Drugs in R&D (2019) 19:1–14
https://doi.org/10.1007/s40268-018-0259-3

REVIEW ARTICLE

# Monitoring the Efficacy and Safety of Artemisinin-Based Combination Therapies: A Review and Network Meta-analysis of Antimalarial Therapeutic Efficacy Trials in Cameroon

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Published online: 17 January 2019


## Abstract

**Introduction** Artemisinin-based combination therapies (ACTs) are the first-line antimalarial drugs used to treat uncomplicated *Plasmodium falciparum* alaria in many endemic countries worldwide. The present work reviewed the therapeutic efficacy of ACT in Cameroon more than 10 years after the initial change in national drug policy in 2004.

**Methods** A PubMed literature search was performed to analyse clinical trials conducted in Cameroon from 2001 to May 2017. Clinical studies that evaluated ACT for the treatment of uncomplicated falciparum malaria in children or adults, and reported efficacy and/or safety, were included. In addition, a small network meta-analysis (NMA) with a frequentist approach was performed.

**Results** Six papers were selected from 48 articles screened and were full-text reviewed. The efficacy of both artemether-lumefantrine (AL) and artesunate-amodiaquine (ASAQ) ranged from moderate to high, with polymerase chain reaction-corrected cure rates ranging from 96.7 to 100% and 88.2 to 100%, respectively, in per-protocol analysis, and 86.2 to 96.7% and 74.0 to 90.6%, respectively, in intention-to-treat analysis. The malaria evidence network suggested that AL and ASAQ efficacies were comparable. The highest day 3 parasite positivity rate was 8.2% for ASAQ and 4% for AL. A novel ACT, artesunate-atovaquoneproguanil (ASATPG) was tested once and showed a cure rate of 100%. Based on an ITT approach, the NMA revealed that AL was more efficacious than ASAQ, but the difference was not statistical significant (706 participants, three randomised clinical trials (RCT); OR 1.25, 95%CI 0.78–2.00). Adverse events ranged from mild to moderate severity but were not directly attributed to drug intake.

**Conclusion** ACTs are still effective and safe in Cameroon; however, there are insufficient data on their efficacy, safety and tolerability, therefore more RCTs should be conducted, including novel ACTs.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s40268-018-0259-3) contains supplementary material, which is available to authorized users.

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**Key Points**

At present, the available evidence suggests that artesunate-amodiaquine (ASAQ) and artemether-lumefantrine (AL) are effective in treating a large majority of uncomplicated malaria cases in Cameroon.

Data on the efficacy, safety and tolerability of artemisinin-based combination therapies, including the first-line drugs ASAQ and AL are insufficient to draw a more solid conclusion in Cameroon.

Surveillance of antimalarial drug efficacy and safety should be reinforced to detect possible future changes in parasite sensitivity to ACT, and more randomised clinical trials should be conducted, including novel ACTs.

## 1 Introduction

Approximately half of the world's population is at risk of malaria infection. According to the World Health Organization (WHO), in 2016 an estimated 216 million cases and 445,000 deaths were reported [1]. Approximately 90% of these fatal cases occurred in children under the age of 5 years in Africa, where malaria claims the life of a child every 2 min [1].

In 2001, a WHO expert panel recommended the use of artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated falciparum malaria in all endemic countries [2]. The 2003 WHO protocol required a 28-day follow-up to assess clinical and parasitological response, but since the 2009 updated protocol, 28- or 42-day follow-up is recommended, depending on the elimination half-life of the drug partner of artemisinin [3, 4]. The current WHO-recommended combinations include artemether-lumefantrine (AL), artesunate-amodiaquine (ASAQ), artesunate-mefloquine (ASMQ), dihydroartemisinin-piperaquine (DHPP), and artesunate-sulfadoxine-pyrimethamine (ASSP) [5]. Two of these ACTs, AL and ASAQ, have been adopted as first-line therapies by many countries in sub-Saharan Africa, including Cameroon.

ASAQ and AL were officially adopted in Cameroon in 2004 and 2006, respectively, due to increasing resistance to monotherapies [6, 7]. In Cameroon, malaria is the major cause of illness and is responsible for 40% of medical consultation. ACTs are widely deployed in that country, even in the peripheral health facilities, for the treatment of uncomplicated malaria [7, 8]. ACT drugs are available and affordable, but their accessibility needs to be improved for the practice of self-medication in home-based management, and the private sector should be a partner for the distribution of ACT medicines [9]. At present, several unapproved ACTs are circulating in the informal sector, which requires the attention of the Cameroonian Ministry of Public Health to enforce regulations to reduce the sales of illicit drugs and illicit drug trade, and to implement a national pharmacovigilance system [9].

Following reports on the emergence of artemisinin-resistant clinical isolates of *Plasmodium falciparum* in Southeast Asia, and the threat of their spread to other malaria-endemic countries [10–12], country-specific evidence based on reliable data is urgently required to monitor drug efficacy and support timely review and implementation of malaria treatment guidelines. Surveillance of antimalarial efficacy is crucial to enable early detection of drug resistance before it spreads, as happened with chloroquine and sulfadoxine-pyrimethamine monotherapies [5, 11]. Information generated from such surveillance will provide evidence to relevant national and international authorities for policy formulation and review, and will also provide an update on country-specific performance of ACT after its wide-scale deployment for treating uncomplicated falciparum malaria.

Since clinical response to treatment is the source of most relevant information for clinicians and policy makers, and is also considered as the gold standard for assessing antimalarial drug resistance, the aim of the present study was to review the implementation of therapeutic efficacy testing in Cameroon before and after nationwide deployment of ACT, and monitor the efficacy of ACT for the treatment of uncomplicated malaria. Greater emphasis will be placed on descriptive analyses to show treatment efficacy over time. In addition, the present study included the description of parasite and fever clearance time and safety data reported in clinical trials involving ACTs in Cameroon.

## 2 Methods

### 2.1 Search Strategy

We searched the published literature in PubMed and included papers published from January 2001 to May 2017, using the following 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' and 'Cameroon AND malaria AND artesunate-sulfadoxine-pyrimethamine'. In addition, the Worldwide Antimalarial Resistance Network (WWARN) reference list was screened to identify other studies [13]. Inclusion criteria were clinical trials conducted in Cameroon between 2001 and 2017, involving at least one ACT for the treatment of uncomplicated falciparum malaria,

and reporting drug efficacy and/or safety. The search started in 2001 because that was the year the WHO advocated use of ACT for treating uncomplicated falciparum malaria [2].

