



# Efficacy and Safety of Artemisinin-Based Combination Therapy for the Treatment of Uncomplicated Malaria in Pregnant Women: A Systematic Review and Meta-Analysis

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**Introduction:** Malaria is one of the infectious diseases with substantial risks for pregnant women, the fetus and the newborn child. Thus, prevention and treatment of malaria with safe and effective drugs is of paramount importance. Pregnant women are mostly excluded from clinical trials, and systematic approaches of pharmacovigilance in pregnancy are limited. This means the safety and efficacy of antimalarial agents during pregnancy are unclear.

**Purpose:** This study was designed to carry out a systematic review and aggregate data meta-analysis of literature published on efficacy and safety of artemisinin-based combination therapy (ACT) for uncomplicated malaria in pregnant women.

**Methods:** A search of literature published between 1998 to 2020 on efficacy and safety of artemisinin-based combination therapy (ACT) in pregnant women was made using Cochrane Library, Medline and the Malaria in Pregnancy Consortium Library. Data were extracted independently by two reviewers, and any discrepancies were resolved by consensus. Meta-analysis was carried out using Open Meta-Analyst software. Random effects model was applied, and the heterogeneity of studies was evaluated using Higgins  $I^2$ .

**Results:** Twenty-four studies that fulfilled the inclusion criteria were included in the final assessment. Overall, days 28 to 63 malaria treatment success rate was 96.1%. Overall days 28 to 63 cure rates for AL, AS+AQ, AS+MQ, DHA+PQ, AS+ATQ+PG and AS+SP were 95.1%, 92.2%, 97.0%, 94.3%, 96.5% and 97.4%, respectively. Comparison of ACTs with non-ACTs revealed that the risk of treatment failure was substantially lower in patients treated with ACTs than with non-ACTs (risk ratio 0.20, 95% C.I. 0.09–0.43). The overall prevalences of miscarriage, stillbirth and congenital anomalies were 0.3%, 2.1% and 1.0%, respectively, and found to be comparable among various ACTs. There was comparable tolerability across ACTs during pregnancy.

**Conclusion:** ACTs demonstrated a high cure rate, safety and tolerability against *Plasmodium falciparum* infection in pregnant women. The higher treatment success and comparable tolerability could be used as an input for decision makers to support the continued usage of ACTs for treatment of uncomplicated falciparum malaria in pregnant women.

**Keywords:** efficacy, safety, artemisinin-based combination therapy, uncomplicated malaria, pregnant women, systematic review and meta-analysis

## Introduction

Although the global malaria burden has tended to decline with time (238 million in 2000, 231 million in 2017, 229 million cases in 2019); it still remains a significant health problem, particularly in Africa, which is home for the large majority of cases

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Received: 30 August 2021  
Accepted: 12 December 2021  
Published: 22 December 2021



(with an estimated 215 million cases in 2019, accounting for about 94% of cases).<sup>1</sup> Malaria is one of the infectious diseases with significant mortality and morbidity in pregnancy, posing substantial risks for the pregnant woman, the fetus and the newborn child.<sup>2</sup> Analysis of the prevalence of malaria in pregnancy by sub-region of Africa showed that it was highest in West Africa and Central Africa, each with 35%, followed by East and Southern Africa (20%). Thus, prevention and treatment of malaria with safe and effective drugs are required.<sup>1,2</sup> However, clinical trials are scarce in pregnant women and systematic approaches of pharmacovigilance in pregnancy are limited, indicating a lack of enough evidence on the safety and efficacy of antimalarial agents during pregnancy.<sup>3,4</sup>

Artemisinin-based combination therapy (ACT) is a combination of artemisinin family of drugs and other non-artemisinin partners. Even though both the artemisinin and non-artemisinin components are essential for the antimalarial efficacy, the artemisinin component is vital to decrease parasite density in the early days of treatment. The remaining parasites are cleared by the partner drug.<sup>5</sup> Therefore, the two drugs achieve effective clinical and parasitological cures and it is also believed that using this combination protects each other from development of resistance.<sup>6</sup> The most important challenge in the global fight against malaria is *Plasmodium* resistance to antimalarial medicines. Regular monitoring of efficacy of antimalarial agents supports early identification of changes in how well the recommended treatments work so as to mitigate any impact of resistance and prevent its spread.<sup>1</sup>

Currently, the World Health Organization (WHO) recommends ACTs for the treatment of uncomplicated malaria in pregnant women in the 2nd or 3rd trimester.<sup>7</sup> Seven days of quinine with clindamycin is recommended for the management of malaria in the first trimester.<sup>8</sup> However, the use of ACTs in the first trimester of pregnancy is recommended if: (i) ACTs are the only treatment option immediately available; (ii) failure occurs after treatment with 7-day quinine plus clindamycin; or (iii) adherence is a challenge with the 7-day treatment.<sup>7</sup>

As evidenced by animal studies, ACT derivatives were found to be embryotoxic and teratogenic.<sup>3</sup> The studies suggested that the critical time period for exposure in humans is in the first trimester. Various organs including uterus, ears, brain and eyes are still in development and growth phase in the second trimester, and are therefore sensitive to exogenous substances that can result in malformations.<sup>9</sup> However, data from animal studies do

not always predict the effects observed in humans. Indeed, observational studies and randomized controlled clinical trials (RCTs)<sup>10–16</sup> did not report increased risk of adverse pregnancy outcomes such as stillbirth or miscarriage after taking artemisinins during pregnancy compared with those taking non-artemisinins as well as those with no antimalarial agents. Periodic evidence synthesis from several clinical and observational studies on therapeutic efficacy and safety of ACTs in pregnant population is required, which may indicate any evolving changes or trends in the clinical use of ACTs. Hence, our study aimed to conduct a systematic review and meta-analysis, and to generate comprehensive evidence on the efficacy and risk of adverse pregnancy outcomes associated with the use of ACTs during pregnancy.

## Methods

### Eligibility Criteria

Eligible studies for this review were interventional, observational cohort and pharmacokinetic studies enrolling pregnant women at first, second and third trimesters of pregnancy and receiving an ACT with or without comparative arm interventions for the treatment of uncomplicated *P. falciparum* or *P. vivax* mono-infections. Only published articles in English were included. Studies on non-pregnant adults and pediatrics, not involving artemisinins treatment or using artemisinin monotherapy, on malaria prevention or prophylaxis, and that did not report either efficacy or pregnancy safety outcomes were excluded.

### Search Strategy

A literature search was performed to identify articles that included safety and efficacy outcomes of ACT exposure during pregnancy. The electronic search was carried out on February 28, 2020 through the Cochrane Library, Medline and Malaria in Pregnancy Consortium Library using keywords and MeSH terms with no restriction for time of publication. The search followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (S1 Table).<sup>17</sup> The search terms consisted of (Pregnant women OR pregnant\* AND malaria) AND (Artemisinin\* OR artemisinin combination therapy OR ACT OR artemether OR artesunate OR dihydroartemisinin OR arteflene\* OR artemotil OR arteether OR dihydroarte\* OR treatment) AND (safety OR serious adverse event OR miscarriage OR stillbirth OR pregnancy loss OR spontaneous abortion OR birth defect OR congenital

abnormalities OR congenital malformations OR congenital anomalies).

## Data Extraction

Decision to select a retrieved article was made by two reviewers (AM and GA) who worked independently through screening of titles and abstracts followed by full text assessment. A data abstraction format was used for screening purposes and an article is selected when there is an agreement between the two reviewers. Any disagreements were resolved by discussion and consensus. Data related to author (s) of the articles, year of publication, year the studies were conducted, geographic location of the study, duration of the study, trimester of pregnancy, age, weight, parity and gravida of participants, type of malaria species, baseline parasite density and temperature, and type of study design (observational, interventional) were extracted from each article. Data regarding the types of malaria treatment agents, treatment duration, treatment outcome measures, pregnancy outcome (miscarriage, still birth, birth weight, intrauterine growth retardation rate, gestational age and prematurity) and other adverse events including laboratory abnormalities were also extracted and included in the systematic review and meta-analysis.

## Quality Assessment

The two reviewers independently assessed methodological quality of studies using revised tool for assessing risk of bias in randomized trials (ROB 2)<sup>18</sup> for RCTs and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies.<sup>19</sup> The observational studies were categorized as high quality (over 75% of the STROBE checklist) and low quality (under 75% of the STROBE checklist). The quality of the included clinical trials was assessed and quality was categorized as “low risk of bias”, “some concerns” or “high risk of bias”.

