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Comparison of Efficacy and Safety of Artemisinin-Based Combination Therapies for Treating Uncomplicated Falciparum Malaria in Sub-Saharan African Countries: An Update on the Changes in Efficacy Using Network Meta-Analysis

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Abstract

Background: Several artemisinin-based combination therapies (ACT) are available to treat uncomplicated malaria in Africa. The present study aimed to assess the ranking of their efficacy and tolerance. **Methods:** A database of randomized controlled trials was retrieved from published papers. Network meta-analysis was used to compare efficacy on day 28 and day 42 after initiation of treatment. Age covariate effect on treatment outcome was assessed, and a modeling approach to reduce heterogeneity among trials was evaluated under the hypothesis of consistency in a meta-regression. Safety and adverse events were compared among different ACTs. A Bayesian analysis was performed to implement the consistency models using WinBUGS software. The results were compared to those of the frequentist approach using the R software. **Results:** Eighty-one articles, in which a total of 15 different ACTs were tested in more than 36,000 patients, were included. On day 28, dihydroartemisinin-piperaquine (DHPP) was more effective than artemether-lumefantrine (AL) before (odds ratio [OR], 1.83; 95% confidence interval [CI], 1.31 - 2.56) and after age-covariate adjustment (OR, 1.70; 95% CI, 1.20 - 2.43). The result was similar on day 42. DHPP occupied the top rank. The risk of having cough,

diarrhoea or headache post-treatment was significantly lower with DHPP than AL. Artesunate-mefloquine (ASMQ) was associated with a significantly lower prevalence of vomiting or nausea (OR, 0.80; 95% CI, 0.48 - 1.30) and headache (OR, 0.53; 95% CI, 0.40 - 0.68) compared to AL. On the contrary, vomiting and nausea occurred more frequently after fixed-dose artesunate-amodiaquine formulation (ASAQf) than with AL (OR, 1.45; 95% CI, 1.18 - 1.78). The risk of anaemia was higher with ASAQf and co-blistered artesunate-amodiaquine (ASAQc) than with AL. There was no significant difference in risk of anaemia ($P > 0.05$) between AL and different formulations of ASAQ. **Conclusions:** Based on the available evidence, this study demonstrated the superiority of DHPP, followed by AL, among currently recommended ACTs in terms of efficacy and tolerance. Network meta-analysis could be an alternative analytical tool but needs more data input from therapeutic efficacy studies. The determination of the best available therapy requires data triangulation and data science.

Keywords

Malaria, Dihydroartemisinin-Piperaquine, Artesunate-Amodiaquine, Efficacy, Safety, Network Meta-Analysis

1. Background

Since the World Health Organization (WHO) recommended artemisinin-based combination therapy (ACT) as the first-line treatment of uncomplicated *Plasmodium falciparum* malaria, there has been a growing interest in field-based randomized controlled trials. Most African countries adopted this drug policy during the 2000s, resulting in a large amount of published evidence-based data on the efficacy, tolerability, and safety of these antimalarial drugs. Antimalarial drug efficacy is usually assessed in therapeutic efficacy studies based on the standardized WHO protocol, initially published in 1994 and updated in 1996, 2003, and 2009 [1] [2] [3] [4]. The amount of data being generated in the field is ever-increasing, and the results of many, but not all studies, have been published. Because of this growth of evidence-based data, novel methods to collect, analyze, and summarize clinical data to identify the best available therapy have become indispensable.

Systematic reviews and meta-analyses have become a common approach to extracting relevant information from therapeutic efficacy studies based on either individual patient data or study level data (*i.e.*, aggregate data) [5] [6] [7] [8]. However, analysis requires an identification of the event of interest and study of effect modifiers. The event of interest can be both a good or poor outcome (*i.e.*, treatment success or treatment failure) and a time-fixed or time-dependent variable. The use of network meta-analysis (NMA), a meta-regression analysis with dummy variables for treatments that can be used to analyze effect within cova-

riate levels, is advocated by some authors [6] [7].