For each included study, the data included year and duration of the study, the target population, follow-up period, sample size, parasitaemia at inclusion, and the level of malaria transmission. The primary endpoint for efficacy was the polymerase chain reaction (PCR)-corrected proportion of adequate clinical and parasitological response (ACPR). ACPR is defined by the WHO as the "absence of parasitaemia on day 28 (or day 42), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure" [4]. The secondary endpoints were fever clearance, parasite clearance, and gametocyte carriage in each treatment group. Drug tolerability was assessed comparing adverse events and modification of biological parameters between days 0 and 7.

### 2.2 Statistical Analysis

Clinical efficacies were extracted on an intention-to-treat and per-protocol (PP) basis. The binomial exact test was used to derive the 95% confidence interval (CI) for proportions.

Recently, network meta-analysis (NMA) has been used to synthesize data from randomised clinical trials (RCTs) comparing two or more antimalarial drugs in Africa [14]. NMA is a generalisation of pairwise meta-analysis that compares all pairs of treatments within a number of treatments under the same condition. In the present study, the method was performed using the *netmeta* command in R software [15] in order to compare drugs using a dichotomous outcome (ACPR vs. non-ACPR). This analysis used a frequentist approach based on a random effect model and the consistency hypothesis and homogeneous variance (i.e. the study variance is the same among pairwise contrast). Heterogeneity was assessed using the $I^2$ statistic, and the principal summary measure was the odds ratio (OR). Indirect estimates were derived under the consistency assumption to take into account the multi-arm trial correlation.

## 3 Results

The literature search yielded 48 articles, and 11 duplicates were removed. The titles and abstracts of the remaining 37 articles were screened based on the inclusion criteria, and 12 qualified for a full-text review. Of these 12 articles, six were multicentre trials in Africa, including Cameroon, however these were removed from our initial analysis because of difficulties in obtaining country-level data from the authors [16–21], but sensitivity analysis was performed. Therefore, six articles with access to data in Cameroon were fully reviewed (Fig. 1).

One article presented a series of five individual clinical trials [22], resulting in a total of 11 clinical trials published in six articles. One of these articles (an RCT) reported mutations associated with drug resistance in addition to ASAQ and AL efficacy [23]. In eight clinical trials (of which three involved ASAQ and AL), children < 5 years of age, the target population in that country, were recruited [22–24].

### 3.1 Studies Conducted to Test the Efficacy of Artemisinin-Based Combination Therapies (ACTs) in Cameroon

Before and after the official adoption of ACT for the treatment of uncomplicated malaria in Cameroon, six articles including 11 clinical trials (each trial refers to one or more ACT) assessed the efficacy, tolerability and/or safety of ACT (see Table 1 for a summary of their characteristics). The studies were conducted either in the northern, central or southwestern part of Cameroon (a map of Cameroon showing the locations where the reviewed studies were conducted is provided in electronic supplementary file 1). Of six articles, one was a synthesis of multiple randomised trials conducted in the central region, and one was a non-randomised study in Maroua (far north) that included both children and adults [22]. All six articles reported results on the WHO-recommended ACTs. One clinical trial assessed the efficacy and safety of a novel, non-WHO-recommended ACT, artesunate-atovaquone-proguanil (ASATPG) [25]. In three papers, treatment compliance was assured by supervised administration of the study drug under direct observation on days 1, 2 and 3. Three studies were performed under partial supervision, i.e. the first dose was administered under supervision at the health facility, while the second and third doses were given to patients for intake at home without supervision. For AL, which requires a total of six doses (one dose in the morning and one dose at night, for 3 days), the morning doses were directly observed over 3 days, while the evening doses were given to patients for intake at home; empty sachets returned the next day served as evidence of intake of the drug [23]. One randomised study compared drug efficacy on both day 28 and day 42 [24], while another study had its endpoints on days 28 and 63 [26].

### 3.2 Treatment Outcome in Studies that Reported the Efficacy of ACT

The majority of the studies assessed efficacy on day 28. The percentage of ACPR and the 95% CI are presented in Table 2. Few studies [24, 26] assessed the outcome on days 42 and 63. The PCR-corrected cure rates of ASAQ ranged from 88.2 to 100% in the PP approach and 74 to 90.6% in the ITT approach. The highest cure rate was reported in the studies conducted in Yaounde in 2005. In the trials that tested

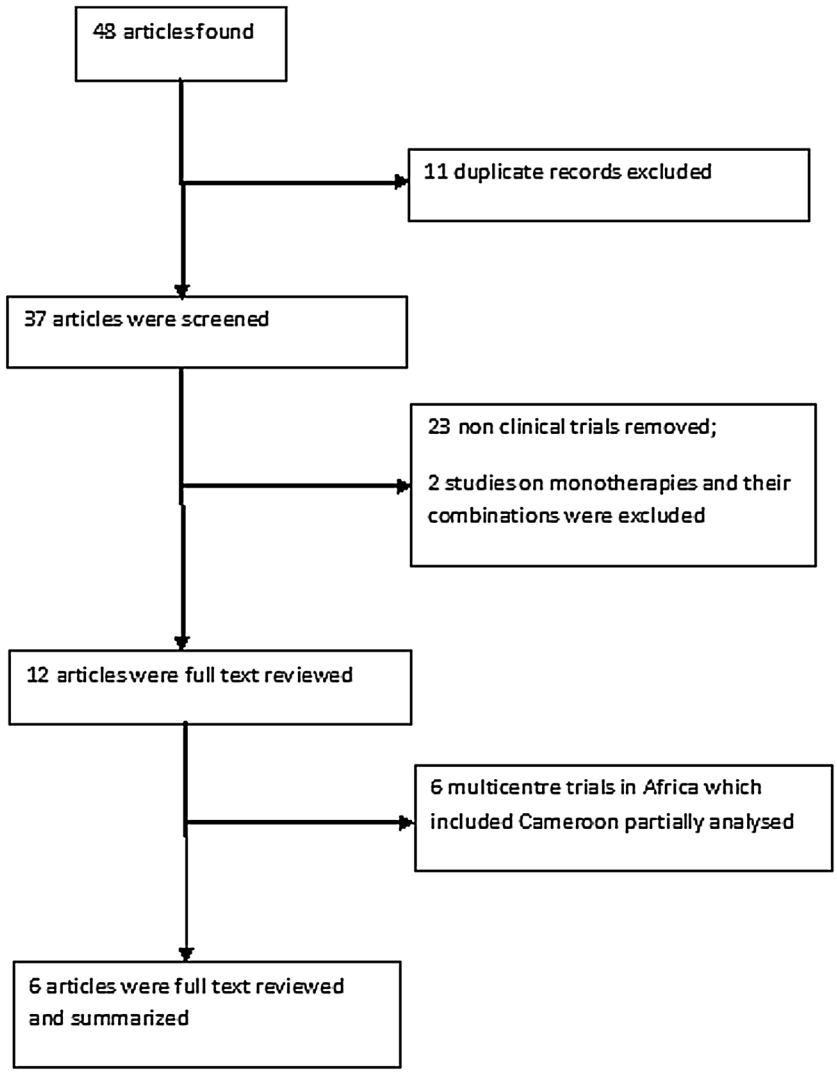


**Fig. 1** Article selection process. A total of 48 published articles were identified and six were included in the present analysis