## Outcome Definitions

Days 28 to 63 (whichever was reported latest) PCR-corrected adequate clinical and parasitological response (ACPR) was taken as primary outcome of efficacy for the meta-analysis. ACPR was defined as absence of parasitemia on day 28 irrespective of axillary temperature without previously meeting any of the criteria of early treatment failure or late clinical failure or late parasitological failure.<sup>20</sup> The primary outcomes for safety included

mean birth weight and gestational age as well as prevalence of low birth weight, prematurity, congenital abnormalities, stillbirth, and miscarriage. To evaluate tolerability, we assessed the prevalence of adverse effects, including tinnitus, anesthesia, dizziness, poor appetite, nausea, and vomiting.

## Statistical Methods

The meta-analysis of malaria treatment efficacy was performed by OpenMeta Analyst software for Windows.<sup>21</sup> Cochrane Q and the  $I^2$  statistic were employed to evaluate heterogeneity of the included studies. Cochrane Q with  $P < 0.10$  and  $I^2 > 50$  were taken as standard to indicate the presence of heterogeneity of the included studies.<sup>22</sup>  $P < 0.05$  was used to declare statistical significance.

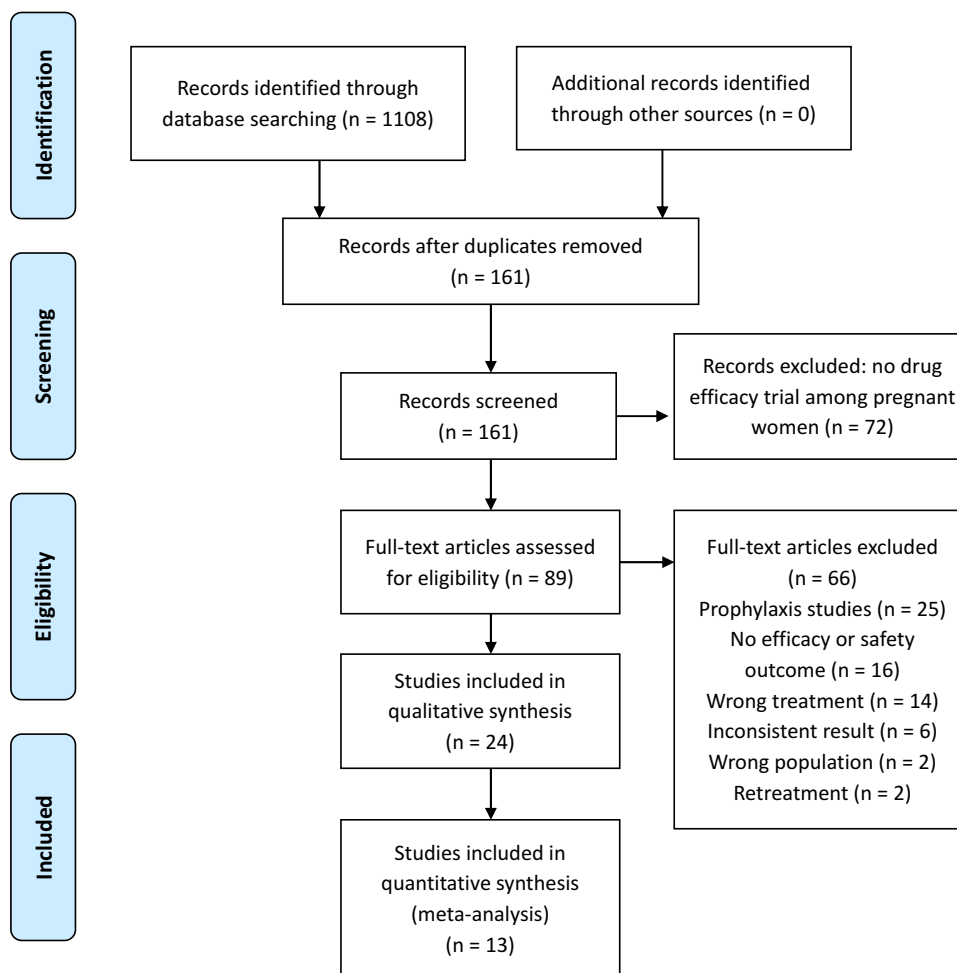
## Results

### Study Characteristics

Out of 1108 studies identified, 89 were included for review of the full text. Of these, 24 studies met the inclusion criteria (Figure 1). Studies based on the same cohort were considered as a single study. As indicated in Table 1, 18 studies were from sub-Saharan Africa, including 3 studies from Nigeria,<sup>23–25</sup> 2 studies from Tanzania,<sup>26,27</sup> 2 studies each from Sudan<sup>28,29</sup> and Uganda,<sup>10,30</sup> 1 study each from Burkina Faso,<sup>31</sup> Congo,<sup>32</sup> Ghana,<sup>33</sup> Malawi,<sup>34</sup> and Rwanda,<sup>11</sup>. One study was reported from four African countries (Burkina Faso, Ghana, Malawi, Zambia, Congo).<sup>35</sup> The outcome of pregnancy and infant mortality from this study was reported separately.<sup>36</sup> As part of the study from the four African countries,<sup>35</sup> the output from Zambia was reported separately.<sup>37</sup> The other 8 studies were from Asia; one from India<sup>38</sup> and one from the Thai-Myanmar border<sup>39</sup> and six studies from Thailand.<sup>13–15,40–42</sup>

The studies were conducted between May 1986 and April 2015 but published between 1998 and February 2020. Sixteen of the studies were clinical trials (one double blind and 15 open-label, all were RCTs but one), 7 were prospective observational studies, two studies one of which is part of a clinical trial,<sup>43</sup> were pharmacokinetic studies and the remaining was a single arm study<sup>29</sup> (Table 2). By type of malaria infection, 25 studies involved falciparum malaria, but two observational studies involved both falciparum and vivax malaria infections.<sup>13,39</sup>

ACTs used in the trials include artemether-lumefantrine (15 studies), amodiaquine-artesunate (7 studies),



**Figure 1** PRISMA flow diagram for search results February 28, 2020.

**Notes:** PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*. 2009;62(10). Creative Commons.<sup>17</sup>

mefloquine-artesunate (8 studies), sulfadoxine-pyrimethamine (SP-artesunate (4 studies), atovaquone-proguanil-artesunate (2 studies), artemether-mefloquine (1 study), artemether-lumefantrine with quinine (1 study), dihydroartemisinin + piperazine (4 studies) and unspecified artemisinin derivative (1 study).

In most of the studies, durations of ACTs were 3 days. But there were exceptions, where 5 days of artemether injection and artemether-lumefantrine combination therapy was used in Nigeria<sup>44</sup> and Congo,<sup>32</sup> respectively, as well as 7 days of artesunate therapy in Thailand.<sup>15,41</sup>

Other antimalarial drugs used in the studies included quinine (5 studies), SP (3 studies), mefloquine (2 studies), SP in combination with azithromycin (1 study), SP with amodiaquine (1 study), amodiaquine (1 study), chloroquine (1 study), atovaquone with proguanil (1 study) and chlorproguanil and dapsone (CD) (2 studies). Detailed

description of studies included in this systematic review and meta-analysis is indicated in a supplementary file ([S2 Table](#)).

## Characteristics of the Study Participants

A total of 9482 pregnant women were exposed to antimalarial agents, with the majority (6860, 72.3%) of them exposed in the 2nd or 3rd trimester, and 2622 (27.7%) in the first trimester. In addition, 2482 pregnant women were unexposed controls in the 24 studies but included for comparison purpose. In one of these studies, 30 healthy non-pregnant women were included as comparators.<sup>24</sup> Twenty-four non-pregnant women on AS+MQ were also compared with pregnant women.<sup>31</sup>

A total of 6600 women in the 24 studies received ACT during the first, second and third trimesters of pregnancy ([Tables 1 and 2](#)). The most common ACT exposures were:

**Table I** Description of the Studies Identified in the Systematic Review and Meta-Analysis of Safety and Efficacy of Artemisinin-Based Therapy in Pregnant Women