WHO-recommended ACTs include the following drug combinations: artesunate-amodiaquine (ASAQ), artesunate-sulfadoxine-pyrimethamine (ASSP), artemether-lumefantrine (AL), dihydroartemisinin-piperaquine (DHPP), and artesunate-mefloquine (ASMQ) [9]. The sixth combination, artesunate-pyronaridine (ASPY), has undergone field evaluation, and it was recently added to this list of WHO-approved ACTs [9] [10] [11]. There are also several non-WHO-recommended ACTs, including artesunate-sulfamethoxypyrazine-pyrimethamine (ASSMP), dihydroartemisinin-piperaquine-trimethoprim triple combination (DHPPT), artesunate-atovaquone-proguanil (ASATPG), artemisinin-naphtoquine (ASNAPH), artesunate-amodiaquine-chlorpheniramine (ASAQCPH), and arterolane maleate-piperaquine phosphate (AMPP), that are used in some countries to treat *P. falciparum* malaria [12] [13] [14]. In addition, a non-ACT combination, amodiaquine-sulfadoxine-pyrimethamine (AQSP), had been deployed during the transition period in the 2000s before the full adoption of ACTs in many African countries, and its efficacy had been compared to that of ACTs in randomized clinical studies [15] [16] [17].

The doses of ACT are variable, and for ASAQ, several different doses and formulations have been used. Most ACTs are administered as a single daily dose for three days. The fixed-dose AL is an outstanding exception, requiring twice daily doses for three days (a total of six doses administered over three days, with an 8-hr interval between the first and second dose). ASAQ is administered as a once daily fixed-dose combination (FDC) or twice daily doses for three days [18] [19]. ASAQ dose varies due to the availability of three formulations: non-fixed dose combinations (NFDC), which may be either loose NFDC (ASAQl) or co-blistered NFDC (ASAQc), and fixed-dose combinations (ASAQf) [20]. The dose effect should be taken into consideration in the comparison of antimalarial drugs.

AL, ASAQ, and DHPP have been found to be safe for use in children, but a non-negligible number of adverse events have been associated with the intake of ACT [5]. In an earlier work [21], DHPP was identified as the best available ACT to treat uncomplicated falciparum malaria in terms of efficacy and safety. At the point where the public health community needs a comprehensive, reliable and timely information to slow the emergence of antimalarial drug resistance and maintain the efficacy of antimalarial treatments, there is a need for an update on the efficacy, safety, and tolerability of available ACTs and a strategy to reduce heterogeneity in the evaluation of treatment by considering baseline characteristics of the study. Given an increasing number of ACTs and published studies on their safety profile in children, the aim of the present study was to investigate the modifiers of treatment effect by analyzing treatment by covariate interactions and adverse events associated with each ACT.

2. Methods

2.1. Data Collection and Extraction of Effect Modifiers

Data were extracted from a recent database of randomized clinical trials involv-

ing children and adults (excluding pregnant women) with uncomplicated falciparum malaria [21]. In that previous work, several articles were selected, involving 13 ACT drug regimens to treat approximately 36,000 patients in children and adults in sub-Saharan African countries. Indeed, a new search using the same criteria as the previous work [21] was performed between August 2017 (the month of the publication of the previous work) and December 2017, and more recent studies published between 2017 and December 2020 were added. For the present study, the completed database was re-assessed, and studies that evaluated adverse events and polymerase chain reaction (PCR)-corrected efficacy on days 28 and 42 were retrieved. The primary outcome considered in the present study was the PCR-corrected rate of adequate clinical and parasitological response (ACPR). Secondary outcomes were fever clearance, parasite clearance, gametocyte carriage on days 0, 7, or 14, and change in haemoglobin from baseline values on day 0 (minimum 28-day follow-up). Adverse events that were assessed (any time after drug administration) included headache, dizziness, palpitation, anorexia, abdominal pain, vomiting, nausea, diarrhoea, fatigue or weakness, anaemia, drowsiness, asthenia, cough, pruritus, and rash. Serious drug-related adverse effects were also included.

The intention-to-treat approach (ITT) was used to extract the number of participants randomized and assigned to each treatment group with the aim of restoring the integrity of the randomization process. For the dichotomous outcome of both efficacy (*i.e.*, treatment success or treatment failure) and safety (the presence or absence of adverse events), the number of participants who experienced the event on each follow-up day up to 28 days was evaluated. Covariates were age, parasite density, weight, and baseline body temperature. Age was standardized, and parasite density was transformed to logarithmic values to derive normally distributed covariate values. The effects of different doses and formulations of ASAQ and adverse events for each treatment were also evaluated. Randomized clinical trials analyzed in this work reported the study type (multi-centre, randomized, open-label), with details and outcome of all randomized participants (complete follow-up, withdrawal, lost-to-follow-up, and exclusion).