AL, PCR-corrected cure rates ranged from 96.7 to 100% and 80.5 to 96.7% in the PP and ITT approaches, respectively. The highest cure rate of AL was observed in trials conducted in 2005 in Maroua, in 2006 in Yaounde, and in 2013 in Ngaoundere. A forest plot of the day 28 results can be found in electronic supplementary file 2, while the changes in effectiveness of ASAQ and AL over the study period are presented in Fig. 2. Before and after 2006, the percentages of ACPR in the PP population remained above the threshold set by WHO (90%).

The combination DHPP was assessed twice and showed cure rates of between 84.3 and 97.6% on day 28. On day 42, the cure rate was 89% (95% CI 85.3–92.8) using the ITT approach, and 96.3% (95% CI 92.9–98.2) using the PP approach. ASSP was tested in three studies. The PCR-corrected cure rate ranged from 85.9 to 94.7% (PP approach). In 2006, the combination ASMQ had the highest cure rate on day 28 in Yaounde (100% using the PP approach, and 88% using the ITT approach). Furthermore, in 2010, the observed cure rate decreased to 96.5% on day 28, and to 78.8% on day 63 (data not shown in Table 2). Using the Kaplan–Meier estimation technique, the authors found that the cure rates were comparable on days 28 and 63 (96.6%) [26].

A novel but non-WHO-recommended ACT, ASATPG, was tested once and showed a cure rate of 100% on day 28 in Yaounde. This ACT was a highly effective alternative treatment that was not associated with any recrudescence or re-infection during the 28-day follow-up period [25].

### 3.3 Network Meta-Analysis (NMA) and Indirect Comparisons

Data were extracted in terms of study, treatments, sample size, and outcomes. The ITT and PP analyses were performed for the purpose of comparison. Given ASAQ as the common control group in the randomised controlled trials [22–25, 27], as well as in the network, comparisons were made. Analysis was performed using the *netmeta* package

**Table 1** Study design and baseline characteristics of efficacy trials that assessed ACT in Cameroon

| Study ID | Authors | Study years | Duration (months) | Study site | Population age | Transmission level | Sample size | Follow-up | Parasitaemia inclusion criteria/μL | Pf-GMPD | Supervised |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CMR001_ASSP | Apinjoh et al. [27] | May 2006–October 2006 | 6 | Buea | 6 months–10 years | Intense, perennial | 83 | 28 | 1000–533,334 | 14,346 | Partial |
| CMR001_ASAQ | Apinjoh et al. [27] | May 2006–October 2006 | 6 | Buea | 6 months–10 years | Intense, perennial | 86 | 28 | 1000–533,334 | 9914 | Partial |
| CMR002_AL | Nji et al. [24] | 2009–April 2013 | 40 | Mutengene, Garoua | 6 months–10 years | Low–moderate | 144 | 42 | 1060–100,000 | 14,808 | Yes |
| CMR002_ASAQ | Nji et al. [24] | 2009–April 2013 | 40 | Mutengene, Garoua | 6 months–10 years | Low–moderate | 288 | 42 | 1040–100,000 | 13,555 | Yes |
| CMR002_DHPP | Nji et al. [24] | 2009–April 2013 | 40 | Mutengene, Garoua | 6 months–10 years | Low–moderate | 288 | 42 | 1040–100,000 | 13,690 | Yes |
| CMR003_ASAQ | Tahar et al. [25] | 2008–2009 | 12 | Yaoundé, Nlongkak | 6–60 months | Intense | 70 | 28 | 2120–230,000 | 38,600 | Yes |
| CMR003_ASATPG | Tahar et al. [25] | 2008–November 2009 | 12 | Yaoundé, Nlongkak | 6–60 months | Intense | 100 | 28 | 2020–415,000 | 38,700 | Yes |
| CMR004_ASAQ | Ali et al. [23] | September 2007–December 2007 | 4 | Ngaoundere | 6 months–14 years | Moderate–high | 73 | 28 | 1340–184,000 | 4628.3 | Partial |
| CMR004_AL | Ali et al. [23] | September 2007–December 2007 | 4 | Ngaoundere | 6 months–14 years | Moderate–high | 77 | 28 | 1240–156,000 | 3886 | Partial |
| CMR005a_ASAQ | Whegang Youdom et al. [22] | February 2005–May 2005 | 4 | Yaoundé, Nlongkak | 6–58 months | Intense, perennial | 60 | 28 | 2000–255,000 | 32,940 | Yes |
| CMR005a_ASSP | Whegang Youdom et al. [22] | February 2005–May 2005 | 4 | Yaoundé, Nlongkak | 6–59 months | Intense, perennial | 61 | 28 | 2050–220,000 | 42,950 | Yes |
| CMR005b_ASAQ[a] | Whegang Youdom et al. [22] | July 2005–August 2005 | 1 | Maroua, Djarengol Kodek | 7–660 months | Low–moderate | 64 | 28 | 2010–360,000 | 26,216 | Yes |
| CMR005c_ASMQ | Whegang Youdom et al. [22] | April 2006–June 2006 | 3 | Yaoundé, Nlongkak | 7–60 months | Intense, perennial | 69 | 28 | 2000–300,000 | 34,600 | Yes |
| CMR005d_ASAQ | Whegang Youdom et al. [22] | September 2006–November 2006 | 3 | Yaoundé, Nlongkak | 6–60 months | Intense, perennial | 62 | 28 | 2000–512,000 | 30,261 | Yes |
| CMR005d_AL | Whegang Youdom et al. [22] | September 2006–November 2006 | 3 | Yaoundé, Nlongkak | 6–59 months | Intense, perennial | 62 | 28 | 2000–247,000 | 32,996 | Yes |
| CMR005e_ASCD | Whegang Youdom et al. [22] | December 2006–February 2007 | 3 | Yaoundé, Nlongkak | < 5 years | Intense, perennial | 83 | 28 | 2010–218,000 | 34,377 | Yes |