Author, Year	Country	Study Design	Treatment	N
Sowunmi 1998 <sup>44</sup>	Nigeria	Open-label RCT	AM IM (3.2 mg/kg at day 0, then 1.6 mg/kg daily from day-1 to day-4)	23
			AM+MQ (artemether 3.2 mg/kg at day 0, 7.5 mg/kg mefloquine at day-1 and day-2)	22
Adam 2006 <sup>29</sup>	Sudan	Single arm study	AS+SP (two tablets of 100 mg artesunate on days 0–2 and three tablets of SP (500/25 mg) given as a single dose on day 0.	32
Adam 2009 <sup>28</sup>	Sudan	Prospective follow-up	AM inj., AS+SP or AL	62
Anvikar 2018 <sup>38</sup>	India	Open-label RCT	AS+SP (artesunate 200 mg daily for 3 days and SP 1500/75 mg on day one)	125
			AS+MQ (200/440 mg daily for 3 days)	123
Kaye 2008 <sup>30</sup>	Uganda	Open-label RCT	AL (artemether 20 mg-lumefantrine 200 mg)	55
			CD (chlorproguanil and dapsone)	55
Piola 2010 <sup>10</sup>	Uganda	Open-label RCT	QN 10 mg/kg base PO Q 8 h for 7 days	152
			AL (20/120 mg) 4 tablets at 0 h, 8 h, 24 h, 36 h, 48 h, and 60 h for 3 days	152
Moshia 2014 <sup>26</sup>	Tanzania	Cohort study	AL (164), AL & QN (8), QN (70), SP (66), AQ (11)	319
			None	1464
PREGACT 2016 <sup>35</sup>	Burkina Faso, Ghana, Malawi and Zambia	Open-label RCT	AL (20 mg/120 mg) 4 tablets BID for 3 days	880
			AS+AQ (100/270 mg) 2 tablets daily for 3 days	842
			DHA+PQ (40 mg/320 mg) 3 tablets daily for 3 days	853
			AS+MQ (100/220 mg) 3 tablets daily for 3 days	848
Kalilani 2007 <sup>34</sup>	Malawi	Open-label RCT	SP (3 tablets once; 500/25 mg)	47
			SP (3 tablets) plus AZ (1 g/day for 2 days)	47
			SP (3 tablets) plus AS (200 mg/day for 3 days)	47
Onyamboko 2020 <sup>32</sup>	Congo	Open-label, RCT	AL 20/120 mg tablets 4 tablets twice daily for 3 days	24
			AL 20/120 mg tablets 4 tablets twice daily for 5 days	24
McGready 2012 <sup>13</sup>	Thailand	Prospective follow-up	CQ (429), QN (390), Artemisinin derivatives (92), MQ (32), Other or unknown (2)	945
McGready 2008 <sup>15</sup>	Thailand	Open-label RCT	AS7 (2 mg/kg once daily for 7 days)	128
			AL (20/120 mg): 4 tablets twice a day for 3 d	125
Moore 2016 <sup>39</sup>	Thai–Myanmar	Prospective follow-up	QN (971), MQ monotherapy (25), Artemisinin derivatives (185),	1179

(Continued)

Table 1 (Continued).

Author, Year	Country	Study Design	Treatment	N
Mutabingwa 2009 <sup>27</sup>	Tanzania	Open-label RCT	SP (3 tabs of 500/25 mg per tablet) orally at once	28
			CD (1.2/2.4 mg/kg for 3 days)	81
			SP+AQ (SP 3 tablets once + AQ 10 mg/kg for 3 days)	80
			AQ+AS (10/4 mg/kg for 3 days)	83
Nambozi 2017 <sup>37</sup>	Zambia (part of PREGACT Study)	Open Label RCT	AL (20/120 mg per tablet, 4 tablets twice per day over 3 days)	300
			AS+MQ (100/220 mg per tablet at 3 tabs once per day over 3 days)	300
			DHA+PQ (40/320 mg per tablet, 3 tablets once per day over 3 days)	300
Nambozi 2019 <sup>36</sup>	Burkina Faso, Ghana, Malawi and Zambia (part of PREGACT Study)	Open Label RCT	AL (20/120mg four tablets BID for 3 days)	822
			AS+AQ (100 mg/270 mg daily for 3 days)	775
			AS+MQ (12/24 mg/kg, 100/220 mg 3 tablets daily for three days)	765
			DHA+PQ (40/320 mg 3 tabs daily for 3 days)	765
Osarfo 2017 <sup>33</sup>	Ghana	Open-label, RCT	AS+AQ over 3 days	205
			DHA+PQ over 3 days	212
Iribhogbe 2017a <sup>23</sup>	Nigeria	Open-label RCT	AS+AQ (100/270 mg) 3 tablets once daily for 3 days	40
			AL (20/120 mg) 4 tablets twice daily for 3 days	40
Iribhogbe 2017 <sup>24</sup>	Nigeria	Non-randomized Open-label clinical trial	Non-pregnant control	30
			Pregnant control	40
			AS+AQ (4 and 10 mg/kg) daily for 3 days	50
McGready 1998 <sup>41</sup>	Thailand	Prospective follow-up	Artesunate alone	61
			Artesunate + mefloquine	26
			Artemether + mefloquine	3
McGready 2000 <sup>14</sup>	Thailand	Open-label RCT	AS+MQ (MQ 25 mg base/kg given as 15 mg/kg on day 1 and 10 mg/kg on day 2 and AS 4 mg/kg per day in one dose on days 0, 1, and 2)	66
			QN 10mg/kg base PO Q8 h for 7 days	42
McGready 2003 <sup>42</sup>	Thailand	Prospective follow-up	AS+ATQ+PG (artesunate 4 mg/kg/day, atovaquone (20 mg/kg/day), and proguanil)	19
			AS+ATQ+PG (artesunate (2 mg/kg/day), atovaquone (20mg/kg/day), and proguanil)	7
			ATQ+PG, no artesunate	1
McGready 2005 <sup>40</sup>	Thailand	Randomized, Open-label Clinical Trial	QN7 10 mg salt/kg every 8 h for 7 days	42
			AS+ATQ+PG (4/20/8mg/kg/day), each for 3 days	39

(Continued)



Table I (Continued).

Author, Year	Country	Study Design	Treatment	N
Rulisa 2012 <sup>11</sup>	Rwanda	Cohort study	Exposed cohort (Pregnant women treated with AL for malaria)	1072
			Non-exposed cohort (Pregnant women without malaria)	978
Tarning 2009 <sup>43</sup>	Thailand	Population Pharmacokinetic Study cohort of reference 15	AL (20/120 mg 4 tabs twice a day for 3 days with 200–250 mL of chocolate milk containing 6–7g of at with each dose)	103
Ukah, 2015 <sup>25</sup>	Nigeria	Double-blind RCT	AS+AQ (100 mg/270 mg one tab twice daily for 3 days)	75
			AL (80mg/480mgone tab twice daily for 3 days)	75
Valea 2014 <sup>31</sup>	Burkina Faso	Open-label clinical trial	Mefloquine and artesunate (pregnant women)	24
			Mefloquine and artesunate (non-pregnant women)	24

**Abbreviations:** AL, artemether-lumefantrine; AL5, artemether-lumefantrine for 5 days; AM, artemether; AM+MQ, artemether followed by mefloquine; AS+AQ, artesunate + amodiaquine; AS+ATQ+PG, artesunate + atovaquone + proguanil; AS+MQ, artesunate + mefloquine; AS+SP, artesunate + sulfadoxine-pyrimethamine; AS7, artesunate for 7 days; CD, chlorproguanil-dapsone; CQ, chloroquine; DHA+PQ, dihydroartemisinin + piperaquine; GA, gestational age; QN, quinine; QN+CL, quinine + clindamycin; RCT, randomized control trial; wks, weeks.

artemether-lumefantrine (AL) (n= 2624), artesunate-amodiaquine (AS+AQ) (n = 1295), artesunate-mefloquine (AS+MQ) (n = 1158), dihydroartemisinin-piperaquine (DHA+PQ) (n= 1068), artesunate -sulfadoxine-pyrimethamine (AS+SP) (n = 215), artesunate atovaquone-proguanil (AS+ATQ+PG) (n = 65), artesunate-clindamycin (n = 50), artemether-mefloquine (AM+MQ) (n = 25) and AL and quinine (n = 8) and unspecified artemisinin derivatives were provided for 92 pregnant women.

Documented fever ranged from 2–74% at enrollment. Among the documented mean or median body weights, participants from Sudan<sup>28</sup> and Nigeria<sup>23,24,44</sup> had the highest body weight compared with those from Thailand.<sup>15,40</sup> Detailed description of study participants included in this systematic review and meta-analysis is indicated in a supplementary file ([S3 Table](#)).

## Efficacy of ACTs

Among the 24 studies, 16 reported the efficacy of ACTs in the management of malaria in pregnant women ([S2 Table](#)). Among these efficacy studies, PCR was corrected in 12 studies. Studies with PCR correction of day-28 or later cure rate were included for meta-analysis. In addition, two studies<sup>29,30</sup> with no late treatment failure were also included in the meta-analysis ([Figure 2](#)). The detailed results observed in individual studies are given in the supplementary materials ([S2 Table](#) and [S3 Table](#)).

