bias was analyzed using funnel plots and Egger's test statistics. The review protocol is registered in PROSPERO, number CRD42020201859.

**Results**: Out of studies screened, fifteen studies fulfilled the inclusion criteria, and were included in final analysis with a total number of 1523 participants. Treatment success of AL for uncomplicated falciparum malaria in all combined studies was 98.4% [(95% CI 97.6–99.1), $P$< 0.001]. Polymerase chain reaction (PCR)-corrected AL treatment success rate of 98.7% [(95% CI 97.7-99.6), $P$<0.001)]. The efficacy of AL with PCR-corrected cure rates ranging from 95.0 to 99.4% in per-protocol analysis, and 88.8 to 97.4% in intention-to-treat analysis. Based on the analysis, Cochrane chi-square test ($X^2$) test and inverse variance index ($I^2$) indicated that the included studies with heterogeneity ($X^2$=20.48, (df=14), $P$=0.116 and $I^2$=31.65%). The highest parasite positivity rate at day-3 was 5.7%. Adverse events ranged from mild to serious but were not directly attributed to the drug.

**Conclusion**: The present review has shown that AL is efficacious and safe for treatment of uncomplicated malaria in Ethiopia. However, few therapeutic efficacy studies were conducted in Ethiopia after treatment guideline was revised in 2004. AL has been used more than a decade in the study population without other alternative artemisinin-based combination therapy in Ethiopia and considering that the potential evolution of drug resistance is of a great concern, regular and continuous monitoring of its efficacy is warranted.


## Background

Malaria still represents a major public health issue in the tropics, with an estimated 228 million cases and 405,000 deaths in 2018[1, 2]. Approximately 92% of the cases and 93% of the deaths were from sub-Saharan Africa [1], and the only tool for treatment is a small arsenal of anti-malarial drugs [1, 2]. The pivotal losses of two key drugs (chloroquine and pyrimethamine) during the last few decades have led to millions of deaths [2]. The lost clinical efficacy of these compounds is suspected to have contributed to millions of additional malaria deaths in young African children in the 1980s [4].Since 2001, the World Health Organization (WHO) has recommended artemisinin based combination therapy (ACT) for uncomplicated malaria treatment in all endemic countries [4]. Five ACT recommended by WHO for treatment of uncomplicated *P .falciparum* malaria are: artemether-lumefantrine(AL), artesunate-amodiaquine(ASAQ), artesunate mefloquine(ASMQ), artesunate plus sulfadoxine-pyrimethamine(ASSP) and dihydroartemisinin-piperaquine(DHP) [6, 7]. Nearly all countries in sub-Saharan Africa recommend AL, ASAQ, or either of these regimens for the treatment of uncomplicated malaria [3, 7]. The Ethiopian Federal Ministry of Health (EFMoH) adopted AL as the first-line treatment of uncomplicated *P. falciparum* malaria in 2004 [8]. A 3-day AL treatment regime will cover three erythrocytic cycles with adequate concentration of the artemisinin component to kill parasites demonstrating a delayed clearance. Moreover, EFMoH and the World Health Organization (WHO) recommends use of single low-dose primaquine (0.25 mg/kg), a *P. falciparum* gametocytocidal drug; for blocking transmission in low-transmission areas in combination with ACT irrespective of glucose-6-phosphate dehydrogenase enzyme status [6, 7, 8].

Unfortunately, artemisinin resistance (ART-R), characterized by delayed *P. falciparum* clearance following treatment with artemisinin monotherapy or an ACT [9, 10], is now wide-spread in the Greater Mekong subregion (GMS), which consists of Cambodia, Thailand, Vietnam, Myanmar and Laos [11, 12].Mutations in the propeller domain of a kelch gene on chromosome 13 (PF3D7_1343700, K13 gene) constitute the primary determinant of ART-R [9, 13]. These mutations are suspected to reduce Pfkelch13 function, which is required for parasite-mediated endocytosis of host hemoglobin in the newly invaded intra-erythrocytic ring stages [14, 15]. The artemisinin agents are rapidly acting and significantly reduce the biomass of sensitive parasites corresponding to a single cycle of a sexual blood stage of *P. falciparum* in 48 h.The use of short acting artemisinin (half-life < 1 h) and long-lasting partnerdrug (lumefantrine, amodiaquine, or piperaquine) in ACT, has contributed to an estimated 30% reduction in global rate of malaria associated mortality in the past decade [1, 2, 3]. Pfkelch13 C580Y is the most widespread allele in Southeast Asia (SEA) [12, 16] and has recently been detected in Guyana [17] and Papua New Guinea [18]. Non-synonymous Pfkelch13mutations associated with delayed parasite clearance or day 3 positivity (day 3+) in the GMS (F446I, Y493H, R539T, I543T, P553L, R561H, P574L, C580Y, A675V) that are associated with elevated ring-stage survival rates in vitro and long parasite clearance half-lives (> 5 h), have only been rarely reported, if at all, in Africa[ 19, 20]. Resistance to the partner drugs piperaquine and mefloquine is also now common in the GMS, causing high rates of ACT treatment failure. Resistance selection might be less likely in Africa compared with other areas because of the high level of immunity in African populations, the high level of complexity of African infections, and other factors, which limit the emergence of relatively unfit resistant strains [21]. Nonetheless, resistance to multiple classes of antimalarial drugs has spread to Africa, and as transmission decreases in some areas, the likelihood of emergence of resistance might increase. Hence, monitoring the efficacy of anti-malarial drugs is a key component of malaria control and subsequent elimination.

Recent report from Rwanda showed that Pfkelch13R561H mutation was identified in 7.4% patients in Masaka. This study provides evidence for the de novo emergence of Pfkelch13-mediated artemisinin resistance in Rwanda, potentially compromising the continued success of antimalarial chemotherapy in Africa [22]. Besides,several case reports have described failed therapy with ACT in individuals who have returned to other countries after acquiring malaria in Africa;

A Chinese man presented in 2013 with *P falciparum* malaria in China about 6 weeks after returning from Equatorial Guinea, where he was treated for malaria six times over 20 months[23]. The patient was treated with directly observed DHP, and had persistence of parasitaemia on day 3 after initiation, but clearance by day 7; the infecting parasite had a K13 mutation; a switch from a methionine to an isoleucine at amino acid position 579 (M579I). Four patients in Sweden treated with AL in 2012-15[24], four patients in the UK treated with AL in 2015-16[25], and two patients in Italy treated with DHP in 2014-16[26, 27]; all with uncomplicated P falciparum malaria acquired in Africa, experienced late treatment failures. Most of these patients were non-immune European individuals, compliance with treatment regimens was uncertain, and all infecting parasites had wild-type K13PD sequences. Considering these case reports, treatment failures are of concern in Africa.