2.2. Antimalarial Drugs

Drugs were assigned numbers from 1 to 13 as in our previous study [21]. With two additional formulations of ASAQ found in the database, the numbering for drug combinations was extended to 15, *i.e.*, AL was assigned treatment number 1, which represents the common comparator drug, 2 = AQSP, 3 = ASAQc, 4 = ASAQf, 5 = ASAQl, 6 = ASAQCPH, 7 = ASATPG, 8 = ASCD, 9 = ASMQ, 10 = ASNAPH, 11 = ASPY, 12 = ASSMP, 13 = ASSP, 14 = DHPP, and 15 = DHPPT.

2.3. Measures of Treatment Effect and Statistical Analysis

The primary outcome, *i.e.*, the proportion of ACPR, was combined and pre-

sented using the OR in the ITT population. Direct and indirect comparisons were extracted. The global statistical modeling based on a randomly mixed effect model was presented in some research works [21] [22]. In addition to that model, a meta-regression analysis was developed using the existing code, with age covariate to assess the change in efficacy of the different interventions. All analyses were based on a random effect model to account for different end-point evaluations. Heterogeneity was explored using I_2 statistics and test of inconsistency. To account for heterogeneity in the patient populations, a dummy random variable was defined as 1 if the patient was a child less than 15 years and 0 for other patient populations. In addition, meta-regression was used to assess the changes in treatment effect with the same heterogeneity variance assumed for every comparison and the effect of covariates on treatment effect. The age covariate was used to fit an NMA-regression model. Studies with missing covariates were excluded. AL was the main comparator drug.

2.4. Choice of Prior Probability Distribution

All treatment effect was given uniform priors between −10 and 10. This strategy avoids numerical "traps" encountered when running the model with a uniform prior between 0 and 20 [23]. Prior age covariate effect distribution was given a flat normal distribution N (0, 10^{-5}). Vague prior between-trial standard deviation was a uniform distribution between 0 and 20.

2.5. Treatment Ranking

To measure how the treatment was comparatively better than another treatment, P-scores were used and averaged over different treatments [24]. The method was found to be comparable with the surface under the cumulative ranking curve (SUCRA) [25]. All analysis was carried out using WinBUGS and the R package net meta [26].

3. Results

3.1. Description of Included Studies

Table 1 presents the number of studies for each treatment arm and the number of comparisons between different ACTs and the comparator drug AL on days 28, 42, and 63. Of 85 studies, 81 assessed the efficacy on day 28 (Supplementary Table 1), 2 studies on day 35 [14] [15] (Supplementary Table 1), 4 studies on day 42 only (Supplementary Table 1), 2 studies on day 28 and 63 (Supplementary Table 1), and 20 studies on day 28 and day 42 (Supplementary Table 1). Among these studies, the efficacy of different doses of ASAQ was assessed in 17 studies. A total of 71 studies had an age covariate available with a 28-day endpoint. The studies that reported adverse events (n = 43) are summarized for each treatment in Supplementary Table 2 and Supplementary Table 3.

Table 1. Description of the number of studies for each treatment arm and adverse events.

Treatments	No. of studies with adverse events*	Total randomized sample	No. of studies with adverse events at each time point		No. of studies with PCR-corrected ACPR**	No. studies/No. of patients with PCR corrected ACPR (total assessed)			
			Day 28	Day 42		Total randomized participants with ACPR on Day 28	Day 28	Total randomized participants on Day 42	Day 42
AQSP	5	793	4	5	10	2623	10/1684		1/439
AL	41	8979	38	12	63	13,435	63/11,546		20/3420
ASAQc	5	1226	3	2	5	1441	3/1185		2/282
ASAQCPH	1	54	1	1	1	54	1/47		
ASAQf	10	2478	9	4	17	4225	17/3832	1085	6/856
ASAQl	9	929	8	1	22	2857	22/2407	238	2/199
ASATPG	1	100	1	0	1	70	1/60	0	0
ASCD	3	1505	2	0	3	677	1/521	359	1/302
ASMQ	3	552	2	1	5	683	5/646	302	2/204
ASPY	1	355	1	0	1	673	628	565	673
ASSMP	3	837	3	0	4	1087	4/1022		
ASSP	2	750	2	0	14	1976	13/1790	135	1/112
DHPP	15	4938	14	7	24	6972	24/5655	2400	9/2111
DHPPT	1	212	1	0	1	212	204		

Zero or empty cells means that there were no studies evaluated at that time point. *43 studies reported adverse events. **81 studies assessed the efficacy of day 28.

