Clinical Efficacy and Safety of Artemisinin-based Combination Therapies in the Treatment of Uncomplicated *Plasmodium Falciparum* Malaria in Cameroon: A Systematic Review and Meta-Analysis from Individual Patient Data (2004-2020)

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Abstract

Background: Cameroon remains a high malaria endemic country. The rapid emergence and spread of *Plasmodium falciparum* resistant parasites compelled the World Health Organisation (WHO) to recommend the change from monotherapies to artemisinin-based combination therapies (ACTs). This study aimed to assess the clinical efficacy and safety of artemisinin-based combination therapies in the treatment of uncomplicated *Plasmodium falciparum* malaria in Cameroon from 2004 to 2020.

Methods: The preferred reporting items for systematic review and meta-analysis (PRISMA) statement were adopted for the selection of studies. The heterogeneity of the included studies was determined using Cochrane Q and the $I^2$. The random effects model was used as standard to combine studies showing heterogeneity of Cochrane Q with $P<0.10$ and $I^2 > 50$.

Results: Out of the 4,920 articles and unpublished datasets screened, 16 records with a sample size of 3,737 participants on 8 generic ACTs fulfilled the inclusion criteria. The per protocol (PP) analysis pooled efficacy of the ACTs was 97.9% (95% CI, 97.2-98.7, $P<0.01$). Sub-group analyses were performed for ASAQ, AL and DHAP. The aggregated efficacies of ASAQ, AL and DHAP were 97.5% (95% CI, 96.3-98.8, $P<0.01$), 99.4% (95% CI, 98.6-100.0, $P=0.39$), 98.0% (95% CI, 96.3-99.7, $P=0.28$) respectively. The pooled efficacies were above the WHO minimum benchmark of 90.0%. The ACTs are well tolerated and common adverse events reported were asthenia, diarrhoea, abdominal pain, anorexia, nausea and vomiting, headache and dizziness.

Conclusion: This study reported a high pooled efficacy for all ACTs. AL and DHAP were found to have higher cumulative efficacies than ASAQ. The ACTs are still efficacious and well tolerated for the treatment of malaria in Cameroon. However, there is need for continuous monitoring of efficacy of ACTs despite the high cure rates as resistance seems inevitable.

Background

Malaria is a major public health disease in Cameroon with *Plasmodium falciparum* responsible for most of the cases [1]. In 2018, malaria accounted for 228 million cases and 405,000 related deaths worldwide (1). Early diagnosis and treatment of clinical cases remain the main tools for the control of malaria in several regions of Africa [2]. In Cameroon, until 2002, the first-line recommended therapy for uncomplicated falciparum malaria was chloroquine (CQ) and later amodiaquine (AQ) monotherapy between 2002 and 2004 [3]. However, this policy was threatened by the emergence and spread of *Plasmodium falciparum* resistance to chloroquine (CQ), amodiaquine (AQ) and sulphadoxine-pyrimethamine (SP) in most malaria endemic countries. This resulted in major challenges to malaria control in sub-Saharan Africa [2, 4]. Parasite resistance to monotherapies compelled WHO to recommend combination of dual or triple therapy, which combines molecules with independent modes of action or distinct target enzymes [5]. Therefore, WHO recommended the adaptation and implementation of artemisinin-based combination therapies (ACTs) as the first-line treatment for malaria since early 2000 in
most countries with endemic *P. falciparum* malaria (6). Five ACTs are currently recommended by WHO for the treatment of uncomplicated *Plasmodium falciparum* infection: artemether-lumefantrine (AL), artesunate-amodiaquine (ASAQ), artesunate-mefloquine (ASMQ), artesunate-sulphadoxine-pyrimethamine (ASSP), dihydroartemisinin-piperaquine (DHAP) [7]. The basis for the use of ACT relies on the rapid reduction of the parasite biomass, reduction of transmission (reducing gametocytes), protection of partner drug against resistance, and rapid fever reduction [8]. In January 2004, Cameroon officially aligned with the recommendations of WHO and adopted artesunate-amodiaquine (ASAQ-75%) and later included artemether-lumefantrine (AL-25%) in 2006 as first-line treatment of uncomplicated malaria [9]. These drugs are distributed by those proportions in public facilities, while AL is relatively predominant within the private health facilities and vendors [10]. A recent network meta-analysis (NMA) study on ACTs in Cameroon revealed that AL was more efficacious than ASAQ [11]. The advantage of the NMA approach is that it provides estimates of the effect of each intervention relative to each other [12]. However, the method adopted for the NMA study is not without limitations namely: non-inclusion of observational studies, use of intention-to-treat (ITT) approach and the non-adoption of the individual patient data (IPD) in quantitative syntheses [11]. The adoption of multiple first line ACTs has the potential to delay the emergence of parasites resistant to the anti-malarials [13]. This study was done to provide additional information on the pooled per protocol (PP) efficacy of ACTs using IPD. Hence, this study aimed to assess the clinical efficacy and safety of Artemisinin-based combination therapies in Cameroon from January 2004 to June 2020 with emphasis on ACTs adopted for first-line treatment of uncomplicated *falciparum* malaria.