There have been some reports of delayed parasite clearance during routine therapeutic efficacy studies of ACT in Africa. However, these reports have not been consistent over time [28]. A study from the coast of Kenya in year 2005–2008 showed decreased rates of parasite clearance and increased recrudescence over time after treatment with AL or DHP. These results might suggest decreases in drug efficacy, but a more likely explanation is a decrease in antimalarial immunity in a region with decreasing malaria transmission intensity over this time frame [29]. In Uganda, among 78 children diagnosed with severe malaria, three had isolates with the Ala578Ser K13PD mutation, and parasite clearance was delayed in these children compared with the full cohort [30]. In a 2013 trial comparing AL and DHP for uncomplicated malaria, genotype-corrected recrudescence at 28 days was reported in 12% of children treated with AL in Zaire Province with cure rate of 88.1% (81–95) AL efficacy [31].A pooled analysis involving 1179 subjects in 2017 in Ethiopia also showed efficacy rates of AL, which are the first-line drug for uncomplicated falciparum malaria, was 97.1% (PCR corrected) [8]. Considering that the referred pooled-analysis data wasover the last three years, recent data are needed to update the understanding of the current efficacy of AL in Ethiopia according to WHO recommendations [28, 32, 33].

For the purpose of ensuring good performance and detection of emergence of resistance of anti-malarial drugs, especially those used as a first-line and second-line treatment in a country, the World Health Organization (WHO) recommends regular monitoring of their efficacy at least every two years in malaria-endemic countries [28]. In Ethiopia, the Federal ministry of Health (FMOH), in collaboration with its partners, including President's Malaria Initiative (PMI), research institutions, universities, WHO country office and Global fund, have been conducting regular therapeutic efficacy studies (TESs). The efforts of the FMOH to ensure regular TESs have also been complemented by TESs conducted by independent researchers. Thus, regular implementation of TESs is one of the priority activities of the FMOH, which provides useful data for monitoring the efficacy of AL for falciparum malaria and detecting emergence of drug tolerance/resistance to these and other anti-malarials used in the country. The findings of these studies have been used to guide the FMOH in reviewing and changing anti-malarial drug policy in the past [32, 33]

Although there are several studies that were conducted to assess the efficacy of malaria treatment agents yielding different success rates in Ethiopia, there has been no up-to-date systematic review and/or meta-analysis conducted that organized the available evidence about the outcome of malaria treatment. The present paper reviewed the implementation of *in-vivo* efficacy testing in Ethiopia after deployment of AL in order to monitor the efficacy of AL for the treatment of uncomplicated *P. falciparum* malaria. The paper compares the cure rates, parasite clearance and fever clearance times and safety data reported in efficacy study involving AL in Ethiopia that where published between 2004 and 2020. It provides updates on country-specific performance of AL after its wide scale deployment for treating uncomplicated falciparum malaria and provides evidence-based guidance for monitoring the early signs of artemisinin resistance and effective case management that will be critical in optimizing malaria control and containment efforts

## Methods

# Study protocol registration

This review was conducted in line with the 'preferred reporting items for systematic reviews and meta-analyses' (PRISMA) guidelines [34]. The completed PRISMA checklist is available in Additional file **1**: Table S1. The review protocol was registered in a repository of systematic review protocols prior to starting the research (PROSPERO, protocol number CRD42020201859) [35].

# Search strategies

The search strategy was performed using approaches that enhance methodological transparency and improve the reproducibility of the results and evidence synthesis. In this sense, the search strategy was elaborated and implemented prior to study selection, according to the PRISMA checklist as guidance [34]. Additionally, using the Population, Intervention, Comparison, Outcome and Study design (PICOS) strategy [36] we elaborated the guiding question of this review in order to ensure the systematic search of available literature: 'what is the therapeutic efficacy of AL for the treatment of uncomplicated falciparum malaria in Ethiopia over the last sixteen years?' The following major databases were searched: PubMed, Google Scholar, and ClinicalTrials.gov databases. In order to reflect contemporary practice, a search of the literature from the last 16 years (January 2004 to October 2020) was performed. The starting year (i.e., 2004) was purposely chosen because that was the year when Ethiopia adopted use of AL for treating uncomplicated falciparum malaria [8]. The date of the last search was 30th October 2020.

The search terms were developed in line with the Medical Subject Headings (MeSH) thesaurus using a combination of the big ideas (or "key terms") which derived from the research question. The domains of the search terms were: "efficacy", "therapeutic efficacy", "artemether-lumefantrine", "Coartem", "*Plasmodium falciparum* malaria", "faciparum malaria", "antimalarial drug", and "Ethiopia". We combined these terms using the Boolean operator "OR" and "AND" accordingly [37]. Search was limited to studies published in English language until October 2020. Full search strategy for the databases is provided in Additional file **2**: Table S2. Two reviewers (AbAb, and WA) reviewed the search results independently to identify relevant studies. Also, the bibliographic software EndNote X5 citation manager (Thomson Reuters, New York, USA) was used to store, organize and manage all the references and ensure a systematic and comprehensive search.

## Study selection criteria

Interventional and observational studies that have been published in the last sixteen years (2004 to 2020) in English language and reported the therapeutic efficacy of AL for the treatment of uncomplicated falciparum malaria in Ethiopian context were included. A summary of the participants, interventions, comparators and outcomes considered, as well as the type of studies included according to PICOS strategy, which is provided in Additional file **3**: Table S3.

## Screening and data extraction

Initial screening of studies was based on the information contained in their titles and abstracts and was conducted by two independent investigators (AbAb and WA). When the reviewers disagreed, the article was re-evaluated and, if the disagreement persisted, a third reviewer (DaYi) made a final decision. Full-paper screening was conducted by the same independent investigators.