**Table 1** (continued)

| Study ID | Authors | Study years | Duration (months) | Study site | Population age | Transmission level | Sample size | Follow-up | Parasitaemia inclusion criteria/μL | Pf-GMPD | Supervised |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CMR005e_ ASSP | Whegang Youdom et al. [22] | December 2006–February 2007 | 3 | Yaoundé, Nlongkak | < 5 years | Intense, perennial | 85 | 28 | 2010–472,000 | 30,199 | Yes |
| CMR005f_ ASAQ | Whegang Youdom et al. [22] | September 2007–November 2007 | 3 | Yaoundé, Nlongkak | < 5 years | Intense, perennial | 92 | 28 | 2100–500,000 | 45,034 | Yes |
| CMR005f_ DHPP | Whegang Youdom et al. [22] | September 2007–November 2007 | 3 | Yaoundé, Nlongkak | < 5 years | Intense, perennial | 91 | 28 | 2050–310,857 | 40,171 | Yes |
| CMR006_ ASMQ[a] | Tietche et al. [26] | December 2007–March 2009 | 19 | Yaoundé, Nlongkak | < 5 years | Intense, perennial | 213 | 63 | 1000–248,000 | 36,476 | Partial |

[a]Non-randomised controlled trial

*Pf-GMPD Plasmodium falciparum* geometric mean parasite density of asexual parasites per microlitre of blood, *ACT* artemisinin-based combination therapy

found in R software. Figure 3 shows the network of eligible comparisons for NMA (malaria evidence network) obtained from trials conducted in Cameroon, and the results are summarised in Table 3. Forest plots of these results are in electronic supplementary file 2.

In the available network, heterogeneity was absent based on the ITT approach ($\tau^2 = 0.02$, $I^2 = 14\%$, $p$ value of the heterogeneity 0.32). AL was more efficacious than ASAQ, but the difference in efficacy was not statistically significant (706 participants, three RCTs; OR 1.25, 95% CI 0.78–2.00). Only one RCT compared ASATPG with ASAQ, and ASATPG was found to be threefold more efficacious than ASAQ (170 participants; OR 3.15, 95% CI 1.02–9.70). DHPP was compared with ASAQ in two clinical trials and their efficacies were found to be statistically non-significant (759 participants; OR 1.06, 95% CI 0.67–1.69). In addition, the efficacy of ASSP was not statistically different from that of ASAQ (two trials, 290 participants; OR 0.98, 95% CI 0.50–1.95). Direct comparison of the efficacies of AL and DHPP (one trial, 432 participants, given AL as the reference group) showed no statistically significant difference (OR 1.04, 95% CI 0.62–1.76), which is coherent with the evidence obtained from the network, taking into account the correlation in the loop (ASAQ-AL-DHPP), given AL as the reference (OR 1.18, 95% CI 0.74–1.87).

Indirect comparison of ASSP and DHPP (608 patients, DHPP as the reference) yielded an OR of 1.08 (95% CI 0.47–2.48), suggesting a slight but statistically non-significant increase of efficacy. The indirect estimate of ASATPG and DHPP (479 patients, DHPP as the reference) likewise showed decreased efficacy that was not statistically significant (OR 0.34, 95% CI 0.1–1.13). By contrast, the evidence network showed a statistically significant increased efficacy of ASATPG (reference group) when compared with ASSP (329 participants; OR 3.21, 95% CI 1.60–6.42), which is consistent with the descriptive statistics reported in the studies [22, 25, 27].

### 3.4 Sensitivity Analysis: NMA

A sensitivity analysis was performed with the multicentric studies that were partly conducted in Cameroon. Their description can be found in electronic supplementary file 3. Data from three studies whose results were aggregated either in a PP or ITT approach were included [17, 18, 21]. An alternative, non-WHO-recommended ACT, such as artesunate-sulfamethoxypyrazine-pyrimethamine (ASSMP), was evaluated and showed a 28-day cure rate of 99% (84 cases of ACPR among 85 included patients analysed) [17]. In addition, dihydroartemisinin-piperaquine-trimethoprim (DHPPT) was assessed in 40 patients, but the study did not report the percentage of ACPR [20]. This latter study was subsequently excluded from further analysis. NMA

**Table 2** Treatment outcome reported in efficacy trials in Cameroon

| Study ID | PP PCR-corrected percentage cure rate (95% CI), day 28/day 42 | ITT PCR-corrected percentage cure rate (95% CI), day 28/day 42 |
|---|---|---|
| CMR001_ASSP | 85.9 (78.2–93.6) | 82.7 (74.5–90.9) |
| CMR001_ASAQ | 90.2 (83.8–96.6) | 86.0 (78.7–93.3) |
| CMR002_AL | 96.7 (91.8–99.1)/96.7 (91.3–98.9)[a] | 86.2 (79.3–91.5)/ 92.0 (85.9–95.7)[a] |
| CMR002_ASAQ | 95.3 (91.9–97.5)/98.1 (95.2–99.2) | 87.1 (82.6–90.8)/91.0 (89.3–95.7) |
| CMR002_DHPP | 96.3 (93.1–98.3)/96.3 (92.9–98.2) | 84.3 (79.4–88.3)/89.0 (85.3–92.8) |
| CMR003_ASAQ | 88.2 (78.1–94.7) | 85.7 (75.3–92.9) |
| CMR003_ASATPG | 100 (96.2–100) | 95.0 (88.7–98.3) |
| CMR004_ASAQ | 96.4 (87.7–99.6) | 74.0 (62.3–83.5) |
| CMR004_AL | 100 (94.2–100) | 80.5 (70.0–88.6) |
| CMR005a_ASAQ | 98.2 (90.1–99.9) | 88.3 (77.4–95.0) |
| CMR005a_ASSP | 94.7 (85.3–98.9) | 88.5 (77.8–95.2) |
| CMR005b_ASAQ[b] | 100 (94.0–100) | 90.6 (80.7–96.5) |
| CMR005c_ASMQ | 100 (94.0–100) | 88.4 (78.4–94.8) |
| CMR005d_ASAQ | 96.5 (87.9–99.5) | 88.5 (78.1–95.3) |
| CMR005d_AL | 100 (94.0–100) | 96.8 (88.8–99.6) |
| CMR005e_ASCD | 85.0 (74.0–92.0) | 72.0 (61.3–81.5) |
| CMR005e_ASSP | 94.0 (85.8–97.9) | 87.0 (78.0–93.3) |
| CMR005f_ASAQ | 92.0 (84.3–96.7) | 88.0 (79.6–93.8) |
| CMR005f_DHPP | 98.0 (91.8–99.7) | 92.0 (84.8–96.8) |
| CMR006_ASMQ | 96.5 (93.0–98.6) | 91.0 (86.4–94.5) |
| | 93.8 (89.2–96.9)[c] | 84.1 (78.9–72.8)[c] |
| | 96.6 (93.0–98.4)[b] | |