**Methods/design**

**Searching strategies**

Studies included in this review were selected using the preferred reporting items for systematic review and meta-analysis (PRISMA) statement [14]. A computerised systematic strategy based on key words was used to search articles from PubMed/Medline, Google Scholar, and Science Direct databases. Both interventional and observational studies were retrieved to be included in the review using the following MeSH search terms: ‘Cameroon AND malaria AND artemether-lumefantrine’, ‘Cameroon AND malaria AND artesunate-amodiaquine’, ‘Cameroon AND malaria AND artesunate-mefloquine’, ‘Cameroon AND malaria AND dihydroartemisinin-piperaquine’, ‘Cameroon AND malaria AND artesunate-sulphadoxine-pyrimethamine’, ‘Cameroon AND malaria AND artesunate-atovaquone-proguanil’, ‘Cameroon AND malaria AND artesunate-sulphamethoxypyrazine-pyrimethamine’, and ‘Cameroon AND malaria AND artesunate-chlorguanil-dapsone’. Additional information on Clinical Trials was also obtained from the libraries and from researchers at the Universities of Yaounde I, Buea, Douala, Dschang and Bamenda. The library of the Catholic University of Central Africa based in Yaounde Cameroon was also consulted. Moreover, information was obtained from the OCEAC Bulletin and from the National Malaria Control Programme (NMCP), the Ministry of Public Health annual reports. Furthermore, studies conducted in any of the four sentinel sites in Cameroon were sought from the NMCP or from individual researchers who provided this
information voluntarily. In addition to published studies, unpublished thesis reports were accessed for inclusion in the study.

**Inclusion criteria**

The following studies were included in this systematic review and meta-analysis: original articles of studies that investigated at least one ACT in the treatment of uncomplicated *falciparum* malaria; studies published that included study periods from January, 2004 to June, 2020; studies written in English or French; all multi-centric studies in which Cameroon was one of the sites were included in this report. The population intervention comparator outcome (PICO) format was used to select and include studies (Additional file 1). The primary objective of this review was to assess the efficacy of ACT measured as treatment success at days 14, 28, 42 or 63 for uncomplicated malaria caused by *Plasmodium falciparum*, while the frequency of adverse events (AEs) was the secondary objective. 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 Harmonisation (ICH) guidelines. Studies included in this review are shown in Additional file 1.

**Non-inclusion criteria**

The following papers were excluded from this systematic review and meta-analysis: studies that used artemisinin monotherapies or non-artemisinin monotherapies; non-artemisinin combination therapies; studies that assessed malaria treatment outcomes at times less than 14 days and studies with PCR unadjusted cure rates. Studies that were excluded from this review are shown in Additional file 1.

**Review process**

All of the research articles identified from searches of the electronic databases were screened for eligibility based on title and abstract. Ineligible articles and duplicates were eventually removed using Zotero standalone software version 5.0.56. Full-length articles of the selected studies were read to confirm for fulfilling of the inclusion criteria before data extraction began. Two reviewers (PTNN and CMM) independently screened the titles and abstracts to identify potentially eligible studies and data extracted from full-length articles that fulfilled the inclusion criteria (Figure 1). Discrepancies were resolved by mutual consent after discussion and independent review from the third researcher (AMN). WFM reviewed the whole process.