Data were extracted using a case record form (CRF), including four domains: (1) identification of the study (article title; journal title; authors name; country of the study; language, publication year and study setting); (2) methodological characteristics (study design; stated length of follow-up; sample size; sex; age; intervention details; literature quality assessment characteristics; statistical analyses etc.); (3) main findings(treatment success rates; parasite clearance; fever clearance; adverse events) and (4) conclusions. We base our primary outcome measures on WHO recommendations[28] which advises a 28-day follow-up to capture treatment outcome as follows: treatment failure (early treatment failure (ETF), late parasitological failure (LPF), late clinical failure (LCF)), and the cure rate in terms of adequate clinical and parasitological response (ACPR) were extracted from each study. If the outcome data in the original article were unclear, the corresponding author was contacted via email for clarification. For data extraction, two independent Microsoft Excel spread-sheets were elaborated for two reviewers (AbAb and WA) to summarise the data from the included studies. Then, the spreadsheets were combined into one. Discrepancies between the authors were resolved by adequate discussion.

## Quality assessment

Methodological quality of the reviewed studies was assessed through sensitivity analysis, which classified the included studies into high quality and low quality according to modified Jadad scale [38] and the strengthening the reporting of observational studies in epidemiology (STROBE) statement for observational studies [39]. The modified Jadad scale included eight items: randomization, blinding, withdrawals, dropouts, inclusion/exclusion criteria, adverse effects and statistical analysis. The total score for each article ranged from 0 to 8 and was computed by summing the score of each item. Low quality studies wielded scores of 0 to 3, and high quality studies achieved scores of 4 to 8. The observational studies were categorized as low quality with a score under 75% of the STROBE checklist and high quality with a score over 75% of the STROBE checklist. The reviewers independently assessed the quality of the methodology of included studies. Fortunately all of the articles were found to be of good quality (Additional file **4**: Table S4).

## Risk of bias in individual studies

All or most of the studies had high risk of bias because most were open-label, single-arm studies. Open label, single-arm studies/trials have a high risk of bias by their nature (i.e. considered to have an inherent high risk of bias); therefore, they were not further assessed for bias.

## Synthesis of results

The data extracted from the included studies were fed into Microsoft Excel. Descriptive statistics, such as simple counts, ranges, and percentages, were used to present the synthesized data. A systematic narrative synthesis was provided in which summary results were presented using text and table. To compute the pooled ACPR with its 95% CI, meta-analysis was done using OpenMeta Analyst software for Windows [40] assuming a random effect model. In this review, following AL therapy, the primary endpoint (or efficacy evaluation) was cure rate (or ACPR), corrected to exclude re-infection using polymerase chain reaction (PCR), at day 28. Statistical heterogeneity was evaluated with the Cochran chi-square test ($X^2$) test and inverse variance index ($I^2$). A *P*-value of < .10 and/or an $I^2$ statistic > 50% as indicating substantial heterogeneity[41].

## Publication bias

Assessments for publication bias were made by visual inspection for asymmetry in a funnel plot and the Egger's test [42, 43]. Egger's linear regression and rank correlation tests are statistical tests for examining the association between the effect estimates and their standard errors (SEs). A funnel plot with asymmetry or Egger's test with *P*-value < 0.1 suggests publication bias.

## Outcome definitions

The definition of the following terms was adopted from cited references [7, 28, 41, 44]. Adequate clinical and parasitological response (ACPR): refers to *P. falciparum* parasitological clearance at day 28 irrespective of axillary, oral, rectal or tympanic temperature without previously meeting the criteria of early treatment failure or PCR corrected late treatment failure. Early treatment failure (ETF): signs of severe malaria/clinical deterioration requiring rescue medication on days 0, 1, 2, or 3, in the presence of *P. falciparum* parasitemia. Late clinical failure (LCF): signs of severe malaria/ clinical deterioration requiring rescue medication after day 3 in the presence of *P. falciparum* parasitemia, without previously meeting any of the criteria of ETF. Late parasitological failure (LPF): presence of *P. falciparum* parasitemia on any day from day 7 onward and the absence of fever without previously meeting any of the criteria of ETF/or LCF. PCR-corrected: refers to the use of molecular testing to differentiate recrudescence from re-infection when evaluating efficacy. Recurrent parasitemia classified as recrudescence if it was due to the same parasite strain as that on day 0 (if similar alleles were found in the pre- and post treatment samples) and as a new infection if it was due to a genetically different strain (if the alleles of the pre- and post treatment samples were distinct).

AEs were defined as ' signs and symptoms that first occurred or became more severe post- treatment' or 'as a sign, symptom, or abnormal laboratory value not present on day 0, but which occurred during follow-up, or was present on day 0 but became worse during follow up'. Serious adverse events were defined

according to International Conference on Harmonization (ICH) guidelines. Studies included and excluded in this review are shown in Additional file **3**: Table S3. Studies were excluded, if they did not meet the inclusion criteria.

## Results

### Literature search results

A total of 1043 studies were retrieved from the database and manual searching. Among these, 724 duplicated studies were excluded. From the remaining 319 articles, 303 of them were excluded after evaluation of their title and abstract confirming non relevance to this study and one paper [45] was excluded following full text review as data collection for the study was conducted before official adoption of AL in Ethiopia. Finally, a total of 15 papers were met the eligibility criteria and were included in this systematic review and meta-analysis (Fig. 1).

## Baseline characteristics of studies conducted to test the efficacy of AL in Ethiopia

The summary characteristics of the included studies are shown in Table 1.Fifteen studies satisfied the inclusion criteria and were included in this systematic review and meta-analysis with a total sample size of 1523 participants that ranged from 60 patients [46] to 315 patients [47]. Seven of the studies were interventional [47, 48, 49, 50, 51, 52, 53], and the other eight studies were observational study [46, 54, 55, 56, 57, 58, 59, 60].These studies were conducted in different malarious parts of the Country with varied transmission intensity **(**Fig. 2). Most (10/15, 66.7%) of the studies included patients who were ≥ 6 months of age(Table 1).Treatment outcomes in all studies were assessed using clinical and parasitological criteria according to WHO guidelines [28, 61, 62].In majority of the studies(86.7%), treatment compliance was assured by supervised administration of the study drug under direct observation on days 1, 2 and 3, i.e. the morning doses were directly observed over 3 days, while the evening doses were given to patients for intake at home by health extension workers. The endpoint was day 28 in all studies, while one study compared drug efficacy on both day 28 and/or day 42 [28]Table 1.