## Artemether-Lumefantrine (AL)

There were eight studies that included AL as intervention group. The Ugandan study compared AL with quinine and reported high efficacy and the non-inferiority of AL relative to quinine.<sup>10</sup> Mean fever clearance as well as parasite clearance was also comparable in a similar study in Uganda.<sup>30</sup> However, a Thai study comparing AL and artesunate treatment in women with positive blood smears (AL, 125 women; AS, 128 women) reported a cure rate of less than 95% for AL at day 42 and for both treatments at delivery (or day 42 if later).<sup>15</sup>

The PREGACT study in four African countries (Burkina Faso, Ghana, Malawi and Zambia) compared the efficacy of AL, AS+AQ, DHA+PQ and AS+MQ. In this study, there was no significant difference among the AS+AQ, DHA+PQ, and AS+MQ groups. However, the cure rate in the AL group was significantly lower than the rate in the other three arms.<sup>35</sup>

The Congolese study compared the efficacy of a 5-day regimen of AL with the standard 3-day treatment in 48 pregnant women with uncomplicated falciparum malaria in an open-label RCT. The PCR-corrected clinical and parasitological response was 100% in both treatment arms, indicating that both the current and extended regimens of AL are highly efficacious.<sup>32</sup>

A comparative clinical study in Nigeria was conducted on two commonly used fixed dose ACTs, AS+AQ and AL,

**Table 2** Characteristics of Participants at Enrollment in the Studies Evaluating Efficacy and Safety of Artemisinin-Based Therapies in Pregnancy

Author, Publication Year	Trimester	Treatment (N)	Age (Year)	Weight (kg)	GA (wk)
Sowunmi 1998 <sup>44</sup>	2nd and 3rd	AM (23)	29.9 (21–41)	63.9 (50–119)	
		AM+MQ (22)	28.9 (20–40)	64.1 (53–121)	
Adam 2006 <sup>29</sup>	2nd and 3rd	AS+SP (32)	29.4 ±4.3	68.7±12.7	29.7±8.4
Adam 2009 <sup>28</sup>	1st	AM (48), AS+SP (11), AL (3)	27.6 [17–39]	68.7 [48–89]	17.5 (±3.6) [10–24]
Anvikar 2018 <sup>38</sup>	2nd and 3rd	AS+SP (125)	23.1 ± 3.9		25.5 ± 6.2
		AS+MQ (123)	23.6 ± 3.7		24.8 ± 5.7
Kaye 2008 <sup>30</sup>	2nd and 3rd	AL (55)	23.5±5.29		28.9±5.4
		CD (55)	23.6±5.20		27.3±6.3
Piola 2010 <sup>10</sup>	2nd and 3rd	QN (152)	22.6 (17–38)	58 kg (10)	22.3 (9–38)
		AL (152)	22.5 (15–38)	58 kg (10)	24.7 (10–39)
Mosha 2014 <sup>26</sup>	1st	AL (164), AL+QN (8), QN (70), SP (66), AQ (11), None (1464)	25.8 (13–49)		14.8 (3–20)
PREGACT 2016 <sup>35</sup>	2nd and 3rd	AL (880)	22.6±5.6		
		AS+AQ (842)	23.4±5.9		
		DHA+PQ (853)	22.3±5.4		
		AS+MQ (848)	23.5±5.9		
Kalilani 2007 <sup>34</sup>	2nd	SP (47)	<b>20 (18–24)</b>	53.3 (±5.9)	<b>22 (20–24)</b>
		SP+AZ (47)	<b>20 (18–23)</b>	52.2 (±6.1)	<b>24 (20–24)</b>
		AS+SP (47)	<b>20 (17–24)</b>	52.9 (±5.9)	<b>22 (20–24)</b>
Onyamboko 2020 <sup>32</sup>	2nd and 3rd	AL (24)	28.5 (±6.51)	61.7 (±11.6)	2nd =19.2 (±3.54) 3rd =28.9 (±4.42)
		AL5 (24)	26.63 (±6.18)	63.5 (±9.84)	2nd =18.7 (±3.11) 3rd =24.9 (±5.84)
McGready 2012 <sup>13</sup>	1st	CQ (429), QN (390), ART (92), MQ (32), Other (2)	26±7 (13–45)		
McGready 2008 <sup>15</sup>	2nd and 3rd	AS (128)	27±8 (14–44)	49 ±7 (3–71)	24.8±7.6 (13.1–39.4)
		AL (125)	26 ±7 (14–42)	50 ±6 (35–65)	23.7±6.8 (13.1–39.2)
Moore 2016 <sup>39</sup>	1st	QN (971), MQ (25), ART (185),	23 (13–46)		8.4 [0.1–14.0]
Mutabingwa 2009 <sup>27</sup>	2nd and 3rd	SP (28)	<b>21 (19–26)</b>		<b>6 mon (5–8)</b>
		CD (81)	<b>21 (19–27)</b>		<b>7 mon (6–8)</b>
		SP+AQ (80)	<b>20 (19–25)</b>		<b>7 mon (5–7)</b>
		AS+AQ (83)	<b>21 (19–26)</b>		<b>6 mon (5–7)</b>

(Continued)



Table 2 (Continued).

Author, Publication Year	Trimester	Treatment (N)	Age (Year)	Weight (kg)	GA (wk)
Nambozi 2017 <sup>37</sup>	2nd and 3rd	AL (300)	20 (18–24)		2nd=50% 3rd=50%
		AS+MQ (300)	19 (18–24)		2nd=50% 3rd=50%
		DHA+PQ (300)	20 (18–24)		2nd=43.7% 3rd=56.3%
Nambozi 2019 <sup>36</sup>	2nd and 3rd	AL (822)	21 (18–26)		38 (36–38)
		AS+AQ (775)	22 (19–27)		38 (38–40)
		AS+MQ (765)	22 (19–27)		38 (36–40)
		DHA+PQ (765)	20 (18–25)		38 (36–38)
Osarfo 2017 <sup>33</sup>	2nd and 3rd	AS+AQ (205)			22.3
		DHA+PQ (212)			22.7
Iribhogbe 2017a <sup>23</sup>	2nd and 3rd	AS+AQ (40)	27.21±0.51	68.97±0.87	
		AL (40)	31.02±0.47	68.23±0.25	
Iribhogbe 2017 <sup>24</sup>	2nd and 3rd	Control Pregnant (30)	26.88±0.94	68.12± 2.04	27.28± 0.99
		Control Non-Pregnant (40)			
		AS+AQ (50)			
McGready 1998 <sup>41</sup>	1st, 2nd and 3rd	Recrudescence infections (61)	25 (17–38)		1st (18%), 2nd–3rd (82%)
		Hyperparasitemia (13)	22 (1–32)		
		Inadvertent exposures (16)	29 (15–40)		1st (88%), 2nd–3rd (12%)
McGready 2000 <sup>14</sup>	2nd and 3rd	AS+MQ (66)	24 (15–37)	48 (36–68)	24 (12–40)
		QN (42)	23 (16–36)	50 (41–67)	24 (15–38)
McGready 2003 <sup>42</sup>	1st, 2nd and 3rd	AS+ATQ+PG (artesunate 4 mg/kg/day) (19)	25 (16–38)	NA	28.2
		AS+ATQ+PG (artesunate 2 mg/kg/day) (7)			
		ATQ+PG (1)			
McGready 2005 <sup>40</sup>	2nd and 3rd	QN (42)	26±7 (16–39)	50 ±7 (30–68)	21 ±4.5 (14.9–30.2)
		AS+ATQ+PG (39)	26 ± 6 (16–37)	49±7 (40–69)	21 ±5.3 (10.1–36.2)
Rulisa 2012 <sup>11</sup>	1st, 2nd and 3rd	AL (1072)	26.0 (17–48)		25.8 (95% CI: 25.3, 26.4)
		Non-exposed (978)	27.0 (16–47)		28.5 (95% CI: 28.0, 29.0)
Tarning 2009 <sup>43</sup>	2nd and 3rd	AL (103)	24 (15–42)	49 (35–65)	22.6 (13.1–39.0)

(Continued)