**Data extraction procedure**
Data on the types of study design (observational versus interventional), year the studies were conducted, duration of study, and geographic location of the study area was first extracted. Participants’ age ranges were then extracted. Finally, data regarding the types of anti-malarial treatments, treatment outcome measures (including treatment success rates, treatment failure rates), treatment duration, and adverse events (AEs) were extracted to be included in the systematic review and meta-analysis.

Methodological quality assessment and sensitivity analysis

The 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 for randomised controlled trials (RCTs) [15] and the strengthening the reporting of observational studies in epidemiology (STROBE) statement for observational studies [16]. Modified Jadad scale assesses the quality of a trial with the range from 0 to 8 (randomisation and its appropriate use, blinding and its appropriate use, withdrawals and dropouts, description of inclusion and exclusion criteria, assessment of adverse effects, and description of statistical analysis). The score for the modified Jadad scale range of 0-3 represents low or poor quality and score ranges of 4–8 represents good to excellent quality. The observational studies were categorised 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.

Assessment of treatment outcomes

Treatment outcome was assessed as treatment failure and treatment success. The outcomes of all the studies included in this review were assessed and analysed on the 14th, 28th, 42nd and 63rd day of treatment. Treatment failure included: early treatment failure (ETF), late parasitological failure (LPF) and late clinical failure (LCF). The indicator for treatment success was adequate clinical and parasitological response (ACPR). ACPR was defined as absence of parasitaemia by the end of treatment (days 14, 28, 42, 63) irrespective of axillary temperature without previously meeting any of the criteria for early treatment failure or late clinical failure or late parasitological failure (17–20). The treatment success was defined based on PCR genotyping according to current World Health Organisation (WHO) recommendation.

Publication bias

Publication bias was assessed using funnel plot with the standard error of each study plotted against its effect size (Additional file 2). The Egger test was also used to assess publication bias.

Data analysis and heterogeneity assessment
The traditional meta-analysis that estimates a common effect of the same intervention A, B and C by pooling individual patient data (IPD) from various studies was adopted. The R software package version 3.5.2 was used to carry out all the meta-analyses of malaria treatment efficacy. The heterogeneity of the included studies was investigated using Cochrane Q and the $I^2$. The random effects model was used as standard to combine studies showing heterogeneity of Cochrane Q with $P < 0.10$ and $I^2 > 50$ [21]. Heterogeneity using was classified as low (0-49%), moderate (50-74%) and high (75-100%).

**Ethical considerations**

The PRISMA guideline 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.

**Results**

**Study identification and selection process**

A computerised systematic strategy was used to identify and screen articles from PubMed, Google Scholar, and Science Direct databases for eligibility (Figure 1).

**Qualitative synthesis**

The search of studies published from 2004 to 2020 identified 13 articles important to the topic under review [22–34], out of which 10 were RCTs [22–30, 33, 34] and 3 non-comparative clinical trials without randomisation [31, 32] (Additional file 1). Data from 3 unpublished studies that were conducted by the Cameroon National Malaria Control Programme and independent researchers were also included in this review. A total of 39 studies from 16 records with the same or different ACTs fulfilled the inclusion criteria and were included in this systematic review and meta-analysis with a total sample size of 3,747 participants that ranged from a minimum of 48 patients [22] to a maximum of 255 patients [30]. Treatment outcomes in all studies were evaluated by adopting clinical and parasitological criteria based on WHO guidelines [17–20].

**Quantitative synthesis**

A total of 8 generic ACTs were included in this review and meta-analysis. The overall efficacy of the ACTs was 97.9 % (95 % CI, 97.2-98.7) and heterogeneity, $Q=82.3$, $I^2=61 \%$, $X^2=97.9$ (df=38), $P<0.01$. Most of efficacies were above the WHO limit of 90 % with the exceptions of AS-CD and AS-SP with values of 84.5 % and 86.0% respectively. The most common ACTs included DHAP, AL, and ASAQ with a total of 4, 9, 16 and studies respectively (Figure 2).
Sub-group analyses were carried out for ASAQ, AL and DHAP. The pooled efficacy of ASAQ was 97.5\% (95 \% CI, 96.3-98.8) with heterogeneity, $Q=37.7, I^2=60 \%$, $X^2=37.7$ (df=15), $P<0.01$ (Figure 3). The overall efficacy of AL was 99.4 \% (95 \% CI, 98.6-100.0) with heterogeneity, $Q=5.4, I^2=6 \%$, $X^2=8.5$ (df=8), $P=0.39$ (Figure 4). The aggregated efficacy of DHAP was 98.0 \% (95 \% CI, 96.3-99.7) with heterogeneity, $Q=3.8, I^2=22 \%$, $X^2=3.8$ (df=3), $P=0.28$ (Figure 5).