Table 1
Summary characteristics of included studies on the efficacy and safety of artemether-lumefantrine for treatment of uncomplicated *P. falciparum* malaria in E 2004–2020(N = 1523)

| Study[ Ref.No] | Study Settings | Study design | Study duration (Months) | Inclusion for age | Transmission level | Patient Enrolled (N)[a] | Patient available (n)[b] | Mean Hg | Pf-GMPD | Length of follow up (days) |
|---|---|---|---|---|---|---|---|---|---|---|
| Abamecha A et al. 2020[48] | Ilu-Harar Health Center, Chewakadistrct, Ethiopia | Open-label single-arm study | September-December 2017 | Above 6 months of age | Moderate | 80 | 76 | 11.7 | 12374.3 | 28 |
| Teklemariam M et al. 2017[54 ] | SetitHumera, Northwest Ethiopia | Open-label single-arm study | October 28, 2014 and January 9, 2015 | ≥ 6 months of age | High | 92 | 79 | 13.2 | 27798.0 | 28 |
| Deressa T et al. 2017[58] | Kola Diba Health Center (KHC) in the Dembia district, Northwest Ethiopia | Prospective observational cohort study | April 2015 to February 2016 | Above 6 months of age | High | 80 | 75 | n/a | 8377.8 | 28 |
| Nega D et al. 2016[52] | Metehara Health Centre, Eastern Ethiopia | Open-label single-arm study | October 2014 to January 2015 | ≥ 6 months of age | Low-moderate | 91 | 85 | 12.4 | 11509.6 | 28 |
| Wudneh F et al. 2016[60] | Gendewuha (Metema) Health Center, Northwest Ethiopia | One-arm prospective, observational cohort study | October 2014 to January 2015 | Above 6 months of age | Moderate | 91 | 81 | 13.7 | 13441.6 | 28 |
| Kanche ZZ et al. 2016 [59] | Baddessa Health Center,Wolaita Zone, Southern Ethiopia Wolaita Zone, Southern Ethiopia | One arm, prospective observational cohort study | February - March 2015 | > 5 years old | Moderate | 86 | 88 | 10.8 | 4238.8 | 28 |
| Mekonnen SK *et al.* 2015[50] | Omo Nada health center in southwestern Ethiopia | Open-label, single arm, *In-vivo* therapeutic efficacy study | August-December 2011 | Above 6 months of age | Moderate | 88 | 86 | 11.6 | 8404.0 | 28 |
| Ebstie YA et al. 2015[57] | Bahir Dar district, Northwest Ethiopia | Prospective observational cohort study | March and July 2012 | > 5 years old | Moderate | 93 | 89 | 10.8 | 8675.3 | 28 |
| Getnet G et al. 2015[51] | Enfranze Health Centrer, Northwest Ethiopia | One-arm, *In-vivo* therapeutic efficacy study | January and May 2013 | Above 6 months of age | Moderate | 134 | 130 | 12.3 | 7898.0 | 28 |
| Mulu A et al. 2015[55] | Kemisie Health Center, Northeast Ethiopia | Prospective observational cohort study | September, 2012 to May, 2013 | Above 6 months of age | Moderate | 80 | 80 | NR | 10454.0 | 28 |
| Eshetu T et al. 2012[47] | Agaro Health Centre, Jimma Health Centre, Serbo Health Centre, and Asendabo Health Centre | Open-label, single arm, *In-vivo* therapeutic efficacy study | November 2008 and January 2009 and between August and December 2009 | > 1 year | Moderate | 348 | 315 | NR | 9720.0 | 28/42 |

**Key**: N/R: Not reported; TES: Therapeutic efficacy study Hg: Hemoglobin; Pf-GMPD:*Plasmodium falciparum*geometric mean parasite density of asexual paras microlitre of blood

[a] *P.falciparum*patients enrolled in study as per manuscript

[b]Patients available for analysis from study

| Study[ Ref.No] | Study Settings | Study design | Study duration (Months) | Inclusion for age | Transmission level | Patient Enrolled (N)[a] | Patient available (n)[b] | Mean Hg | Pf-GMPD | Length of follow up (days) |
|---|---|---|---|---|---|---|---|---|---|---|
| Kinfu G et al. 2012[46] | Tumuga health center Alamatadistrict,Tigrai regional state, North Ethiopia | Prospective observational cohort study | August–November 2009 | Above 6 months of age | Moderate | 66 | 60 | N/R | 20672.0 | 28 |
| Hwang J et al. 2011[49] | Bishoftu Malaria Clinic and Bulbula Health Center, Oromia Regional State, Ethiopia | Open-label, single arm, *In-vivo* therapeutic efficacy study | October and November 2009 | Above 6 months of age | Moderate | 73 | 71 | 12.6 | 16374.0 | 28/42 |
| Assefa A et al.2010[53] | Serbo Health Center, Kersa District, Southwest, Ethiopia | *In-vivo* therapeutic efficacy study | November 2007 and January 2008 | N/R | Moderate | 119 | 112 | 12.2 | 22660.0 | 28 |
| Kefyalew T et al. 2009[56] | AlabaKulito Health Center, Southern Ethiopia | *In-vivo* therapeutic efficacy study | October - December 2007 | > 1 year | Low - moderate | 102 | 102 | 11.4 | 8264.3 | 28 |

**Key**: N/R: Not reported; TES: Therapeutic efficacy study Hg: Hemoglobin; Pf-GMPD:*Plasmodium falciparum*geometric mean parasite density of asexual paras microlitre of blood

[a] *P.falciparum*patients enrolled in study as per manuscript

[b]Patients available for analysis from study

# Treatment outcome

Meta-analysis was conducted to investigate the overall treatment outcomes of AL across the included studies in the different areas of Ethiopia(Fig. 2). From the analyses of 15 studies included, only seven studies used PCR-corrected cure rates of AL [47, 48, 49, 50, 51, 52, 53] while PCR-uncorrected AL cure rates were used for the remaining studies. Overall, a significant high malaria treatment success of 98.4% (95% CI 97.6–99.1)(Fig. 3) was noticed. PCR-corrected AL treatment successrate of 98.7% (95% CI 97.7–99.6) (Fig. 4) was observed. The proportion of recurrence infection, ranging from 1%-5.6% at 28-day follow-up period after treatment with AL.