*PP* per-protocol, *PCR* polymerase chain reaction, *CI* confidence interval, *ITT* intention-to-treat, *ACPR* adequate clinical and parasitological response

[a]For this second study, the cure rates were reported on day 42

[b]Kaplan–Meier estimate of the proportion of subjects with ACPR and 95% CI was similar for both day 28 and day 63 in the ASMQ arm; CMR002 assessed the efficacy on day 42

[c]Percentage of ACPR on day 63

was conducted using the PP approach. In comparison with ASAQ, AL was more efficacious, but the result was not statistically significant (OR 1.53, 95% CI 0.71–3.31). The corresponding network and the forest plots are shown in electronic supplementary file 2.

### 3.5 Fever and Parasite Clearance and Biological Parameters

Eight supervised trials comprising ASAQ and AL reported fever clearance on day 1 (Table 4), and also reported the proportion of patients with complete parasite clearance on day 3. The highest day 3 parasite positivity rate was 5% (i.e. 95.0–99.8% parasite clearance) for ASAQ and 0.15% (99.8–100%) for AL. The proportions of patients with parasite clearance varied depending on ACT.

Three articles reported biological parameters with ASAQ and AL [22–24]. One study found a slight decrease in mean haemoglobin level in the ASAQ, AL, and DHPP treatment groups between days 0 and 7; this decrease was statistically significant in the AL treatment group ($p = 0.003$) [24]. In patients treated with ASAQ, there was a statistically significant decrease in total white blood cells (WBCs; $p = 0.04$), as well as an increase in platelet count ($p = 0.001$), between days 0 and 14 [23]. Similarly, patients treated with AL showed a statistically significant decrease in total WBCs ($p = 0.025$) and a significant increase in platelet count from days 0 to 14 ($p = 0.002$) [23].

The same study found that with ASAQ, the mean alanine aminotransferase (ALT) decreased slightly during follow-up, but there was no statistically significant decrease from days 0 to 14. In addition, there was a small increase in the mean creatinine and bilirubin values between days 0 and 14, which was not statistically significant. Similarly, the mean ALT and bilirubin were found to decrease slightly during follow-up in the AL-treated group, but there was no statistically significant decrease from days 0 to 14 [23]. In another study, the percentage of

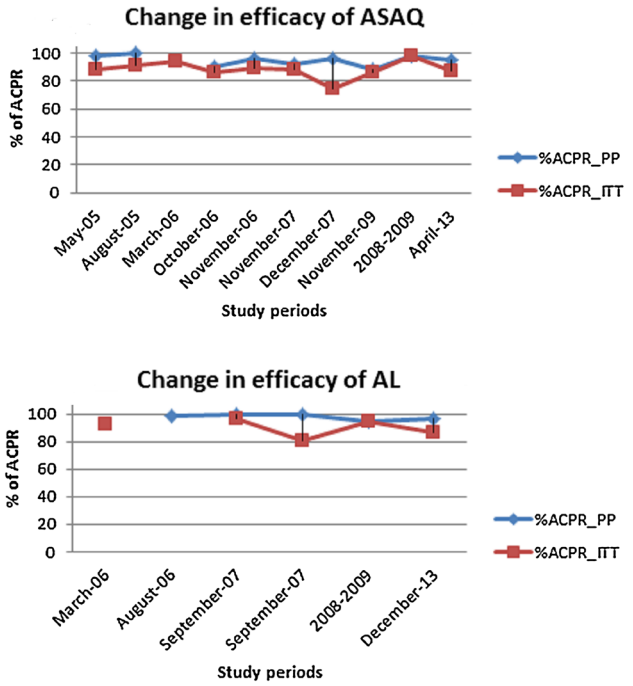


**Fig. 2** Change in efficacy of ASAQ and AL during the study periods. Diamonds represent the ACPR (%) in the PP population, and squares represent the ACPR (%) in the ITT population. *ACPR* adequate clinical and parasitological response, *ASAQ* artesunate-amodiaquine, *AL* artemether-lumefantrine, *PP* per-protocol, *ITT* intention-to-treat

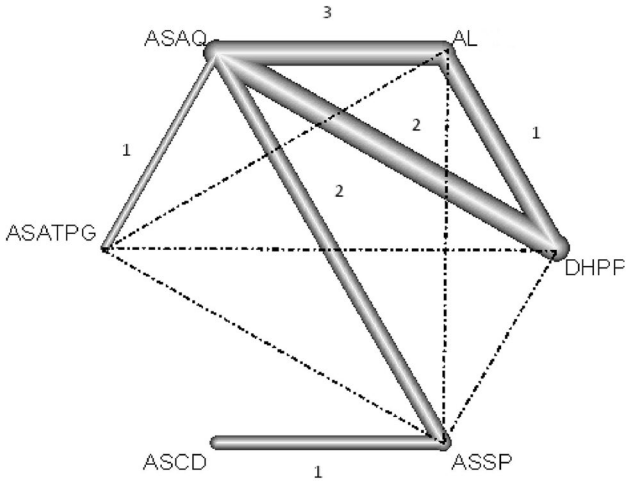


**Fig. 3** Malaria evidence network in Cameroon. The thickness of the line joining two treatments is proportional to the number of clinical trials and the number of participants. The network provides the possibility of comparing ASATPG and DHPP, ASATPG and ASSP, ASATPG and AL, as well as AL and ASSP, and DHPP and ASSP, even if they were not directly compared, and these are represented by the dotted lines. Non-randomised clinical trials were excluded. The descriptions are based on the ITT outcomes. *ASAQ* artesunate-amodiaquine, *ASATPG* artesunate-atovaquone-proguanil, *DHPP* dihydroartemisinin-piperaquine, *ASSP* artesunate-sulfadoxine-pyrimethamine, *ASCD* artesunate-chlorproguanil-dapsone, *AL* artemether-lumefantrine, *ITT* intention-to-treat

gametocytaemia at enrolment (19.8%) decreased significantly at the end of follow-up [27].