Table 2. Multiple comparison of therapeutic efficacy among various ACTs and a non-ACT combination on day 28.

WinBUGS			**R**		
With age covariate n = 71 studies	AL as the comparator	Without age covariate; n = 81 studies	ASAQf as the comparator	Without age covariate; n = 81 studies	ASAQl as the comparator
	OR; 95% credibility intervals		OR; 95% credibility intervals		OR; 95% credibility intervals
AQSP	0.9 [0.5; 1.6]	AQSP	0.64 [0.34; 1.21]	AQSP	0.99 [0.54; 1.80]
ASAQc	1.03 [0.48; 2.23]	AQASc	0.66 [0.26; 1.64]	AQASc	1.02 [0.41; 2.50]
ASAQf	1.37 [0.9; 2.08]	AQASl	0.65 [0.37; 1.12]	AQASf	1.53 [0.88; 2.67]
ASAQl	0.96 [0.64; 1.44]	AL	0.77 [0.51; 1.16]	AL	1.18 [0.80; 1.76]
ASAQCPH	1.51 [0.33; 6.81]	ASAQCPH	1.01 [0.20; 5.33]	ASAQCPH	1.56 [0.31; 7.79]
ASATPG	3.24 [0.54; 19.38]	ASATPG	2.04 [0.30; 14.05]	ASATPG	3.15 [0.49; 19.95]

Continued

ASCD	0.7 [0.36; 1.36]	ASCD	0.61 [0.27; 1.37]	ASCD	0.94 [0.41; 2.11]
ASMQ	1.25 [0.52; 2.98]	ASMQ	0.90 [0.37; 2.14]	ASMQ	1.37 [0.57; 3.27]
ASNAPH	0.01 [2×10^{-5}; 1.38]	ASNAPH	0.01 [0.004; 2.32]	ASNAPH	0.14 [0.0061; 3.57]
ASPY	1.9 [0.66; 5.45]	ASPY	1.30 [0.42; 3.93]	ASPY	1.98 [0.65; 6.03]
ASSMP	1.4 [0.55; 3.57]	ASSMP	0.96 [0.41; 2.24]	ASSMP	1.48 [0.60; 3.66]
ASSP	1.03 [0.61; 1.74]	ASSP	0.69 [0.36; 1.30]	ASSP	1.06 [0.63; 1.78]
DHPP	1.88 [1.27; 2.78]	DHPP	1.25 [0.75; 2.06]	DHPP	1.92 [1.16; 3.17]
DHPPT	1.99 [0.35; 11.37]	DHPPT	1.10 [0.18; 6.74]	DHPPT	1.70 [0.28; 10.34]

81 studies met the criterion of 28-day PCR-corrected ACPR. The comparator was varied to enable comparison with different ASAQ doses.

Table 3. Assessment of the efficacy of WHO-recommended ACTs on day 42.

ACT	Estimate of therapeutic efficacy		
	Odds ratio	95% confidence interval	*P*-value
AL	1.00	[0.34; 3.41]	(comparator drug)
AQSP*	0.78	[0.36; 1.70]	0.53
ASAQ	0.94	[0.587; 1.489]	0.77
ASMQ	1.07	[0.34; 3.41]	0.90
ASPY	1.42	[0.64; 3.12]	0.39
ASSP	1.78	[0.49; 6.48]	0.38
DHPP	1.65	[1.06; 2.56]	0.02**

Twenty studies were combined, and comparison was made with other treatments, using AL as the comparator drug. *AQSP, a non-WHO-recommended, non-ACT combination, was included for comparison since several African countries have adopted it during the transition period in the 2000s before full implementation of ACT-based antimalarial drug policy. Quantifying heterogeneity/inconsistency: $tau^2 = 0.2940$; tau = 0.5422; $I^2 = 76.3\%$ [62.3%; 85.1%]. **Statistically significant ($P < 0.05$).