The PCR-corrected cure rates of AL ranged from 95.0 to 99.4% in per-protocol analysis and 88.8 to 97.4% in intention-to-treat analysis.The percentage of ACPR and the 95% CI are presented in Table 2.The highest cure rate 99.4 %( 95% CI 97.4–100.0) was reported by study conducted in Jimma Zone, Southwest Ethiopia in 2012[47], and97.4%(95% CI: 93.9–100) reported by study conducted in Bishoftu Malaria Clinic and Bulbula Health Center, Oromia Regional State, Ethiopia 2011[49].

Table 2
Treatment Outcome of AL Therapy reported in efficacy studies in Ethiopia

| Study | PP PCR-corrected percentage cure rate (95% CI), day-28 | ITT PCR-corrected percentage cure rate (95% CI), day-28 |
|---|---|---|
| Abamecha A et al. 2020 | 96.0(91.6–100) | 94.9(90.1–99.8) |
| Nega D et al. 2016 | 98.8(96.5–100) | 92.2(86.7–97.8) |
| Mekonnen SK *et al.* 2015 | 97.8(94.7–99.8) | 96.7(93.0-100) |
| Getnet G et al. 2015 | 95.0(90.2–100) | 97.4(93.9–100) |
| Eshetu T et al. 2012 | 99.4(97.4–100) | 89.9(86.7–93.1) |
| Hwang J et al. 2011 | 99.1(91.6–100) | 94.1(89.9–98.3) |
| Assefa A et al.2010 | 96.3(92.3–100) | 88.8(82.2–95.3) |

# Fever and parasite clearance rate

Among the five partially supervised efficacy studies that reported fever clearance, more than 75% of the patients cleared fever by day 1 post-treatment with AL [50, 51, 52, 54, 55].Some authors did not measure fever clearance on subsequent days post drug administration and only choose day-3 for this clinical

measurement [53, 57].Among the fifteen studies that reported parasite clearance, five studies showed day-3 parasitaemic cases of 5.7%,5.1%, 5%, 3.9 and 3.8%[48, 51, 57, 58, 59].Table 3shows the overall progress of fever and parasite clearance in the first three days of AL treatment.

Table 3
Fever and parasite clearance reported in efficacy studies in Ethiopia (2004–2020)

| Study | Patient Enrolled (N) | Patient available | Patient Included | Fever clearance (%) | | | Parasite clearance (%) | | | Supervised |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | D1 | D2 | D3 | D1 | D2 | D3 | |
| Abamecha A et al. 2020 | 80 | 76 | 72 | 52.5 | 87.2 | 97.5 | 61.2 | 81.2 | 96.2 | Partial |
| Teklemariam M et al. 2017 | 92 | 79 | 78 | 80.0 | 97.8 | 100.0 | 33.0 | 84.4 | 100.0 | Partial |
| Deressa T et al. 2017 | 80 | 75 | 69 | 62.5 | 93.7 | 97.5 | 67.5 | 85.0 | 95.0 | Partial |
| Nega D et al. 2016 | 91 | 85 | 83 | 78.7 | 94.3 | 97.7 | 69.7 | 95.5 | 100.0 | Partial |
| Wudneh F et al. 2016 | 91 | 81 | 80 | 69.6 | 97.8 | 100.0 | 23.6 | 91.0 | 100.0 | Partial |
| Kanche ZZ 2016 | 88 | 86 | 86 | N/R | 59.1 | 93.2 | N/R | 72.2 | 94.3 | Partial |
| Mekonnen SK *et al.* 2015 | 93 | 89 | 84 | 88.1 | 94.4 | 100.0 | 88.8 | 96.6 | 100.0 | Partial |
| Ebstie YA et al. 2015 | 134 | 130 | 128 | NR | NR | 87.9 | NR | 85.9 | 96.1 | Partial |
| Getnet G et al. 2015 | 80 | 80 | 74 | 75.0 | 91.3 | 96.2 | 73.8 | 91.3 | 94.9 | Partial |
| Mulu A et al. 2015 | 66 | 60 | 58 | 89.4 | 98.5 | 100.0 | 84.8 | 93.9 | 100.0 | NR |
| Eshetu T et al. 2012 | 348 | 315 | 312 | NR | 96.7 | 99.1 | NR | 98.2 | 99.4 | non-supervised |
| Kinfu G et al. 2012 | 73 | 71 | 69 | NR | NR | 100.0 | NR | 100.0 | 100.0 | Partial |
| Hwang J et al. 2011 | 119 | 112 | 111 | 65.2 | 90.5 | 93.0 | NR | 93.1 | 99.1 | Partial |
| Assefa A et al.2010 | 90 | 82 | 79 | NR | NR | 100 | 98 | NR | 100.0 | Partial |
| Kefyalew T et al. 2009 | 102 | 102 | 102 | 44.1 | 82.4 | 93.1 | NR | NR | NR | Partial |

## Safety outcomes

The current meta-analysis showed that twelve (80%)out of the included studies (15) reported adverse drug reactions (ADRs)to AL which were observed in 36.1%, (550/1523)patients. All of the ADRs were mild and resolved spontaneously. Two serious adverse events (SAE) were observed (Additional file **6**: Table S5).

## Quality assessment

Seven interventional studies [47, 48, 49, 50, 51, 52, 53] were assessed using the modified Jadad scale [38] with high qualities with a value score of 4 (Additional file **4**: Table S4) and while the remaining eight observational studies [46, 54, 55, 56, 57, 58, 59, 60] were assessed with the STROBE statement [39]with high qualities a range of 81.8 % to 91 % (Additional file **4**: Table S4.).

## Assessment of publication bias

The lack of funnel asymmetry in the results of the Egger's test (*P-value* = 0.58) suggest no clear evidence of publication bias (Additional file **5**: Table S5). However, these assessments for publication bias should be interpreted with the caution in the setting of limited numbers of studies and the inclusion of studies with small sample sizes [42, 43].