In short, the mean values of routine haematological and biochemical values were similar in patients treated with ASAQ or AL. Moreover, there were no significant differences in the proportions of children with abnormal biochemical test results in the two treatment groups.

### 3.6 Safety Profile of ACTs and Tolerance

The safety profile of ACTs evaluated in Cameroon is summarised in Table 5. In one study, two patients (one treated with ASAQ and the other treated with AL) presented with a mild transient increase in ALT and creatinine levels, respectively, without any accompanying clinical signs [23]. Insomnia was found to be a drug-related neuropsychiatric adverse effect in the ASMQ group [26]. AL, ASAQ and DHPP did not differ with respect to the types of adverse events [24]; however, ASAQ (35.5%) had a higher proportion of patients reporting adverse effects than AL (27.5%) [24]. One serious adverse effect was reported in a child who experienced severe fatigue after AL administration [24].

**Table 3** Relative treatment effects extracted from the network analysis

| Control group (ASAQ) | PP analysis [OR (95% CI)] | ITT analysis [OR (95% CI)] |
|---|---|---|
| AL | 2.44 (1.03–5.78) | 1.25 (0.78–2.00) |
| ASATPG | 12.24 (2.68–55.85) | 3.15 (1.02–9.70) |
| ASCD | 0.47 (0.10–2.00) | 0.39 (0.14–1.15) |
| ASSP | 1.21 (0.49–2.99) | 0.98 (0.49–1.95) |
| DHPP | 1.87 (0.83–4.18) | 1.06 (0.67–1.69) |

Each ACT (taken as reference) was compared with the efficacy of ASAQ (control group) on day 28. Quantifying heterogeneity and inconsistency were $\tau^2 = 0.0622$ and $I^2 = 10.8\%$ ($p = 0.3441$) and $\tau^2 = 0.0289$ and $I^2 = 13.9\%$ ($p = 0.3254$) for PP and ITT analysis, respectively. *ACT* artemisinin-based combination therapy, *AL* artemether-lumefantrine, *ASAQ* artesunate-amodiaquine, *ASATPG* artesunate-atovaquone-proguanil, *ASCD* artesunate-chlorproguanil-dapsone, *ASSP* artesunate-sulfadoxine-pyrimethamine, *DHPP* dihydroartemisinin-piperaquine, *PP* per-protocol, *ITT* intention-to-treat, *OR* odds ratio, *CI* confidence interval

## 4 Discussion

Surveillance of antimalarial drug efficacy is crucial to enable early detection of emergence of drug resistance

**Table 4** Fever and parasite clearance in efficacy trials in Cameroon

| Study ID | Fever clearance (%) | | | Parasite clearance (%) | | | Supervised |
|---|---|---|---|---|---|---|---|
| | Day 1 | Day 2 | Day 3 | Day 2 | Day 3 | Day 7 | |
| CMR001_ASSP | 25 | 50 | 90.9 | NR | 99 | 99 | Partial |
| CMR001_ASAQ | 25 | 50 | 92 | NR | 99 | 99 | Partial |
| CMR002_AL | 86 | 87.5 | 99.8 | 99.8 | 99.8 | 95 | Yes |
| CMR002_ASAQ | 90 | 96 | 99.8 | 99.1 | 99.8 | 95 | Yes |
| CMR002_DHPP | 90 | 95 | 99.8 | 99.1 | 99.8 | 90 | Yes |
| CMR003_ASAQ | 98.5 | 69 | 98.5 | 80.9 | 97.1 | NR | Yes |
| CMR003_ASATPG | 98 | 100 | 99 | 97.1 | 99 | NR | Yes |
| CMR004_ASAQ | 81 | 90 | 95 | 85 | 95 | 98 | Partial |
| CMR004_AL | 80 | 89.1 | 95 | 90 | 96 | 98 | Partial |
| CMR005a_ASAQ | 90 | 94.7 | 98.2 | 87.7 | 100 | 98.2 | Yes |
| CMR005a_ASSP | 81.90 | 98.2 | 100 | 89.7 | 96.6 | 100 | Yes |
| CMR005b_ASAQ | 92.10 | 98.3 | 98.3 | 87.9 | 98.3 | 100 | Yes |
| CMR005c_ASMQ | 86.8 | 96.9 | 98.3 | 86.2 | 95.3 | 100 | Yes |
| CMR005d_ASAQ | 93.1 | 95.1 | 98.3 | 96.6 | 98.3 | 100 | Yes |
| CMR005d_AL | 78.3 | 93.5 | 98.3 | 93.3 | 100 | 100 | Yes |
| CMR005e_ASCD | 84.9 | 97.6 | 100 | 95.1 | 100 | 100 | Yes |
| CMR005e_ASSP | 96.3 | 96.3 | 100 | 92.9 | 97.6 | 100 | Yes |
| CMR005f_ASAQ | 92.3 | 98.9 | 100 | 94.6 | 98.9 | 98.9 | Yes |
| CMR005f_DHPP | 92.3 | 96.7 | 92.3 | 94.5 | 100 | 100 | Yes |
| CMR006_ASMQ | NR | NR | NR | NR | NR | NR | Partial |

*NR* not reported

before it spreads to most of the parasite population, as happened with chloroquine, sulfadoxine-pyrimethamine, and amodiaquine monotherapies in Cameroon [6, 28–30]. The present review was undertaken to assess the implementation of the efficacy test for monitoring therapeutic efficacy of ACT for the treatment of uncomplicated falciparum malaria in Cameroon before and after policy changes (in 2006).

Our findings showed that 11 clinical trials, extracted from six published articles, were conducted to monitor the efficacy of ACT before and after Cameroon adopted ACT for the treatment of uncomplicated malaria. Of these, only one study had the financial support of the Cameroonian Ministry of Public Health [23], which might be partly due to a lack of funding or complacency attributed to a perceived high therapeutic efficacy of ACT.