3.2. Analysis of the Efficacy Trials on Day 28

The updated malaria network evidence illustrated in Figure 1 shows different drug combinations, including ASAQ with different dosages, which were compared with each other. The comparison between different ACTs and AL in the presence of age covariate, as well as the comparison of different doses of ASAQ in the absence of age covariate, is summarized in Table 2. DHPP was more effective than AL in the presence of age covariate (OR = 1.88, 95% confidence interval [CI], 1.27 - 2.78). In the absence of age covariate with ASAQl as the comparator, DHPP was also more effective (OR = 1.92, 95% CI, 1.16 - 3.17). On the other hand, given either ASAQl or ASAQf as the comparator, a non-statistical difference ($P > 0.05$) was found between different ACTs.

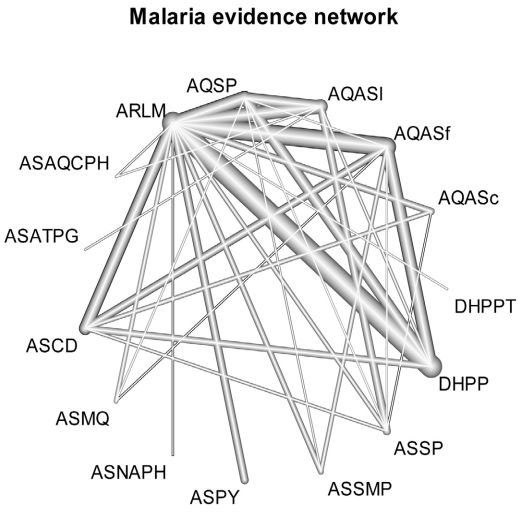

Figure 1. Malaria evidence network. Data from 81 studies were used to build the malaria evidence network of 15 combination therapies assessed on day 28. The number of different ACTs compared in randomized clinical trials is proportional to the thickness of the connecting lines. In the present study, AL and DHPP, followed by AL and ASAQf, were compared most frequently. *AQSP, a non-ACT combination, was included for comparison.

3.3. Clinical Efficacy on Day 42

A total of 20 studies assessed clinical efficacy on day 42 with two or more of the following combinations: AQSP, ASAQ, AL, ASMQ, ASPY, ASSP, and DHPP (Table 3). ASCD was excluded from analysis because this ACT is not recommended, and its production had ceased due to serious adverse effects associated with dapsone in African patients with glucose-6-phosphate dehydrogenase deficiency. By setting AL as the comparator, DHPP was 1.6-fold more efficacious than AL (OR = 1.65; 95% CI, 1.06 - 2.56; $P < 0.05$) (Table 3). On day 42, the difference in therapeutic efficacy between AL and ACTs other than DHPP was not statistically significant ($P > 0.05$).

3.4. Secondary Outcome Results

The safety of AL, as compared with other ACTs, was assessed. Adverse events were extracted from 43 studies. Thirty-eight of 81 studies did not report drug tolerance. The frequency of adverse effects and studies in which they were assessed are presented in Supplementary Table 3. The adverse events reported in different studies are summarized in Table 4 and Table 5. Adverse events were heterogeneous among studies. The common adverse events (≥1/100 and <1/10) among patients receiving AL included the following: anorexia, vomiting, anaemia, diarrhoea, vomiting, and abdominal pain (Table 4). Cough was the only very commonly reported adverse events (≥1/10) of AL and DHPP. The respiratory and gastrointestinal tracts were the most commonly affected organs, constituting 35% and 33% of all reported adverse events in AL-treated children, respectively. The number of events was very low with new alternative drugs (Table 4), while adverse events were more prevalent with ASSMP (Table 5).

Table 4. Organ system classification and frequency of adverse events during follow-up for WHO-recommended therapies from 43 studies.