## Discussion

The findings of this review showed that 15 therapeutic efficacy studies have been conducted to monitor the efficacy of AL after Ethiopia adopted AL in 2004 for treatment of uncomplicated faciparum malaria. This therapeutic efficacy monitoring results from different malarious parts of the Country with varied transmission intensity demonstrate that the AL in use in Ethiopia are still highly efficacious (> 90%)against falciparum malaria, in accordance to the WHO parameters [28], while there is minor variation between the efficacies of AL by study settings. The main finding of this meta-analysis is the high success rate of AL (PCR-corrected ACPR > 98%) in the treatment of uncomplicated falciparum malaria in Ethiopia, suggesting that the AL has retained its ability to treat uncomplicated malaria despite its use in Ethiopia for more than 16 years. Previous meta-analysis reports in 2017 revealed similarly high efficacies of AL [67, 68]. This result is also consistent with neighboring Sudan, a high treatment success rate (98%) of malaria treatment was recently reported in a meta-analysis which included 20 studies with a total of 4070 patients [69].The cure rate 98.7% (95% CI 97.7–99.6) found in this study suggests that, in accordance with WHO parameters [28], AL is still effective as first-line drug for uncomplicated malaria treatment in Ethiopia, but a regular monitoring is necessary.

Artemether is absorbed quickly; peak concentrations of artemether and its main active metabolite, occur at approximately two hours post-dose, leading to a rapid reduction in asexual parasite mass and a prompt resolution of symptoms. Lumefantrine is absorbed and cleared more slowly (terminal elimination half-life 3–4 days in malaria patients), and accumulates with successive doses, acting to prevent recrudescence by destroying any residual parasites that remain

after artemether [70]. There is a concern about the limited post-treatment prophylactic effects of AL in high transmission areas. In this study the proportion of recurrence infection ranging from 1% -5.6% at 28-day follow-up period after treatment with AL. In fact in one study, most recurrent parasitaemia occurred after day 28[47]. The recurrent parasitaemia rate in children ≤ 5 years was surprisingly high with 9.4% in this study which suggests that the partner drug cannot give prolonged protection despite high therapeutic efficacy [71].This observation has also been reported in Democratic Republic of Congo reported high level of resistance to lumenfatrine [72] that threatens the therapeutic usefulness of AL and further monitoring is urgently needed in all malaria-endemic countries where AL is the first-line anti-malarial drug. In most of the studies, a great majority of the recurrent infections were due to re-infections, when assessed with a step-wise PCR genotyping protocol, which signifies that the drugs are still efficacious and the high rates of re-infections could only be attributed to high malaria transmission. In terms of clinical practice, the high re-infection rates are of great concern among clinicians. Clinicians should be clearly guided on what to expect and how to handle such cases with recurrent infections within a period of three to eight weeks post-treatment. The observed high re-infection rates after AL treatment underscores the importance of integrating treatment with the transmission-blocking drugs (e.g. use of Primaquine (gametocytocidal)) and non-therapeutic prevention and control measures (insecticide-treated bednets, indoor residual spraying and other vector control measures) so as to effectively block malaria transmission and prevent recurrent infections [3, 73].

Measurement and reporting of parasite clearance on day-3 after treatment with ACT is particularly important, as this is one of the first signals of emergence of parasite tolerance/resistance to artemisinin [74]. In the present review, five studies showed day-3 parasitaemic cases of 5.7%, 5.1%, 5%, 3.9 and 3.8% after treatment with AL [3, 13 63, 69, 74].However, the day-3 parasite-positive cases are below the 10% threshold recommended by WHO for suspected emergence of artemisinin resistance [74, 75]. Although the proportion of patients with detectable parasitaemia on day 3 serves as a simple measure of parasite clearance time at the population level [74, 76], it is often influenced by the baseline parasite density and the timing of parasite sampling, which can vary within and across studies. On the contrary, parasite clearance half-life doesn't depend on baseline parasite density and is thus considered a more reliable indicator of changes in parasite susceptibility to artemisinin. Clinically, artemisinin resistance manifests as delayed parasite clearance with parasite clearance half-life (PC1/2) exceeding 5 h, resulting in lingering parasitaemia 3 days after initiation of the treatment [77]. Accurate determination of parasite PC1/2 requires sampling of peripheral parasitaemia every 6 h after administration of the artemisinin drug [78]. In resource-limited settings, the day-3 parasite-positive rate can be used as a proxy measure of delayed parasite clearance [74]. Artemisinin resistance affects the ring stage, and dormant ring-stage parasites are able to endure the onslaught of artemisinins and later cause recrudescence of the disease [79]. To capture the ring stage-associated resistance phenotype, an in -vitro or ex-vivo ring-stage survival assay (RSA) measuring the proportion of the 0–3 h ring-stage parasites surviving 6 h of 700 nM dihydroartemisinin treatment was developed [80, 81]. However, most of the studies reviewed in this article were based on 24-hour sampling, which is not the recommended method for assessing parasite clearance and detection of tolerance/resistance to artemisinins.

The safety of AL was assessed by recording the nature and incidence of solicited and unsolicited adverse events and serious adverse events. An adverse event was defined as any undesirable medical occurrence (symptoms, signs or laboratory findings) in a patient once they were enrolled to the studies regardless of whether it was related to the treatment. Adverse events were judged according to their causal association with AL (unlikely, possible and probable) and severity (mild, moderate or severe) [7].In this review, mild adverse events (a headache, cough, fever, diarrhoea, vomiting, perioral ulcer, anorexia, abdominal pain, dizziness and nausea, weakness/fatigue and others) were reported and almost all were resolved soon after completion of the treatment except cough [48, 53, 54]. Similar mild adverse events have been associated with AL, the most common being headache, fever, vomiting followed by gastrointestinal disturbances [65, 69].The observed rate of 36.1%, (550/1523)ADRs was comparable with the rate reported in the previous review in Ethiopia where 269 of 633 patients had ADRs, with a pooled event rate of 41.2% [68].

From the included studies one study reported serious adverse events (SAE) in two infants [47]. These infants had SAE on the day of presentation (day-0) with high parasitaemia (> 95,000/μL), no signs of severe malaria were noticed at admission and did not tolerate oral treatment. After re-dosing and repeated vomiting, the infants were referred to the ward for intravenous treatment; one died the same day. The cause of death was not established and its possible association with AL treatment could not be ascertained. However, close monitoring of patients with a possibility of progressing to severe disease due to danger signs or high parasitaemia(> 100,000 asexual parasites/μl) has been recommended and will be undertaken in future studies.