**Evolution in the efficacies of ASAQ and AL from 2004 to 2020**

A decline in Artesunate-Amodiaquine (ASAQ) efficacy was observed over time from an original 100 \% to a current value of 91.8 \% (Figure 6). The PCR adjusted cure rate of artemether-lumefantrine reduced from an original of 100 \% to a current value of 96.7 \% (Figure 6).

The studies were grouped according to the Littoral, Forest, Savanna and Sahel-Savannah ecological zones similar to the four ecological facets defined by Cameroon's National Malaria Control Programme. It was demonstrated that the efficacy of ASAQ declined faster in some ecological zones when compared to others. The greatest deep in ASAQ was noticed in the Littoral ecological zone (Figure 7).

**Fever and parasite clearance by ACTs**

Fever temperature measurements were mostly axillary and on average were above 38 °C. Fever was rapidly cleared by the ACTs with low proportions with fever on D1 of 17 \% and 5 \% by D3 (Additional file 5). Some authors did not measure fever clearance on subsequent days post drug administration and only choose D3 for this clinical measurement.

Starting parasitaemia with geometric mean densities varied between 3800 to 42000 parasites per ml. Parasite clearance was very rapid sometimes dropping to 7-8 \% on D1 but on average stayed at 30-50 \%. Parasite clearance times were similar across study arms in most studies. Nji et al., observed that there appeared to be a study site effect on parasite clearance between Garoua and Mutengene [30]. Although not significant most participants in Mutengene site (75 \%) (Figure 8), did not clear their parasites as measured by microscopy by the end of D1 post-treatment compared to participants in Garoua (32 \%). Comparing the parasite clearance time across the different treatment arms and site did not show any significant difference by D3 post-treatment (p>0.05). Overall, the proportion of patients with parasites on D2 was much lower than on D1 and even lower on D3 (Figure 8). Apinjoh et al., found a high occurrence of parasitaemia of 17\% and 35\% respectively in ASSP and ASAQ arms in Buea-Tole on D28 [33] and from which study an efficacy of ASAQ of about 92 \% was recorded. The average parasite clearance did not take into account the two studies with outlier figures (Figure 8 and Figure 9). Only two of these studies were interested to have measured parasite levels up till D42 or D63 [30, 32]. It should be noted that parasitaemia tended to re-occur between D14-D63.
Safety and tolerability of ACTs in Cameroon

A total of 12 (76.5 %) articles and unpublished data reported adverse events [23, 24, 26, 28–31, 33]. The ACTs are well tolerated with few adverse events, the most reported across all studies being those of asthenia, diarrhoea, abdominal pain, anorexia, nausea, vomiting, headache and dizziness. Out of 12 studies, 5 reported severe adverse events which included: 1 jaundice, 1 haemoglobinuria, 3 anaemia, 1 convulsion, 1 severe fatigue, 3 severe malaria and 3 deaths (Additional file 5). A three-arm randomised non-inferiority controlled trial to assess the efficacy and safety of ASAQ, DHAP and AL was conducted in Mutengene and Garoua from 2009 to 2013. The authors demonstrated that the frequency of adverse events such as vomiting, cough, rashes, and anorexia was slightly higher in the groups of participants on ASAQ and DHAP. The drugs did not differ with respect to the type of AEs (all p values <0.05). Although there was no significant statistical difference (P=0.09) in the occurrence of all AEs when comparing the trial drugs, ASAQ (35.5 %) and DHAP (37.9 %) had higher number of AEs than AL (27.5 %). One serious AE occurred involving a child who experienced severe fatigue after AL ingestion [30].