**Table 2** (Continued).

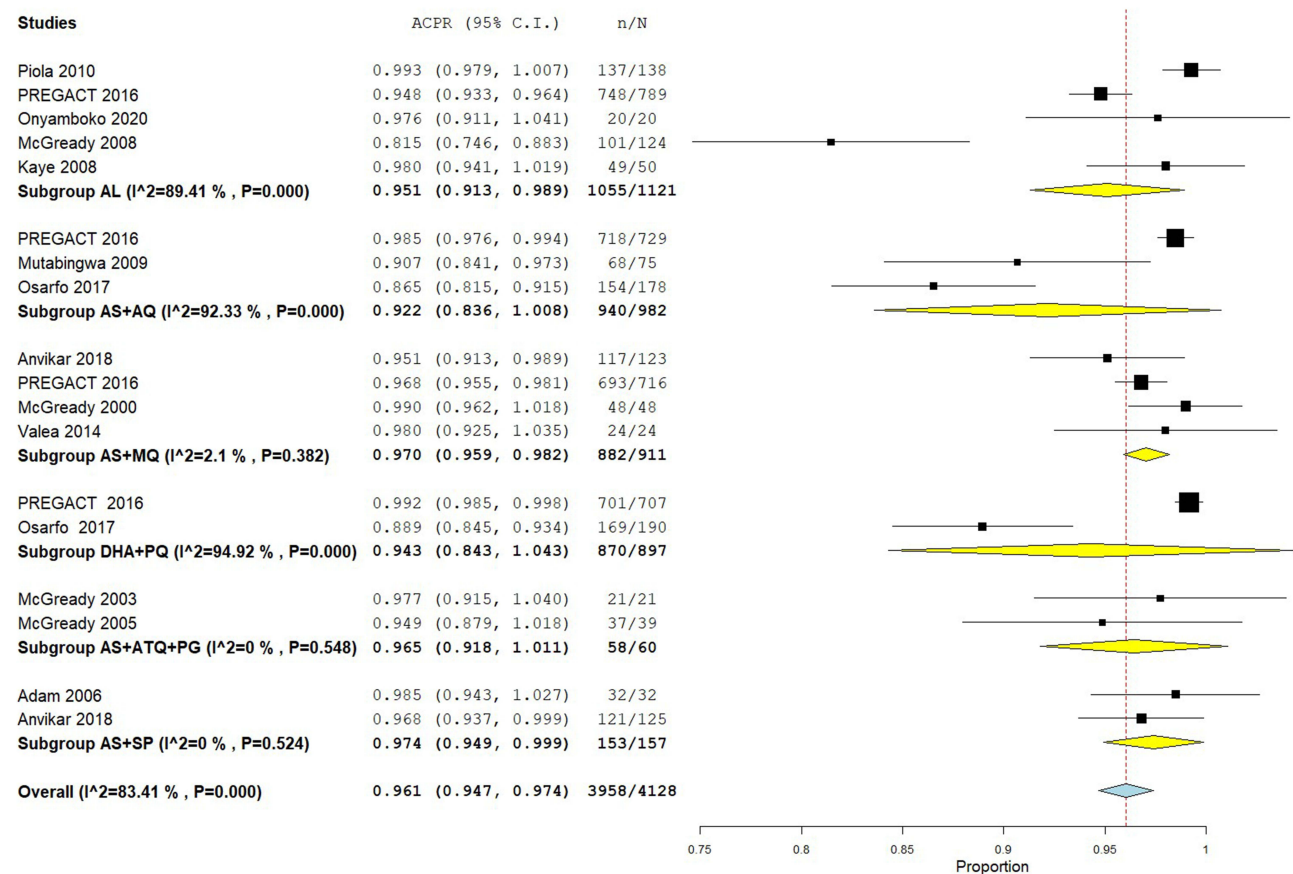
Author, Publication Year	Trimester	Treatment (N)	Age (Year)	Weight (kg)	GA (wk)
Ukah 2015 <sup>25</sup>	2nd and 3rd	AS+AQ (75)	29.2±4.8 (20–42)		28.5±6.8 (14–40)
		AL (75)	29.4±4.6 (18–41)		27.2±7.3 (14–40)
Valea 2014 <sup>31</sup>	2nd and 3rd	AS+MQ (pregnant women) (24)	23.6±6.1	54.1±5.7	2nd trimester = 12 (50%) 3rd trimester = 12 (50%)
		AS+MQ (non-pregnant women) (24)	27.0±8.9	53.5±5.8	

**Note:** Bold: median (IQR).

**Abbreviations:** ACPR, adequate clinical and parasitological response; AL, artemether-lumefantrine; AM, artemether; AM+MQ, artemether followed by mefloquine; AS+AQ, artesunate + amodiaquine; AS+ATQ+PG, artesunate + atovaquone + proguanil; AS+MQ, artesunate + mefloquine; AS+SP, artesunate + sulfadoxine-pyrimethamine; AS7, artesunate for 7 days; CD, chlorproguanil-dapsone; CQ, chloroquine; DHA+PQ, dihydroartemisinin + piperaquine; QN, quinine; QN+CL, quinine + clindamycin.

for the treatment of uncomplicated *P. falciparum* malaria in the second and third trimester of pregnancy. The late parasitological failure observed on day 14 was 2.63% for

AS+AQ and 5.41% for AL. The failure observed may be due to reinfection because there was no PCR-corrected result to rule out recrudescence.<sup>23</sup> Another study from



**Figure 2** Efficacy of ACTs for the treatment of uncomplicated malaria in pregnant women.

**Abbreviations:** ACTs, artemisinin-based combination therapies; AL, artemether-lumefantrine; AS+AQ, artesunate-amodiaquine; AS+ATQ+PG, artesunate-atovaquone-proguanil; AS+MQ, artesunate-mefloquine; AS+SP, artesunate-sulfadoxine-pyrimethamine; CI, confidence interval; DHA+PQ, dihydroartemisinin-piperaquine.

Nigeria, a double-blind randomized trial, was conducted to compare AS+AQ and AL combinations in the treatment of acute uncomplicated *P. falciparum* malaria during pregnancy. Unlike the other studies, the efficacy of the two treatment arms did not differ significantly in this study. High cure rates of both day-3 parasite clearance and day-28 ACPR were reported in this study.<sup>25</sup>

### Artesunate-Amodiaquine (AS+AQ)

Six studies evaluated the efficacy of AS+AQ with other antimalarial agents. As stated above in the PREGACT study, the PCR-corrected cure rate in the AS+AQ treatment group was significantly higher than the AL treatment group.<sup>35</sup>

According to an open-label RCT study in Tanzania, pregnant women with *P. falciparum* malaria were randomized to one of the 4 regimens: SP, CD, SP+AQ or AS+AQ. PCR-corrected parasitological outcomes for AQ+AS were significantly better than for CD (AS+AQ versus CD: AOR for parasitological failure rates was 0.36, 95% CI: 0.14–0.94).<sup>27</sup>

In an open-label, randomized, non-inferiority trial in Ghana, 212 and 205 second and third trimester pregnant women, respectively, with confirmed asymptomatic *P. falciparum* parasitemia were randomized to receive DHA+PQ or AS+AQ. After controlling for age, gestational age, hemoglobin, gravidity and parasite density at enrollment, efficacy was 3.5 (95% CI: –1.5–8.5) and 3.9 (95% CI: –2.7–10.4) - fold higher by days 28 and 42, respectively, for DHA+PQ than AS+AQ. This finding brought out that DHA+PQ was non-inferior to AS+AQ for treatment of malaria infection during pregnancy, although the efficacy was not PCR corrected.<sup>33</sup> The Nigerian studies did not also reveal a significant difference in the clinical and parasitological response between AS+AQ and AL, although PCR adjustment is lacking in both studies.<sup>23,25</sup>

### Artesunate-Mefloquine (AS+MQ)

Five studies compared AS+MQ with other ACTs and quinine. An Indian study on pregnant women in the second or third trimester with *P. falciparum* mono-infection randomized to receive either AS+SP or AS+MQ did not show detectable difference in the probability of treatment failure between the two arms following Kaplan–Meier survival analysis.<sup>38</sup> The PREGACT study did not also reveal significant difference in PCR-corrected cure rate among AS+AQ, DHA+PQ and AS+MQ groups.<sup>35</sup>

An open-label randomized comparison of AS+MQ versus quinine was conducted from 1995 to 1997 in 108 pregnant Thai women with acute uncomplicated *P. falciparum* malaria in the second or third trimesters of pregnancy. AS+MQ treatment arm was more effective than the quinine treatment arm as revealed by the day 63 PCR-corrected cure rates.<sup>14</sup>

### Dihydroartemisinin-Piperaquine (DHA+PQ)

The study in four African countries (Burkina Faso, Ghana, Malawi and Zambia) showed that the cure rate in the AL group was significantly lower than the rate in the DHA+PQ treatment groups.<sup>35</sup>

The Ghanaian study indicated that the differences in efficacy (DHA+PQ versus AS+AQ) after controlling for other variables were 3.5 (95% CI: –1.5–8.5) and 3.9 (95% CI: –2.7–10.4) by days 28 and 42, respectively.<sup>33</sup>

## Meta-Analysis of Efficacy of ACTs

Out of 16 clinical trials identified, only 13 studies were included in the meta-analysis for efficacy of ACTs in the management of uncomplicated malaria in pregnant women. Three studies were excluded (no PCR correction for “Iribhogbe 2017” and “Ukah 2015”, and no efficacy outcome for “Iribhogbe 2017a” as they do not report PCR-corrected efficacy). Overall, PCR-corrected day 28 to day 63 malaria treatment success rate for ACTs was 96.1%. However, we found high heterogeneity (overall  $I^2 = 83.41\%$ ;  $p = 0.000$ , 13 studies, 18 ACTs treatment groups).