The efficacy of AL against uncomplicated *P. falciparum* infections in Cameroon was very high, with PCR-corrected cure rates (PP analysis) ranging from 96.7 to 100%. The efficacy of ASAQ was slightly lower, with PCR-corrected cure rates (PP population) of 88.2–100%. In an ITT analysis, the cure rates with AL and ASAQ were 86.2–96.7% and 74.0–90.6%, respectively. These results are similar to those obtained by Ebai et al. [31] who observed 96% ACPR when using the PP approach, and 71.3% ACPR when using the ITT approach, for ASAQ on day 42, although PCR was not performed. This result indicates that the recommendation of the Cameroonian antimalarial drug policy is appropriate in the present context of resistance to chloroquine, sulfadoxine-pyrimethamine, and amodiaquine monotherapies. The PCR-corrected cure rates of ASAQ in the present review are comparable with those reported elsewhere in Central Africa. For example, the proportion of day 28 ACPR in children treated with ASAQ was 93% in the Central African Republic [32], 90% in Nigeria [33], 98.3% in the Democratic Republic of Congo [34] and 97% in Congo-Brazzaville [35]. These proportions of ACPR were comparatively lower or similar to those of AL, i.e. 100% in the Central African Republic [32], 100% in Nigeria [33], 99.1% in the Democratic Republic of Congo [34] and 96.4% in Congo-Brazzaville [35].

Despite the insufficiency of evidence regarding ACT efficacy in Cameroon, the present review has suggested that the efficacy of ASAQ, which is a first-line antimalarial drug, is decreasing in that country. In 2009, the overall PCR-corrected cure rate was 96.4% in the central region [25]. More recently, the drug was still effective (90.2% PCR-corrected cure rate) in regions around Mount Cameroon in western Cameroon [27]. AL efficacy was reported to have decreased slightly, from 100% in 2006 [22] to 96.7% in 2013 [24], but further studies are required to confirm this tendency. During the same period, ASSP had a lower efficacy rate (85.9–94.7%) than that of ASAQ. Most of the trials were carried out in high transmission areas where the post-therapeutic prophylactic effect of ASAQ and AL is limited.

**Table 5** Adverse events reported in efficacy trials in Cameroon

| Study ID | Tolerability and adverse events from days 1 to 7 | Comments |
|---|---|---|
| CMR001_ASSP | Cough (0.19%); catarrh (0.07%); dizziness (0.07%); fatigue (0.07%); nausea (0.02%) | AEs were probably related to the study drug, and were mainly of minor or moderate intensity |
| CMR001_ASAQ | Abdominal pain (0.02%); cough (0.16%); catarrh (0.06%); diarrhoea (0.01%); dizziness (0.32%); anorexia (0.034%); fatigue (0.26); nausea (0.046%); jaundice (0.03%) | |
| CMR002_AL | Abdominal pain (3.6%); anorexia (0.72%); joint pain (1.4%); cough (6.5%); diarrhoea (2.8%); fatigue (2.2%); rash (2.9%); vomiting (5.8%) | One serious AE occurred in a child who experienced severe fatigue after AL ingestion |
| CMR002_ASAQ | Abdominal pain (2.1%); anorexia (2.9%); joint pain (0.71%); cough (4.7%); diarrhoea (2.8%); fatigue (2.5%); rash (6.4%); vomiting (11.1%) | Abnormal biological values were not accompanied by persistent signs or symptoms suggestive of any serious AE |
| CMR002_DHPP | Abdominal pain (4.6%); anorexia (4.3%); joint pain (0.71%); cough (6.4%); diarrhoea (3.2%); fatigue (1.4%); rash (5.7%); vomiting (9.6%) | |
| CMR003_ASAQ | Individual AEs reported by childrens' legal guardians were headache and gastrointestinal disorder | No serious AE was reported |
| CMR003_ASATPG | Nausea, vomiting, cough during 2–3 days of follow-up | |
| CMR004_ASAQ | Abnormalities (leucopenia, neutropenia and anaemia) in laboratory results (33.8%) | No serious AE was observed |
| CMR004_AL | Abnormalities (leucopenia, neutropenia and anaemia) in laboratory results (30.4%) | No serious AE was observed |
| CMR006_ASMQ | Vomiting (two children over a 3-day period); insomnia (7%); altered eating behaviour (4.7%); headache (3.7%) | Insomnia was a drug-related neuropsychiatric AE in four (1.9%) patients. In addition, aggressive behaviour, vertigo, nightmare and hyperactivity were reported, which were of mild to moderate severity |

*AE* adverse event

Although artesunate-chlorproguanil-dapsone (ASCD) efficacy was evaluated in one study [22], it is no longer available since the manufacturer ceased its production due to severe adverse reactions.

Taking together the available evidence on treatment efficacy in Cameroon, NMA was carried out to derive relative treatment effects compared with ASAQ. The results suggested that ASAQ and AL efficacies are similar. This finding is in agreement with recent work undertaking NMA of antimalarial trials in Africa [14]. One of the advantages of using NMA is that it suggests new clinical trials at a country level. For instance, the combinations of ASATPG and DHPP have not yet been evaluated in an RCT. Therefore, the network of evidence offered the possibility of investigating their relative efficacies in forthcoming studies to allow a consistent network; however, due to the limited evidence, the results may be unreliable. An increased number of existing trials, and performance of new clinical trials, could lead to a coherent network and the availability of sufficient data to support decision making at the country level.

The WHO currently recommends treatment with ACT for 3 days. A triple combination therapy of dihydroartemisinin-piperaquine-trimethoprim (DPT) tested in a multicentric setting, including Cameroon, seemed to be a promising alternative for reducing the treatment period to 2 days, with excellent therapeutic efficacy comparable to AL, and faster parasite clearance [20]. However, further studies will be needed, in particular a comparative study with DHPP.

In 2006, the efficacy of ASMQ was compared with that of AQSP [22]. Because of insufficient safety and tolerability data for ASMQ, its deployment in this setting has been restricted, and there has been concern regarding the use of this combination in African children [35–37]. One reason for this data gap was the lack of an appropriate paediatric formulation until recent years [38, 39]. The efficacy of a fixed-dose paediatric formulation of ASMQ (Artequin Pediatric), administered once daily for 3 days, was evaluated in a non-randomised study [26]. The PCR-corrected cure rate, estimated by survival analysis on days 28 and 63, was 96.6%. Despite the non-comparable study design, and new infections that were observed in 11.2% of evaluable patients on day 63, the new paediatric formulation was well-tolerated and efficacious.