In another study in Buea, it was observed that while administering ASAQ and SPAS, at least one adverse event (AE) was reported in 69.2 % (117/169) of patients in both treatment groups during the post-treatment period that was not present on admission. These were probably related to the study drug and mainly mild or moderate in intensity. The most frequent AEs were cough, dizziness, fatigue, catarrh, and gastrointestinal disorders (nausea, abdominal pain, and diarrhoea). A total of 36 (43.4 %) and 81 (94.2 %) patients in the AS/SP and AS/AQ group, respectively, experienced AEs by day three. By day seven, the number of patients with AEs had reduced to two (4.5 %) and eight (17.7 %) in the AS/SP and AS/AQ groups, respectively [33].

Quality assessment and sensitivity analysis

The articles included in this review were of high qualities according to modified Jadad scale for randomised controlled trials (RCTs) with values ranging from 5 to 8 (Additional file 3) while and the strengthening the reporting of observational studies in epidemiology (STROBE) statement for observational studies with a range of 86 % to 91 % (Additional file 4). There was no need for sub-group analysis because of the high quality of studies included.

Discussion

The systematic review and meta-analysis aimed to assess the pooled clinical efficacy and Safety of artemisinin-based combination therapies from individual participant data for over 16 years after adoption and use for the treatment of uncomplicated *falciparum* malaria in Cameroon. We demonstrated that the cure rates of most ACTs were above the WHO minimum limit of 90% with a cumulative value of 97.9%. This observation is in agreement with cure rate of 98.0% reported in meta-analysis on ACTs used in Sudan [35], but higher than the efficacy of 92.9% recorded in Ethiopia [36]. However, 2 studies on
Artesunate-chloguanil-dapsone (AS-CD) and Artesunate-sulphadoxine-pyrimethamine (AS-SP) failed to meet the WHO, Day 28, PCR-adjusted cut-off of > 90% efficacy [27, 33]. Despite the high success rates of ACTs, resistance to anti-malarial drugs poses a major threat globally and if the parasites develop resistance to these anti-malarial regimens, it is inevitable that treatment would be more difficult, unsuccessful and high rates of relapse could be due to multidrug-resistant malaria. Therefore, monitoring the anti-malarial drug efficacy is important to enable early detection of emergence of drug resistance before it spreads to most of the parasite population, similarly to what happened with chloroquine, sulphadoxine-pyrimethamine, and amodiaquine monotherapies in Cameroon [2, 37, 38]. More so, there is no guarantee how long the currently used anti-malarial drugs will remain effective based on evidence that previous monotherapies were associated with higher rates of treatment failures in \textit{P. falciparum} infected patients [2, 39]. This calls for concerted action for search of new alternative anti-malarial drugs to treat malaria in the near future.

The efficacy of ASAQ the first line treatment adopted in 2004 for the treatment of uncomplicated \textit{falciparum} malaria in Cameroon was 97.5%. Contrary, a slightly lower value of 93.9% was recorded in a multi-centric study on pooled efficacy of ASAQ in sub-Saharan Africa [40]. Moreover, the efficacy of AL, the parallel first-line drug for the treatment of uncomplicated \textit{falciparum} malaria in Cameroon was 99.4%. This is in concordance with the 97.3% (95.9–98.3%, 95% CI) treatment success in children with uncomplicated malaria recorded in the pooled analysis of data from seven studies supported by Novartis [41]. This suggests that the results of treatment success with AL in uncomplicated malaria patients in Cameroon are evenly distributed with other high malaria endemic countries. The aggravated efficacy of DHAP was 98.0%. AL and DHAP were found to have higher pooled efficacies than ASAQ. This finding is in agreement with those of different studies on the efficacy of ACTs assessed using the network meta-analysis approach [11, 12, 42]. DHAP has also been shown to be highly efficacious in the clearance of malaria parasites among Human immunodeficiency virus (HIV) patients in Malawi and Mozambique [43]. The standard uncomplicated malaria treatment guideline for Cameroon recommends a three-days administration of ASAQ or AL depending on the weight and age of the patient [44]. Based on the present evidence, it will be advisable to consider DHAP in the treatment of malaria especially among HIV patients where ASAQ and AL may be contraindicated concurrently taking efavirenz- or nevirapine-based anti-retroviral therapy. It was observed that the efficacy of ASAQ declined an original value of 100% to a current value of 91.8% while that of AL declined from an original value of 100% to a current value of 96.7% over time. It was also shown that the efficacy of ASAQ declined faster in some ecological zones when compared to others. The greatest deep in ASAQ was noticed in the Littoral ecological zone. This change could be due to the decline in the efficacy of ASAQ in Buea [33]. However, it is important to note that the study in Buea was among the first studies to evaluate the efficacy and safety of ACTs in real time.