Subgroup analysis was carried out to assess the heterogeneity. There were five RCTs with efficacy report of AL.<sup>10,15,25,32,35</sup> Overall PCR-corrected cure rate was 95.1% for AL (95% CI: 91.3–98.9%;  $I^2 = 89.41\%$ ,  $p < 0.001$ , 5 studies) (Figure 2). AL therapy was associated with  $\geq 95\%$  cure rate in 3 of the 5 studies;<sup>10,30,32</sup> the exceptions were studies from the four African countries (Burkina Faso, Ghana, Malawi and Zambia)<sup>35</sup> and Thailand.<sup>15</sup>

There were three RCTs with efficacy report for AS+AQ.<sup>27,33,35</sup> Overall day 28 to 63 PCR-corrected ACPR for AS+AQ was 92.2% (95% CI: 83.6–100%;  $I^2 = 92.33\%$ ,  $p = 0.000$ , 3 studies) (Figure 2). AS+AQ was associated with  $\geq 95\%$  cure rate in 1 of the 3 studies;<sup>35</sup> but cure rates were  $< 95\%$  in studies from Tanzania<sup>27</sup> and Ghana.<sup>33</sup> There were four RCTs with efficacy report for AS+MQ.<sup>14,31,35,38</sup> Overall day 28 to 63 PCR-corrected ACPR for AS+MQ was 97.0% (95% CI: 95.9–98.2%;  $I^2 = 2.1\%$ ,  $p = 0.382$ , 4 studies) (Figure 2). AS+MQ combination therapies were associated with  $\geq 95\%$  cure rates in all these studies.

There were two RCTs with efficacy report of DHA+PQ.<sup>33,35</sup> Overall day 28 to 63 PCR-corrected ACPR for DHA+PQ was 94.92% (95% CI: 84.3–104.3%;  $I^2 = 94.92\%$ ,  $p < 0.000$ , 2 studies) (Figure 2). DHA+PQ combination therapy was associated with  $\geq 95\%$  cure rate in 1 of the 2 studies;<sup>35</sup> the exception was the study from Ghana.<sup>33</sup>

There were two RCTs with efficacy report of AS+ATQ+PG.<sup>40,42</sup> Overall day 28 to 63 PCR-corrected ACPR for AS+ATQ+PG was 96.5% (95% CI: 91.8–101.1%;  $I^2 = 0.0\%$ ,  $p < 0.548$ , 2 studies) (Figure 2). AS+ATQ+PG combination therapies were associated with  $\geq 95\%$  cure rates in both of these studies.

There were two RCTs with efficacy report of AS+SP.<sup>29,38</sup> Overall day 28 to 63 PCR-corrected ACPR for AS+SP was 97.4% (95% CI: 94.3–102.7%;  $I^2 = 0.0\%$ ,  $p < 0.524$ , 2 studies) (Figure 2). AS+SP combination therapies were associated with  $\geq 95\%$  cure rates in both of these studies. The limited number of available studies with PCR-corrected outcome comparing different ACTs precluded aggregate data meta-analysis.

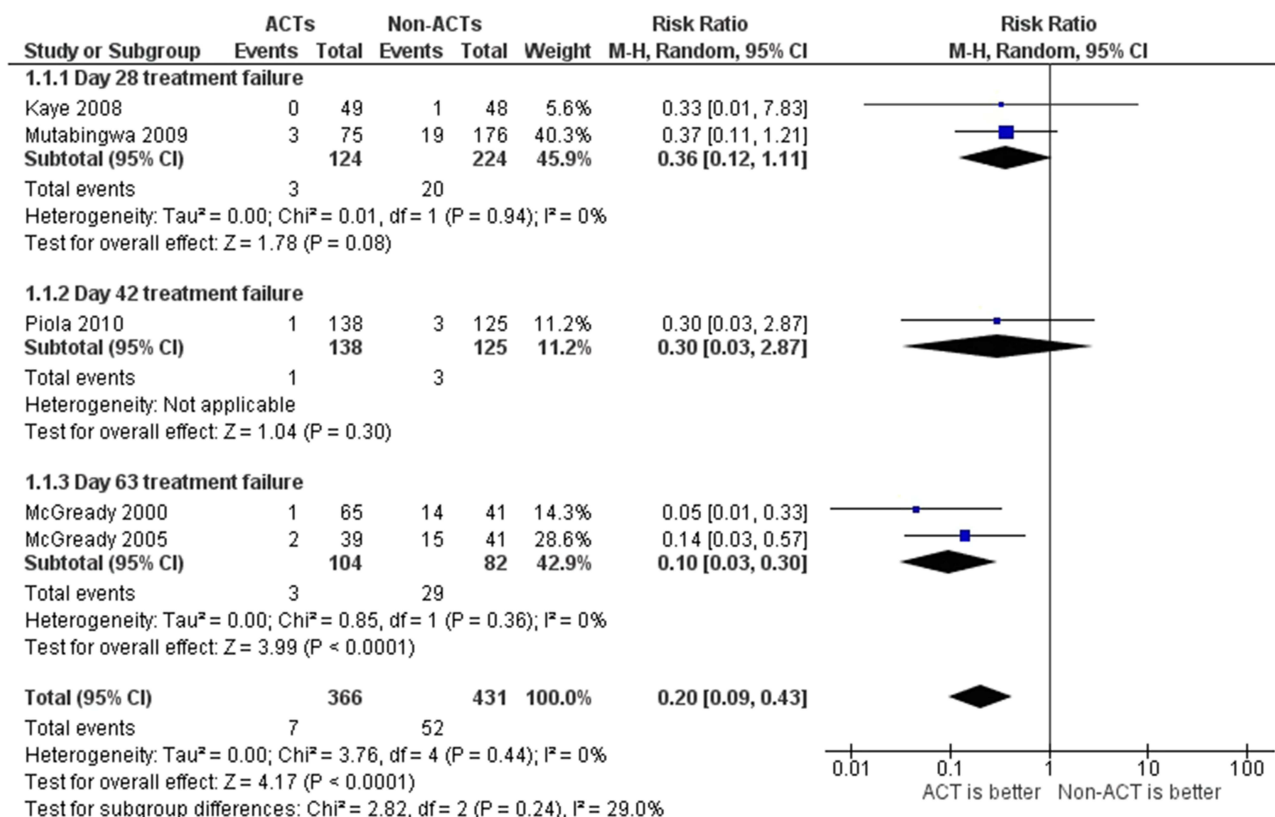
### PCR-Corrected ACPR Comparison of Different Treatments

In the five RCTs that were included for meta-analysis to compare ACTs and non-ACTs, the risk of treatment failure was substantially lower in patients treated with ACTs than in patients treated with non-ACTs (risk ratio 0.20, 95% CI: 0.09–0.43) (Figure 3), although the compared treatments and methodologies differed.

### Safety of ACTs

The safety of AL and quinine was recently compared in an open-label randomized non-inferiority trial in Uganda on second and third trimester pregnant women with uncomplicated *P. falciparum* malaria treated with either AL (152) or quinine (152). No significant differences were observed between the treatment arms in the frequency of miscarriages, stillbirths, early neonatal deaths, malformations, prematurity and low birth weight.<sup>10</sup>

Between 2006 and 2008, an observational study investigated the safety of artemisinins including artemether injection, AS+SP and AL in the first trimester of pregnancy in



**Figure 3** Comparison of days 28 to 63 cure rate or ACPR among artemisinin combination therapy and non-artemisinin therapies in pregnant women. **Abbreviations:** ACT, artemisinin combination therapy; Non-ACT, antimalarial agents other than ACTs.