Organ system		AL	DHPP	ASAQc	ASAQf	ASAQl	AQSP†	ASMQ	ASSP
Cardiovascular	Palpitation	6 (0.7)*		3 (2.5)*					
Central nervous system	Headache	429 (47.8)	270 (54.7)	70 (57.1)		2 (2.2)	66 (8.3)	67 (121.4)	5 (6.66)
	Dizziness	67 (7.5)	23 (4.6)	33 (29.9)	32 (12.9)	57 (61.4)		18 (32.6)	6 (8)
Gastrointestinal	Anorexia	380 (42.3)	344 (69.7)	43 (35.1)	116 (46.8)	56 (60.3)	90 (11.3)		2 (2.66)
	Abdominal pain	425 (65.9)	367 (74.3)	106 (86.5)	23 (9.3)	84 (90.4)	113 (14.2)	24 (43.5)	9 (12)
	Vomiting, nausea	592 (65.9)	360 (72.9)	134 (109.3)	197 (79.5)	131 (141.0)	105 (13.2)	60 (108.7)	69 (92)
	Diarrhoea	445 (49.6)	424 (85.9)	16 (13.0)	136 (54.9)	27 (29.1)	47 (5.9)	3 (5.4)	
General	Weakness	256 (47.3)	54 (10.9)	5 (4.1)	4 (1.6)	43 (46.3)	75 (9.4)	145 (262.7)	
Haematological	Anaemia D7	513 (57.1)	112 (22.7)	107 (87.3)	125 (50.4)	11 (11.8)	57 (7.2)	191 (346.0)	
Haematological	Anaemia > D7	141 (15.7)	158 (32.0)		143 (57.7)	93 (100.1)			
Others	Drug_related_AE	23 (2.6)*	4 (0.8)*		36 (14.5)				
	Drowsiness	12 (1.3)		5 (4.1)	14 (5.6)	13 (14.)	2 (0.2)		
	Asthenia	177 (19.7)	153 (31.0)	107 (87.3)	39 (15.7)				
Respiratory	Cough	1087 (121.1)	1155 (233.9)	40 (32.6)	346 (139.6)	78 (84.0)	162 (20.4)		16 (21.33)
Skin and appendages	Pruritus	51 (5.7)	34 (6.9)	16 (13.0)	49 (19.8)	8 (8.6)	48 (6.0)	5 (9.0)	
	Rash	42 (4.7)	86 (17.4)	1 (0.8)	18 (7.26)	8 (8.6)			
Total studies with treatment arm		41	15	5	10	9	5	3	2
Studies with/without AL and the treatment group				5			4	3	1
Total sample size		8979	4938	1226	2478	929	793	552	750

*Risk per 1000 patients; D: day; AE: adverse event. †AQSP, a non-WHO-recommended, non-ACT combination, was included for comparison.

Table 5. Organ system classification and number of adverse events reported for new alternative ACTs from 43 studies.

Organ system	Adverse events	Sample size*				
		ASAQCPH	ASATPG	ASPY	ASSMP	DHPPT
		54	100	355	837	212
Gastrointestinal	vomit_nausea		29	30	52	21
Haematological	Anaemia D7			49		
Haematological	Anaemia					
Gastrointestinal	Abdominal pain		37		55	5
Gastrointestinal	Diarrhoea				10	2
Skin and appendages	Pruritus				3	6
General	Weakness				11	
Respiratory	Cough			44		1
Gastrointestinal	Anorexia				19	
Central nervous system	Headache				24	
Skin and appendages	Rash					1
Cardiovascular	Palpitation					
Others	Drowsiness	7				
Others	Asthenia					2
Central nervous system	Dizziness				14	1

*Randomized sample size for each combination. D: day; AE: adverse event.

For studies comparing AL with other ACTs, the risk of adverse event was compared (Table 6). Descriptive statistics for all studies involved in this comparison can be found in Supplementary Table 2. Comparisons showed that the risk of having a headache (relative risk [RR], 0.80; 95% CI, 0.67 - 0.96), diarrhoea (RR 0.85; 95% CI, 0.74 - 0.97), and cough (RR, 0.91; 95% CI, 0.85 - 0.98) was significantly lower ($P < 0.05$) with DHPP than with AL. However, treatment with DHPP resulted in an increased risk of anaemia than with AL (raw RR, 2.23; 95% CI, 1.64 - 3.02). On the other hand, ASMQ was associated with less vomiting and nausea (OR, 0.80; 95% CI, 0.48 - 1.30), anaemia (OR 0.8; 95% CI, 0.74 - 0.99), and headache (OR 0.53; 95% CI, 0.40 - 0.68), compared to AL (Table 6).