Most studies included in the present review achieved a rapid reduction of fevers and parasitaemia between D0 and D3 of assessment. Majority of these studies treated patients with ASAQ, AL and DHAP. A previous aggregate study on the clinical predictors of early parasitological response to ACTs (ASAQ, AL and DHAP) in African patients with uncomplicated falciparum malaria confirmed the rapid decrease of
parasite positivity rate (PPR) from 59.7% (95% CI: 54.5–64.9) on day 1 to 6.7% (95% CI: 4.8–8.7) on day 2 and 0.9% (95% CI: 0.5–1.2) on day 3 [45].

Some studies showed a delayed clearance on D1 with a proportion of 75% persistence of parasite in Mutengene/Garoua [30] and 35% parasitaemia on D28 Buea-Tole [33]. It should be recalled that Buea is in a zone which borders with Limbe and Mutengene which are sites for high chloroquine-resistance [2, 46].

The ACTs, ASAQ, AL and DHAP are well tolerated in spite of a few adverse events such as asthenia, diarrhoea, abdominal pain, anorexia, nausea, vomiting, headache and dizziness reported during different studies. These ADRs were not serious enough to discontinue anti-malarial treatments except for individuals in studies that reported serious adverse events such as jaundice, haemoglobinuria, anaemia, convulsion, severe fatigue, severe malaria and deaths. In the current review, 3 study participant died during treatment [26]. This rate of mortality was not related to the study drugs on patients included in the study with uncomplicated malaria. Similarly, systematic reviews and meta-analyses conducted in Ethiopia and Sudan reported similar adverse events when patients with uncomplicated falciparum malaria were administered ACTs [35, 36, 47].

**Strengths And Limitations Of The Study**

The current study has several strengths. A total of 39 studies with the same or different ACTs derived from 13 published articles and 3 unpublished studies were included that gave a total of 3,747 study participants. The study assessed efficacy of commonly used anti-malarial drugs: ASAQ and AL. Study outcomes were measured both clinically and parasitologically. Most studies evaluated the comparative efficacy of different anti-malarial medications.

However, the current study is not without limitations. The study included only mono-infection with *P. falciparum* with no available data on the other *Plasmodium* species. Moreover, not all studies reported AEs to anti-malarial drugs. Furthermore, there were fewer studies carried out in the Northern Regions of the country compared to the Southern Regions.

**Conclusion**

The present systematic review and meta-analyses reported a high overall efficacy of ACTs (97.9%). The standard regimens, ASAQ, AL and DHAP showed high cure rates of 97.5%, 99.4% and 98.0% respectively. A number of adverse drug events were encountered such as asthenia, diarrhoea, abdominal pain, anorexia, nausea, vomiting, headache and dizziness after the administration of ACTs. However, the ADRs were not serious enough to discontinue the use of anti-malarial treatment except for a few patients who experienced severe adverse events. ACTs in Cameroon are still efficacious and well tolerated albeit with a slight decline in the efficacies of ASAQ and AL over time. There is need for continuous monitoring of
efficacy of ACTs despite the high success cure rates as resistance seems inevitable since cases of anti-malarial drug resistance have been reported in some areas of the world.