# Limitation of the review

This review was intended to assess the implementation of the WHO recommendations of undertaking regular monitoring of antimalarial efficacy studies and also provide Ethiopia-specific current efficacy and safety profile of AL in the treatment of uncomplicated falciparum malaria. The main limitation of this work was the insufficient number of therapeutic efficacy studies (TESs) studies with high-quality and more rigorous design, which prevents us from making a firm conclusion. This may be due to the fact that TESs and long-term follow-up of patients require logistics and incur high cost in the African setup, limiting regular implementation of clinical evaluation within the country. The current study however is the first most comprehensive effort at highlighting the levels of implementation of TESs in Ethiopia and provides an overall country-specific performance of AL after their wide-scale deployment in 2004 as first-line anti-malarials for treating uncomplicated *P. falciparum* malaria in the country.

# Future studies

Given the documentation of K13-propeller polymorphism as a molecular marker for monitoring resistance of artemisinin and its derivatives [20, 21, 22] and recent emergence of Rwandan *Pfkelch13* 561H mutants are the product of recent de novo local emergence confirms that local emergence of ART-R is possible in Africa, especially in high transmission settings [22], future AL efficacy studies should incorporate assessment of this marker as a tool to track parasite tolerance or any changes in parasite sensitivity to AL in the country.

## Conclusions

The present review has shown that few studies have been conducted in Ethiopia to monitor the efficacy and safety of AL. However, the finding revealed that treatment success rate of 98.7% (95% CI 97.7–99.6) was reasonably high and the drug was safe when used for treatment of uncomplicated *P. falciparum* infections in Ethiopia. This findings support continued use of AL for the treatment of uncomplicated falciparum malaria in Ethiopia. More surveillance and monitoring of anti-malarial efficacy and safety should be performed to detect future changes in parasite sensitivity to AL.

## Declarations

# Data availability

All generated data about the review are included in this manuscript. The original data can be accessed from the corresponding author at any time.

# Competing interests

The authors declare that they have no competing interests.

# Author contributions

AbAb and DaYi conceived and designed the review. AbAb and WA conducted the review and synthesized the findings. AbAb conducted the analysis and wrote the first draft of the manuscript. AbAb, DaYi, WA, DeYe and AlAb revised and edited the manuscript. All authors read and approved the final version of the manuscript.

# Acknowledgments

We thank the German Academic Exchange Service (DAAD) and Jimma University, Ethiopia for supporting this review.

# Ethics approval and consent to participate

The PRISMA guideline [34] (Additional file**1:** Table S1.) recommendations were used and strictly followed to carry out this systematic review and meta-analysis. Ethical approval is not recommended and was not needed since it is a systematic review and meta-analysis.

Consent for publication
All authors have given their consent for publication

Funding
This project was supported in part by DAAD In-Country/In-Region scholarship program 2017. The funders had no role in study design

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## Figures

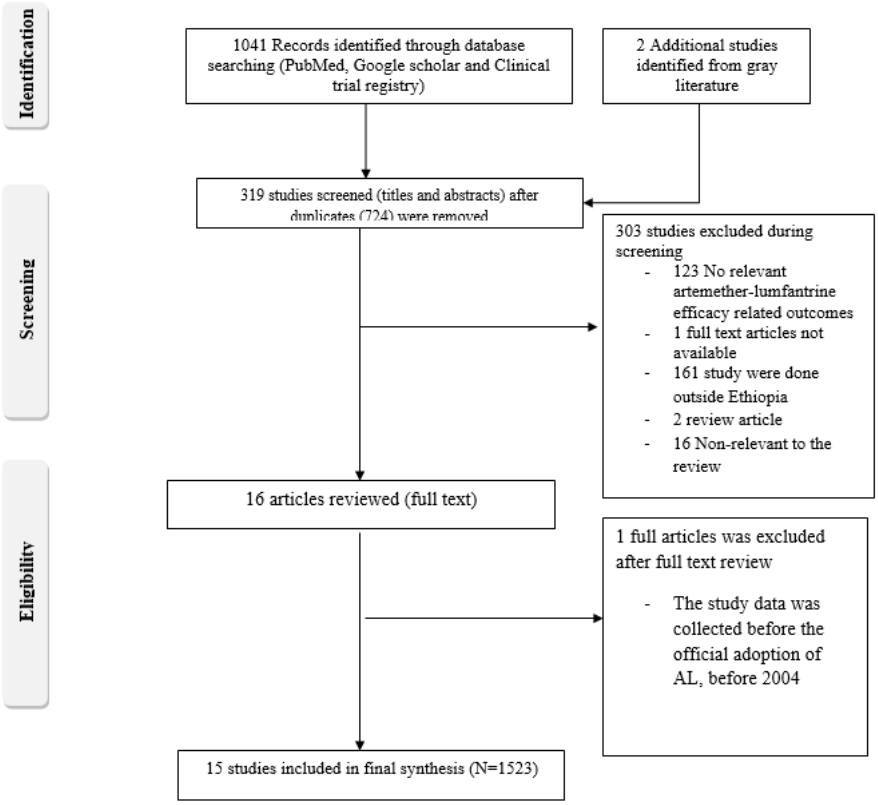


**Figure 1**

PRISMA flow diagram showing study selection process, 2020

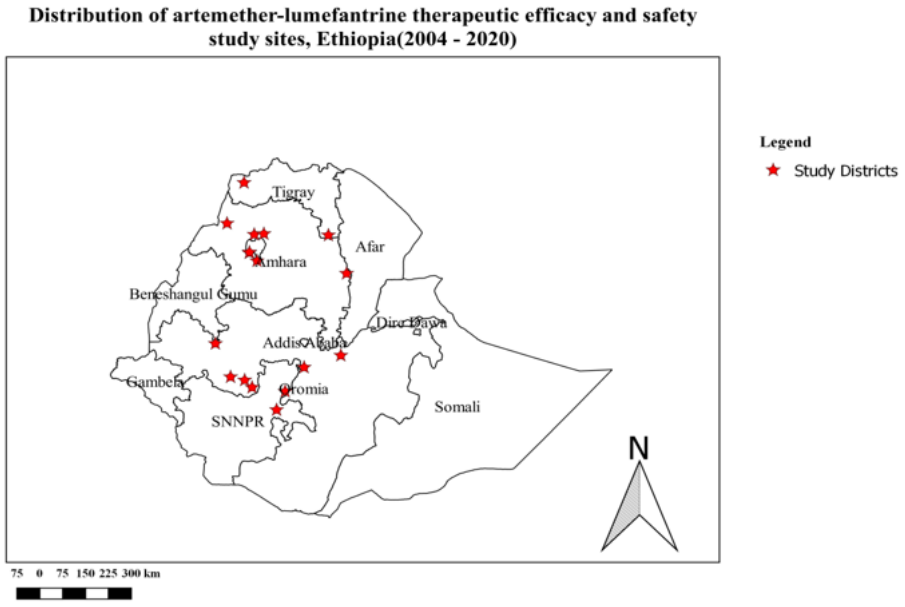


**Figure 2**

Distribution of artemether-lumefantrine efficacy and safety study sites in Ethiopia from 2004-2020. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