Sudan.<sup>28</sup> There was no congenital abnormality documented, but miscarriage occurred in two women who were treated with artemether injection in the first trimester while quinine infusion was administered for a subsequent malaria attack.<sup>28</sup>

Between April 2004 and August 2006, the safety of AL and artesunate was compared in an open-label RCT in the second and third trimesters of pregnancy in Thailand.<sup>15</sup> Pregnant women with acute *P. falciparum* malaria were allocated to AL and artesunate treatment groups. There was no significant birth outcome difference in the two treatment groups. But death rates were significantly more in the artesunate group (6.7%) than the AL group (0.9%), although these deaths were unrelated to the treatments received.<sup>15</sup>

In an observational cohort study conducted in Tanzania in pregnant women in the first trimester, 1783 (82.3%) women completed the study until delivery. Out of them, 319 (17.9%) used antimalarial drugs in the first trimester, of whom 172 were on AL, 78 on QN, 66 on SP and 11 on AQ. Analysis showed that first trimester exposure of quinine was associated with a two-fold increased risk of miscarriage, stillbirth and preterm birth compared with the other treatments.<sup>26</sup>

In the PREGACT study, there were no significant difference in the proportion of live births among the treatment arms. The average birth weight and the incidence of miscarriages, stillbirths, preterm deliveries, and malformations were similar among the treatment arms.<sup>35</sup>

In the Rwandan prospective cohort study from June 2007–July 2009, exposed group (pregnant women with malaria given AL), and a matched non-exposed group (pregnant women without malaria and not exposed to AL) were followed until delivery. The authors noted that the rates of abortion, perinatal mortality, stillbirth and premature delivery were slightly increased in the treatment group and argued that this was probably due to the acute complications of malaria itself instead of the interventions given.<sup>11</sup>

The Indian study that compared AS+SP and AS+MQ reported that low birth weight (< 2.5 kg) was significantly higher in the AS+SP than in the AS+MQ treatment group, however, there was no statistically significant difference in miscarriages, preterm delivery or stillbirths between the treatment arms.<sup>38</sup>

In the Malawian randomized clinical trial, pregnant women with uncomplicated *P. falciparum* malaria were allocated in three treatment arms: 47 women in each of the treatment arms (SP only, SP + Azithromycin and AS

+SP). The authors indicated that the observed abortions, stillbirths and neonatal deaths potentially had other proximal causes than directly related to the interventions provided.<sup>34</sup>

The observational study in the Thai–Burmese border analyzed antenatal register of pregnant women exposed to chloroquine-based, quinine-based or artemisinin-based treatments in the first trimester. The risk of miscarriage and stillbirth was similar in all groups. Congenital anomaly also similarly occurred among babies born from women treated with chloroquine, quinine or artesunate.<sup>13</sup>

In the Tanzanian study from January 2004–September 2006, pregnant women with uncomplicated *P. falciparum* malaria were allocated in four treatment arms: SP, CD, SP+AQ or AQ+AS. In this trial there was no report of apparent excess stillbirths or adverse birth outcomes in any of the arms.<sup>27</sup>

Low birth weight was significantly higher in the DHA+PQ arm as compared with AS+AQ in the Ghanaian study. Furthermore, two cases each of neonatal deaths and stillbirths were recorded in the DHA+PQ arm, while one case of stillbirth was observed in the AS+AQ arm. The authors argued that the higher prevalence of low birth weight in the DHA+PQ arm could be attributed to a chance finding not attributable to DHA+PQ.<sup>33</sup>

In a study from Thailand comparing the safety of QN and AS+ATQ+PG, there was no significant difference in mean birth weight, baby growth parameters and estimated gestational age (EGA) or in the proportion of low birth weight, premature, or intrauterine growth-retarded infants. Identified congenital abnormalities were considered unlikely to be drug related.<sup>40</sup>

## Meta-Analysis of Pregnancy Outcomes

### Miscariage

Seven studies reported a total of 20 miscarriages among 3996 women who received ACTs during pregnancy. The overall prevalence was 0.3% and found to be similar among various ACTs (0.1% for AL, 0.5% for AS+AQ, DHA+PQ and AS+MQ) ([S1 Figure](#)).

### Stillbirth

Six studies reported a total of 90 stillbirths among 3927 women who received ACTs during pregnancy. The overall prevalence of stillbirth was 2.1% and found to be similar among various ACTs (1.7% for AL, 1.9% for AS+AQ, 2.8% for AS+MQ and 2.5% for DHA+PQ) ([S2 Figure](#)).



## Low Birth Weight

Nine studies reported a total of 603 low birthweight newborns among 3891 women who received ACTs during pregnancy. The overall prevalence of low birthweight was 14.2% and found to be higher for AS+SP (23.6%) but it was relatively similar among the other ACTs (16.3% for AS+MQ, 14.4% for DHA+PQ, 12.6% for AL and 10.2% for AS+AQ) ([S3 Figure](#)).

## Congenital Anomalies

Six studies reported a total of 43 congenital anomalies among 3973 women who received ACTs during pregnancy. The overall prevalence of congenital anomalies was 1.0% and found to be similar among the ACTs (1.5% for DHA+PQ, 0.9% for AS+AQ and 1.2% for AL) ([S4 Figure](#)).

## Tolerability of ACTs

According to the Thailand study,<sup>15</sup> tolerability of AL and AS treatments was similar. Hematology, blood chemistry and ECG evaluations detected no difference in the occurrence of abnormal values. However, tinnitus was significantly different in the two treatment groups (AL, 0%; AS, 8.5%).

The PREGACT study in four African countries indicated that there was no significant difference in the occurrence of serious adverse events among the treatment arms.<sup>35</sup> Among these severe adverse events, severe vomiting associated with the AS+MQ arm was considered to be related to the study treatment.<sup>37</sup> The Ghanaian trial of AS+AQ and DHA+PQ documented severe diarrhea associated with AS+AQ, which was thought to be related to the treatment.<sup>33</sup> Other trials, including RCTs, comparing ACT with other ACTs or other antimalarial agents reported no treatment-related severe adverse events in India,<sup>38</sup> Malawi,<sup>34</sup> Nigeria<sup>24</sup> and Thailand.<sup>14,40</sup>

Tinnitus was one of the common adverse events reported in these trials. It was largely noted with treatment of QN as revealed by the Ugandan (QN versus AL),<sup>10</sup> and Thailand studies (AS+MQ versus QN)<sup>14</sup> and (QN versus AS+ATQ+PG).<sup>40</sup> In a comparative study of AL and AS7 conducted in Thailand, tinnitus was once again the only symptom that significantly differed between the treatment arms, which was more frequent in the AS7 arm (8.5%).<sup>15</sup>

Headache, dizziness, nausea, vomiting, poor appetite and asthenia were the other common treatment-related adverse events reported by these trials. In the PREGACT trial conducted in four African countries, significantly higher rate of treatment-related adverse events occurred

in the AS+MQ group and the AS+AQ group than in the DHA+PQ group and the AL group.<sup>35</sup> Other studies also demonstrated that a higher rate of dizziness was noted in the QN than the AS+MQ arm.<sup>14</sup> Vomiting was significantly higher in the AS+MQ than the AS+SP treatment arm in the Indian study.<sup>38</sup> Whilst women in the quinine arm had more frequent adverse events, such as nausea, vomiting, and anorexia than AL group, headache was higher in AL group in the Ugandan study.<sup>10</sup>

## Risk of Bias Across Studies

Fifteen clinical trials were evaluated using a revised tool for assessing risk of bias in randomized trials (ROB 2),<sup>18</sup> while the other eight studies were assessed with the STROBE statement.<sup>19</sup> Two clinical trials were found to have low risk of bias and all observational studies were judged to have high quality ([S4 Table](#)).