**Abbreviations**

ACT
Artemisinin-based combination therapy, AL:Artemether-lumefantrine, ASAQ:Artesunate-amodiaquine, AS-CD:Artesunate-chloguanil-dapsone, AS-MQ:Artesunate-Mefloquine, AS-SP:Artesunate-Sulphadoxine-Pyrimethamine, DHAP:Dihydroartemisinin-Piperaquine, NMA:Network meta-analysis, PRISMA:Preferred reporting items for systematic reviews and meta-analyses, STROBE:Strengthening the reporting of observational studies in epidemiology, SP: Sulphadoxine-Pyrimethamine, SP-AQ: Sulphadoxine-Pyrimethamine-Amodiaquine

**Declarations**

**Ethics approval and consent to participate**

Not applicable because this is a systematic review and meta-analysis.

**Consent for publication**

Not applicable.

**Availability of data and materials**

All data and materials used for the analysis of this systematic review and meta-analysis are included in this write-up and the additional documents.

**Competing interests**

The authors declare that they have no competing interests.

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Authors’ contributions

WFM conceived the research and coordinated the study. AMN, PTNN and CMM conducted the literature search, assessed potentially relevant studies for inclusion into the review, assessed the methodological quality of the included studies, and independently extracted the data. AMN and PTNN performed the statistical analysis, drafted the manuscript, critically reviewed the manuscript, and wrote the final manuscript. AMN and PTNN assessed potentially relevant studies for inclusion into the review, assessed the methodological quality of the included studies, independently extracted the data, and critically reviewed the manuscript. The authors WFM, PMN, IMA, RA, MNM, CMM, DAF, BAT, MSE, RD, JPKC, JDB, AA, EA, ET, RGFL, AT and PR proof read the manuscript. All authors read and approved the final manuscript.

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44. Additional files.
45. Additional file 1. Summary characteristics of all studies of the systematic review and meta-analysis on efficacy and safety ACTs in Cameroon (included and unpublished studies).
46. Additional file 2. Assessment of publication bias on efficacy and safety of ACTs in Cameroon.
47. Additional file 3. Modified Jadad scale for study on efficacy and safety of ACTs in Cameroon.
48. Additional file 4. STROBE quality assessment for study on efficacy and safety of ACTs in Cameroon.
49. Additional file 5. Proportion of Fever Clearance and Adverse Events for ACTs in Cameroon.

Figures

Figure 1

Flow chart showing the number of articles included in the systematic review and meta-analysis on artemisinin-based anti-malarial treatment outcomes in Cameroon
Figure 2

Overall treatment success rate of artemisinin-based combination therapies (ACTs) published between 2004 and 2020 in Cameroon
Figure 3

Cure rates of artesunate-amodiaquine (AS-AQ) published from 2004 to 2020 in Cameroon

Figure 4

Adequate clinical parasitological response of artemether-lumefantrine (AL) published between 2004 and 2020 in Cameroon
### Figure 5

Treatment success rate of dihydroartemisinin-piperaquine (DHAP) published between 2004 and 2020 in Cameroon

| Study                | Efficacy of DHAP | Total samples | Prevalence | 95% C.I.          |
|----------------------|-----------------|---------------|------------|-------------------|
| Whegang et al., 2010 | 84              | 86            | 97.67 [94.49; 100.00] |                   |
| Yavo et al., 2011    | 55              | 56            | 98.21 [94.75; 100.00] |                   |
| Menan et al., 2011   | 49              | 49            | 100.00 [97.24; 100.00] |                   |
| Akindah et al., 2015 | 245             | 254           | 96.46 [94.18; 98.73]  |                   |

**Random effects model**

Heterogeneity: $I^2 = 22\%$, $\chi^2 < 0.0001$, $\chi^2 = 3.83$ ($p = 0.28$)

![Graph showing the efficacy of DHAP over time](image)

### Figure 6

Evolution in the efficacies of ASAQ and AL from 2006 to 2018

![Graph showing the efficacy changes](image)
Figure 7
Evolution of Clinical Efficacy of ASAQ per Ecological Zones of Cameroon

Figure 8
Parasite Clearance with ACTs in Garoua and Mutengene GAR-Garoua and MUT-Mutengene. Delayed parasite clearance was observed among most study participants in Mutengene on D1 post-treatment.
Figure 9

Kaplan-Meier Analysis for Parasite Clearance of ACTs from 2004-2020 The average parasite clearance did not take into account the two studies with outlier figures. In addition, the circles represent the hypothetical situation of no clearance and the squares represent clearance by all ACTs.

Supplementary Files

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