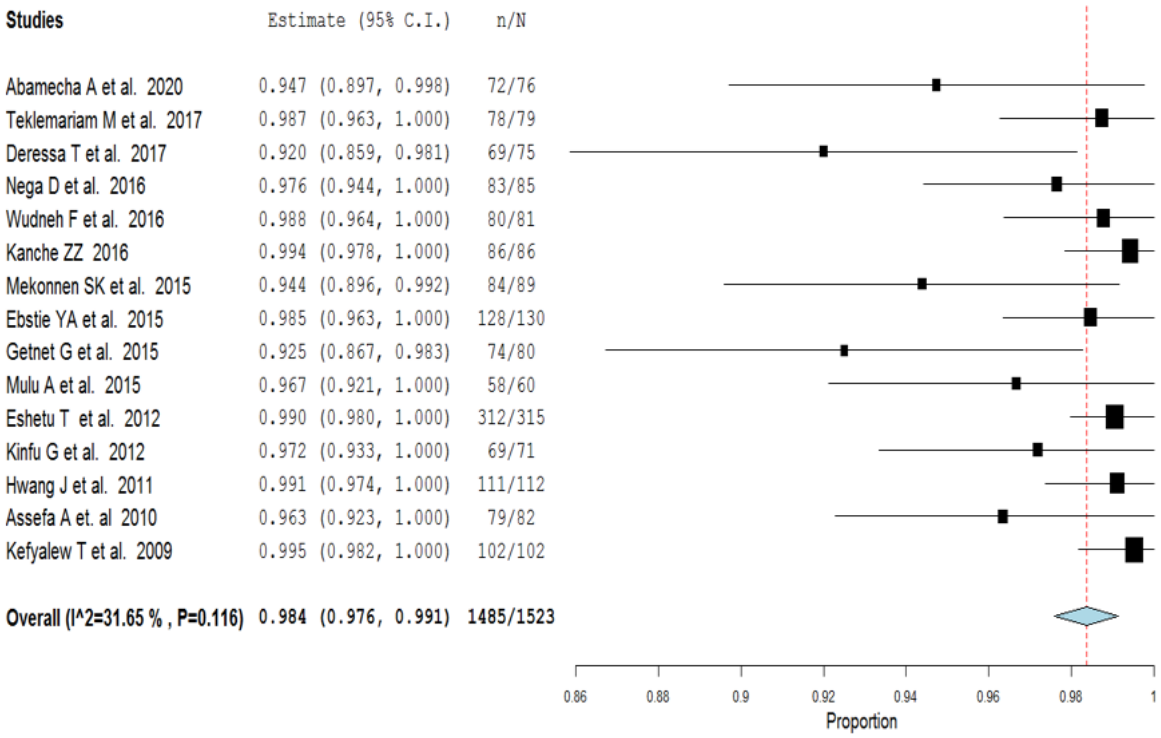


**Figure 3**

The overall treatment success of artemether-lumefantrine therapy

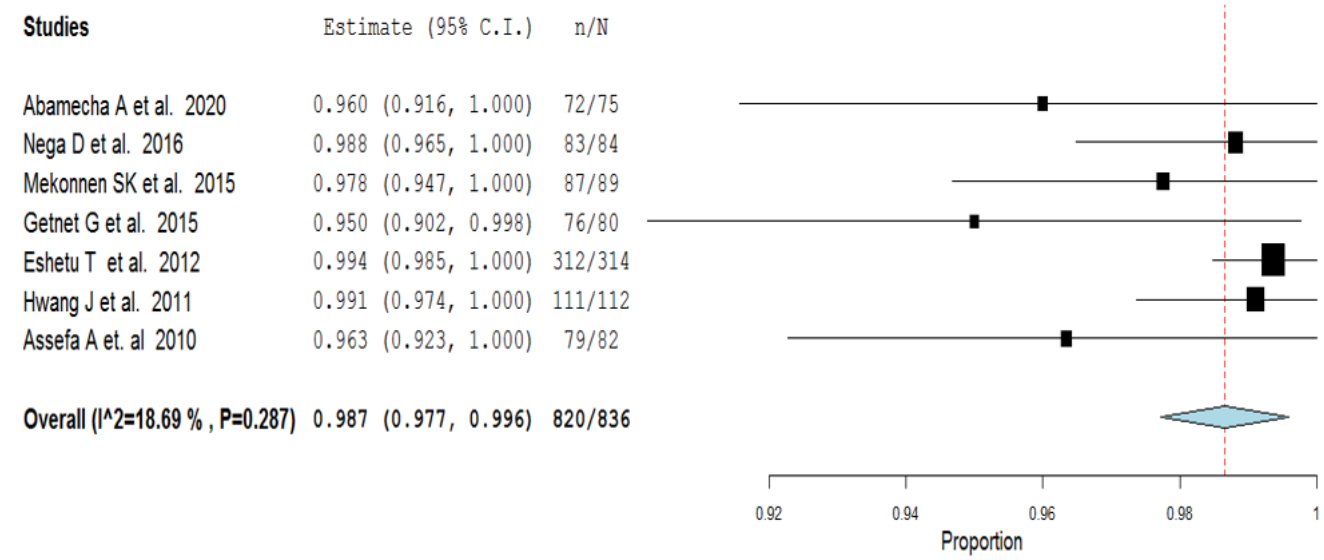


**Figure 4**

PCR-corrected treatment success of artemether-lumefantrine therapy

## Supplementary Files

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