Among 11 clinical trials analysed in this review, two trials tested DHPP for the treatment of uncomplicated malaria—one with a 28-day follow-up [22] and the other with a 42-day follow-up [24]. The PCR-corrected cure rates of DHPP ranged from 84.0 to 92.3%. Although only one study compared AL with DHPP, and there was no statistically significant difference in efficacy as reported by the network, DHPP has been found to be an alternative first-line or rescue treatment in Zambian children under 5 years of age [40]. Although DHPP was more recently reported as the most effective drug combination among WHO-recommended ACTs [14], its day 28 efficacy in this study could have been overestimated because of the long elimination half-life of piperaquine.

The slightly decreased efficacy of ASAQ, compared with AL, could possibly be attributed to the fact that AQ had been extensively used in Cameroon as an alternative first-line antimalarial drug (chloroquine was the other first-line drug) for many years, until 2004. However, AQ monotherapy remained highly effective in Cameroon until 2004, when ASAQ was officially adopted [22]. Cross-resistance between chloroquine and AQ may explain why ASAQ may fail at a faster rate than AL in highly chloroquine-resistant areas. In addition, the presence of mutations associated with AQ resistance was more recently reported in Cameroonian clinical isolates of *P. falciparum* [23, 30].

Other combinations, such as ASATPG, have been tested in Thai subjects, including children < 5 years of age and pregnant woman [41–43]. It has also been tested once in Yaounde, in children aged ≤ 5 years, in an open-label, randomised study that included other antimalarials (ATPG and ASAQ). ASATPG had no treatment failures occurring on or after day 7. In addition, among 98 patients (PP population) treated with ASATPG, only one child still had a parasite-positive smear on day 3, but this patient was afebrile from day 1 onward [25]. ASATPG appeared as a highly effective alternative, with a PCR-corrected cure rate ranging from 95 to 100% (PP and ITT populations).

Regarding drug tolerability and safety, results have shown that some mild or moderate adverse events, such as vomiting, fatigue and anorexia, were more likely to be present in patients treated with ASAQ than AL [24, 27]. A study in Africa, including Cameroon, also revealed that gastrointestinal symptoms (vomiting and diarrhoea) were more often present after AL administration than other ACTs, and less frequent with artesunate-sulfamethoxypyrazine-pyrimethamine (ASSMP) [17]. In addition, respiratory symptoms, including cough, were more frequent in children treated with AL, which is in line with previous findings that showed that respiratory symptoms were commonly observed in African children with malaria, but these adverse events were attributed to symptoms or progression of malaria and not directly to antimalarial drugs [44]. In the present review, one serious adverse event occurred in a child who experienced severe fatigue after AL ingestion [24], but was resolved after a 3-day hospitalisation and adequate clinical care. This finding is similar to that observed in the Democratic Republic of Congo where anorexia and physical weakness were commonly observed after ASAQ treatment, compared with AL [45]. Although these earlier observations lend support to the results of the present review, the limited number of studies on ASAQ, AL and DHPP does not allow a comparison of the safety profiles of different antimalarials. However, in

one study with ASSP treatment, it was reported that adverse events were probably related to the drug [27].

ACT medicines have been deployed because of the widespread resistance of *P. falciparum* to cheap and widely used classical antimalarial drugs, chloroquine and sulfadoxine-pyrimethamine. In addition, an excessive and unjustified utilisation of ACT medicines in unconfirmed malaria could favour the development of drug resistance. A recent survey showed that among febrile individuals in Tanzania, a high proportion without confirmed malaria self-medicate with an ACT and, on the contrary, a low proportion of febrile individuals with confirmed malaria bought an ACT for self-medication [46]. National antimalarial drug policies, including the need for a reliable, laboratory-confirmed malaria diagnosis and choice of drug, are still not well-implemented in the field; therefore, there is a need to better target the individuals who receive ACTs as accurate diagnosis is fundamental to improving healthcare delivery [47]. This suggests a need for qualitative studies to complete RCTs for better monitoring in the field.

### 4.1 Limitation of this review

The main limitation of this work was the insufficient number of trials, which leads to less-conclusive results. This may be due to the fact that clinical studies and long-term follow-up of patients require logistics and incur high cost in the African context, limiting regular or routine implementation of clinical evaluation within the country.

All trials that compared at least two treatments were at low risk of selection bias (electronic supplementary file 4). One non-inferiority trial [24], as well as other studies [17, 18, 23], used single blinding. All trials reported attrition, with details of all randomised participants. Regarding selective reports, four trials were prospectively registered [17, 18, 24, 25], as ascertained from the data presented in the reports and the trial numbers available. Other potential sources of bias were related to the method used to assess adverse events, which was not well-described in one study [26], as well as the randomisation procedure and blinding in the series of trials presented in another study [22]. Another limitation to the present work is the sensitivity analysis. Although sensitivity analysis was conducted with some excluded studies, the assumption in the NMA and its results could be unreliable and would need to be strengthened with more evidence.

Nonetheless, regular assessment of the therapeutic efficacy of first-line antimalarial drugs should be a priority for national malaria control programmes because effective monitoring of ACT has relied, and will continue to rely, largely on clinical studies with adequate follow-up. The WHO recommends that antimalarial drug efficacy studies be performed at sentinel sites at least every 2 years. Furthermore, assessment of drug access in public, private and not-for-profit sectors is needed, as recently initiated in Kenya [48], in order to support decision making.

## 5 Conclusions

This review has shown that available data on the efficacy of ACTs, in particular ASAQ and AL, two first-line antimalarial drugs adopted by the Cameroonian national drug policy, are inadequate. Based on the available evidence, our findings revealed the high efficacy and safety of both ASAQ and AL in the PP population, and support the continued use of these drugs in Cameroon. Information generated from this review of surveillance data will be relevant to national and international authorities for policy formulation and changes. Regular clinical assessment of WHO-recommended ACTs in sentinel sites, together with molecular analysis of relevant markers [Kelch 13, *P. falciparum* multidrug resistance gene 1 (*pfmdr1*), and *P. falciparum* chloroquine resistance transporter (*pfcrt*)], is required to monitor parasite sensitivity to ACT, and consolidate and improve evidence-based national antimalarial drug policies.

**Acknowledgements** The authors would like to thank all researchers who made their data on antimalarial drug efficacy in Cameroon available for scientific purposes. SWY would also like to thank Henri Gwét (National Advanced School of Engineering, Cameroon) for advice and encouragement.

**Funding** No specific funding was obtained for this review.

### Compliance with Ethical Standards

**Conflict of Interest** Solange Whegang Youdom, Andreas Chiabi and Leonardo K. Basco declare that they have no conflicts of interest.

**Availability of Data and Materials** Data used in this study can be found in the text file and in electronic supplementary files 1, 2, 3 and 4.



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