4. Discussion

The efficacy and tolerance of ACTs were updated using the existing database. The primary outcome, *i.e.*, the rate of ACPR, was extended beyond 28 days and the mixed effect model was used to account for the variability of children's responses to different ACTs. Different doses of ASAQ were also accounted for. For instance, in the selected studies, the efficacy of ASAQ FDC was assessed as it was found that this combination ensures optimal dosing and provides higher treatment efficacy.

Table 6. Difference in crude risk of adverse events between each treatment and AL.

Adverse events	Raw relative risk (95% confidence interval)						
	DHPP	ASAQc	ASAQf	ASAQl	AQSP*	ASMQ	ASSP
Vomiting/nausea	1.00 (0.85 - 1.18)	-	1.45 (1.18 - 1.78)	1.24 (0.98 - 1.58)	1.12 (0.82 - 1.53)	0.80 (0.48 - 1.30)	2.54 (1.63 - 3.98)
Anaemia	2.23 (1.64 - 3.02)	1.70 (1.26 - 2.30)	4.18 (2.93 - 5.95)	1.53 (1.26 - 1.86)	0.91 (0.61 - 1.32)	0.85 (0.74 - 0.99)	-
Abdominal pain	1.10 (0.93 - 1.28)	1.63 (1.21 - 2.20)	2.02 (0.97 - 4.21)	1.25 (0.88 - 1.81)	1.10 (0.80 - 1.49)	-	1.07 (0.41 - 2.76)
Diarrhoea	0.85 (0.74 - 0.97)	0.74 (0.39 - 1.40)	0.94 (0.75 - 1.18)	0.71 (0.44 - 1.14)	0.93 (0.60 - 1.44)	-	-
Pruritus	0.77 (0.43 - 1.38)	1.63 (0.74 - 3.58)	10.67 (4.25 - 26.76)	5.94 (0.7 - 50.81)	3.56 (1.85 - 6.83)	-	-
Cough	0.91 (0.85 - 0.98)	1.27 (0.80 - 2.01)	0.91 (0.80 - 1.04)	0.62 (0.48 - 0.77)	-	-	-
Anorexia	0.89 (0.76 - 1.03)	2.19 (1.29 - 3.70)	0.98 (0.76 - 1.25)	1.55 (1.05 - 2.28)	1.95 (1.37 - 2.76)	-	-
Headache	0.80 (0.67 - 0.96)	1.09 (0.79 - 1.52)	-	-	0.60 (0.31 - 1.12)	0.53 (0.40 - 0.68)	2.38 (0.46 - 12.26)
Number of studies with AL	14	5	8	8	4	3	1
Number of children in AL	4740	1250	2471	909	540	711	634
Number of children in trt arm	3681	1226	2222	763	593	552	664

Each treatment was taken as the reference and compared to AL in the same trials that compared both treatments. Data on adverse events occurring at any time during the follow-up period from 43 published studies. *AQSP, a non-WHO-recommended, non-ACT combination, was included for comparison since several African countries have adopted its use during the transition period in the 2000s before full implementation of ACT-based antimalarial drug policy.

Age covariate was used in a meta-regression analysis to assess the benefit of each drug compared to AL while accounting for variation among trials in terms of protocol, patients, and follow-up period. The rate of adverse events was compared between ACTs to assess the safety and tolerability of different pairs of treatment arms.

The inclusion of age covariate did not modify the differences between treatments, as found in previous works [21] [27]. Compared to AL, treatment with DHPP and ASMQ resulted in a statistically significant increase ($P < 0.05$) in the chance of recovery, *i.e.* ACPR, as well as a lower probability ($P < 0.05$) of encountering adverse events in African children. The present analysis showed similar conclusions to a recent study that compared three combinations, DHPP, AL, and ASMQ, in which it was found that the treatment success rate was higher with DHPP compared to AL [28]. In addition, children who received one of these two combinations (DHPP or ASMQ) experienced a lower prevalence ($P < 0.05$) of cough, weakness, abdominal pain, or loss of appetite compared with

those who were treated with AL. In another recent study conducted in Cameroon, there were no major adverse reactions in the DHPP group, further supporting the observation that DHPP is more efficacious, safer, and more tolerated than ASMQ and AL in African children [28] [29]. However, AL efficacy is still very high, with the rate of ACPR above 95% in most clinical studies conducted in Africa [30]. Indeed, despite the observed mild to moderate adverse events reported in the eligible studies, AL has a good tolerability [31] [32].