## Discussion

Systematic review and meta-analysis was conducted to compile and synthesize comprehensive evidence on efficacy and safety of ACT use for treatment of uncomplicated malaria during pregnancy. The overall ACPR of the ACTs was more than 95%, which is in line with WHO recommendations. Except for three treatment arms: AL,<sup>15</sup> AS+AQ<sup>33</sup> and DHA+PQ,<sup>33</sup> all the ACT treatment arms had an ACPR of greater than 90% at day 28 or greater follow-up. The WHO recommends a change in the treatment regimen if the treatment failure of an ACT is greater than or equal to 10%.<sup>20</sup>

In the five RCTs that were included for meta-analysis to compare ACTs and non-ACTs, the risk of treatment failure was substantially lower in patients treated with ACTs than in patients treated with non-ACTs (risk ratio 0.20, 95% C.I. 0.09–0.43). Similar findings were reported in a meta-analysis that compared ACTs with quinine-based therapies (risk ratio 0.22, 95% C.I. 0.07–0.63).<sup>45</sup>

This review revealed that the overall efficacy of AL in pregnant women was greater than 95% with meta-analysis of five trials. Despite this, it was reported that the cure rate in AL treatment group was significantly lower compared with AS+AQ, AS+MQ and DHA+PQ.<sup>35</sup> In one trial a less than 90% cure rate of AL was reported in pregnant patients.<sup>15</sup> This could have resulted from the lower drug concentrations achieved by both artemether and lumefantrine.<sup>46,47</sup> Indeed, an Ugandan study demonstrated that pregnant women had a 27% lower plasma concentration of lumefantrine than non-pregnant women.<sup>48</sup>



According to this review, the overall efficacy of AS+AQ was greater than 90% with the meta-analysis of three of the studies included in this review. One of the trials indicated that AS+AQ had significantly greater cure rate than CD.<sup>27</sup> Previous pharmacokinetic studies on pregnant women in Thailand showed that increasing the usual dose of proguanil was mandatory to achieve comparable plasma drug concentrations.<sup>49,50</sup> Findings of a study indicated the equivalence of AS+AQ efficacy with DHA+PQ.<sup>33</sup>

The overall efficacy of AS+MQ was shown to be 97.0% (95% C.I. 95.9–98.2%), which is greater than 95% with the meta-analysis of four studies included in this review. Studies included in this trial indicated that the efficacy of AS+MQ is comparable with AS+SP,<sup>38</sup> DHA+PQ,<sup>35</sup> AS+AQ<sup>35</sup> but significantly greater than the cure rate of AL<sup>35</sup> and quinine.<sup>14</sup>

The overall ACPR for DHA+PQ was 94.3% (95% C.I. 84.3–104.3%). Studies included in this trial indicated that the efficacy of DHA+PQ is comparable with AS+AQ,<sup>33,35</sup> AS+MQ,<sup>35</sup> but significantly greater than the cure rate of AL.<sup>35</sup> The overall day-28 or greater ACPR of AS+ATQ+PG and AS+SP was greater than 95%.

Trials showed that AL could grant the shortest-range post-treatment preventive activity against malaria as compared with the other ACTs. In the PREGACT study, reinfection rate was the highest in patients managed with AL and time to reinfection was the shortest in this treatment group.<sup>35</sup> One of the crucial factors in the choice of drugs for malaria management is the duration of post-treatment prophylaxis, particularly in regions with a high probability of infection. It was found that lumefantrine has a rapid clearance,<sup>51</sup> followed by amodiaquine,<sup>52</sup> mefloquine,<sup>31</sup> and then piperazine.<sup>53</sup>

In this review, there were 607 pregnant women exposed to artemisinin treatment in the first trimester of pregnancy, as reported by observational studies in Sudan,<sup>28</sup> Tanzania,<sup>26</sup> Thailand,<sup>13,42</sup> Thai-Myanmar<sup>39</sup> and Rwanda.<sup>11</sup> Data on cure rates in the first trimester were only available from observational studies, which posed difficulty to compare the outcomes using aggregated evidences. On top of this, the findings were rarely sorted by trimester, and the assessment of gestational age varied among the studies.

With the available observational studies, the risk of birth outcomes was not found to be higher in women taking ACTs in the first trimester. There was no significant birth outcome difference including miscarriage, stillbirth, early neonatal deaths, malformations, prematurity, low birth weight in various trials comparing combination of

the various treatment groups. Observational studies in the antenatal registers of pregnant women in the first trimester could not also demonstrate the risk of adverse birth outcomes associated with ACTs. From 62 women who received ACTs (including artemether injection, AS+SP and AL) in the first trimester of pregnancy, there was no maternal mortality reported and all newborns were delivered at full term, with no congenital abnormalities.<sup>28</sup> By contrast, first trimester exposure of quinine was associated with an increased risk of miscarriage and stillbirth in the Tanzanian observational cohort study<sup>26</sup> and abortive effect of quinine was linked to induction of uterine contractions.<sup>54</sup> Moreover, the Ugandan study also revealed that oral quinine had nearly two-fold increase in intrauterine fetal deaths than the AL group among women in the second and third trimesters of pregnancy.<sup>10</sup> But, first trimester exposure of pregnant women with chloroquine, quinine or artesunate resulted in similar risk of miscarriage and stillbirth in the Thai–Burmese study based on analysis made using the antenatal registers of pregnant women.<sup>13</sup> Likewise, in an observational study in Thai–Myanmar border, the risk of miscarriage and major congenital anomaly were similar among patients receiving ACT and quinine in the first trimester of pregnancy.<sup>39</sup>

The Indian study that compared AS+SP and AS+MQ reported that miscarriages, preterm delivery or stillbirths were similar in treatment arms but low birth weight (< 2.5 kg) was reported to be higher in the AS+SP treatment group (28.1%) than in the AS+MQ treatment group (16.7%).<sup>38</sup> Higher proportion of low birth weight was not reported in other studies.<sup>28,34</sup> In the Ghanaian trial comparing DHA+PQ and AS+AQ in pregnant women, low birth weight was observed in 9.3% of babies and was higher in the DHA+PQ arm compared with AS+AQ (13.2% versus 4.2%).<sup>33</sup> This finding was not consistent with other studies using DHA+PQ for treatment or prevention of malaria in pregnancy.<sup>35,55–57</sup>

Trials comparing ACT with other ACTs or other anti-malarial agents reported no treatment-related severe adverse events including RCTs in India,<sup>38</sup> Malawi, Nigeria<sup>24</sup> and Thailand.<sup>14,40</sup> Although 10 severe adverse events were reported in the PREGACT study, there was no significant difference in the occurrence of severe adverse events among the treatment arms.<sup>35</sup> Tinnitus was dominantly reported with pregnant women who took quinine than ACTs or other antimalarial drugs.<sup>10,13,14,40</sup> Other adverse events including dizziness, headache, nausea, vomiting, poor appetite and asthenia occurred significantly

at higher rates in the AS+MQ and AS+MQ groups in the PREGACT study.<sup>35</sup>

Even though this review generated comprehensive evidence on efficacy and safety of ACTs in pregnant women, it was subject to some limitations. The studies included were heterogeneous in design. Each study used a different ACT, and the timing of the measurement of the primary efficacy endpoint, the PCR-corrected failure rate varied from days 28 to 63. Indicators for tolerability differed among studies as well as the methods and timing of assessment of many of the secondary efficacy endpoints varied, which made it difficult to pool the information. The number of studies and study participants were limited, and data for studies with first trimester exposure of ACTs were compiled only from observational studies (not RCTs). This may limit the generalizability of the findings.

## Conclusion

Meta-analysis of available evidence indicated that ACTs demonstrated high overall efficacy for treatment of uncomplicated falciparum malaria (96.1%). Overall days 28 to 63 cure rates for AL, AS+AQ, AS+MQ, DHA+PQ, AS+ATQ+PG and AS+SP were 95.1%, 92.2%, 97.0%, 94.3%, 96.5% and 97.4%, respectively. Analysis of treatment failure among ACTs and non-ACTs indicated that risk of treatment failure at days 28 to 63 cure rate was significantly lower in patients treated with ACTs than in patients treated with non-ACTs. Adverse birth outcomes were comparable among ACTs and the risks of pregnancy and neonatal outcomes, and other adverse events were not found to be higher in women taking ACT, supporting the use of ACTs during pregnancy. As evidenced by data from observational studies, first trimester exposure of ACTs was not found to be associated with an increased risk of adverse birth outcomes.

## Abbreviations

ACPR, Adequate clinical and parasitological response; AL, Artemether-lumefantrine; AS+AQ, Artesunate + amodiaquine; AS+ATQ+PG, Artesunate + atovaquone + proguanil; AS+MQ, Artesunate + mefloquine; AS+SP, Artesunate + sulfadoxine-pyrimethamine; DHA+PQ, Dihydroartemisinin + piperaquine; MeSH, Medical subject heading; PICOS, Population, intervention, comparison, outcome, study; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

## Data Sharing Statement

The datasets used during the current study are presented within the manuscript and/or additional supporting files, and also available from the corresponding author on reasonable request.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work is supported by a grant from European and Developing Countries Clinical Trials Partnership (EDCTP) and European Union (Grant number:TMA2016IF-1778).

## Disclosure

The authors declare that there is not any real or perceived conflict of interest.

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