In this work, ASSMP and ASPY were the less studied novel ACTs. Adverse events were reported more frequently with ASSMP than with other ACTs. There is another novel non-WHO-approved ACT, such as AMPP, which, compared to AL, showed high cure rates in the ITT-analysis on day 28 (96.6% vs. 95.0%) and day 42 (94.4% vs. 93.1%), respectively [33]. However, more evidence-based data on the new alternative ACT are required in sub-Saharan Africa to evaluate their efficacy and safety in comparison to the currently WHO-recommended ACTs.

This study has several limitations. First, the study did not re-assess the selection bias for the evidence since this procedure was performed in our previous work [21]. Secondly, the performance of NMA proved to be difficult for one study reporting the outcome on day 42 due to inconsistency in treatment effect and inconsistent variances in a multi-arm study [34]. This methodological problem related to the difficulty in performing estimation with meta-regression analysis of a small number of studies led to an unreliable ranking of treatment efficacy. To overcome this problem, different treatments were ranked using a frequentist approach. Thirdly, because only a small number of studies were available, the rates of adverse events were compared using a fixed effect model. Moreover, a limited amount of evidence with new alternative ACTs did not allow a more precise estimate of treatment effect.

5. Conclusion

This study suggests that continued use of ACTs for treating uncomplicated malaria in Africa is warranted, but more attention should be paid to mild to moderate adverse events that have been reported frequently in different clinical studies and to potential ACT resistance. Indeed, it is essential to understand the mechanisms involved in the acquisition of artemisinin resistance by *P. falciparum* to adapt malaria treatment policies and propose new therapeutic strategies. Understanding the mechanisms of artemisinin resistance, regular updates on the epidemiology of drug-resistant malaria, and surveillance are critical components of the overall strategy to prevent the expansion of artemisinin-resistant *P. falciparum*. Country-specific meta-analyses are also needed to ensure that ACTs remain effective in Africa.

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Availability of Data and Materials

All studies reviewed and involved in the analysis are found in Supplementary Tables 1-3. The subset of data included in the analysis of adverse events is in Supplementary Table 2.

Conflicts of Interest

The authors declare that they have no competing interests.

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Authors' Contributions

SWY reviewed the existing database, added additional studies, performed data analysis, and drafted the manuscript; LKB assisted in the interpretation of results and improved the manuscript. All authors read and approved the final manuscript.

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List of Abbreviations

ACPR: Adequate clinical and parasitological response; ACT: Artemisinin-based combination therapy; AL: Artemether-lumefantrine; AMPP: Arterolane maleate-piperaquine phosphate; AQSP: Amodiaquine-sulfadoxine-pyrimethamine; ASSP: Amodiaquine-sulfadoxine-pyrimethamine; ASAQ: Artesunate-amodiaquine; ASAQc: Co-blistered non-fixed dose artesunate-amodiaquine combination; ASAQf: Fixed-dose artesunate-amodiaquine combination; ASAQl: Loose non-fixed dose artesunate-amodiaquine combination; ASAQCPH: Artesunate-amodiaquine-chlorpheniramine; ASATPG: Artesunate-atovaquone-proguanil; ASCD, Artesunate-chlor-proguanil-dapsone; ASMQ: Artesunate-mefloquine; ASNAPH: Artemisinin-naphtoquine; ASPY: Artesunate-pyronaridine; ASSMP: Artesunate-sulfamethoxypyrazine-pyrimethamine; ASSP: Artesunate-sulfadoxine-pyrimethamine; CI: Confidence interval; DHPP: Dihydroartemisinin-piperaquine; DHPPT: Dihydroartemisinin-piperaquine-trimethoprim; FDC: Fixed-dose combination; ITT: Intention-to-treat; NFDC: Non-fixed dose combination; NMA: Network meta-analysis; OR: Odds ratio; PCR: Polymerase chain reaction; SUCRA: Surface under the cumulative ranking curve; WHO: World Health Organization.

Supplementary Tables

https://docs.google.com/spreadsheets/d/1_Y0EIXjaeA4_yoqpGWTXvAGWm4pc4k1cfIK079pse1w/edit#gid=374421604