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Blocking malaria transmission to *Anopheles* mosquitoes using artemisinin derivatives and primaquine: a systematic review and meta-analysis

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Abstract

Background: Among the currently used drugs in malaria case management, artemisinin derivatives and primaquine have an impact on the transmissible stages of *Plasmodium falciparum*. Hence, they reduce the transmission of the parasite from the patient to the mosquitoes. The present study aimed to assess evidence for this hypothesis from controlled trials.

Methods: All controlled clinical trials evaluating the transmission blocking activity of artemisinin derivatives and primaquine with or without other antimalarials were included in this systematic review. PubMed, Google Scholar, Web of Science, ScienceDirect, Medscape and the Cochrane library were systematically searched without language, publication status or date restrictions. The literature references were also scanned manually. The last search was run on July 15, 2013. Search terms included artemisinin derivatives, primaquine, malaria transmission, transmission blocking/reducing drugs and mosquito infection. The outcome measure was the mosquito infectivity rate after treatment of patients. Data were compared using odds ratio (OR), in random effects models.

Results: Nine trials with a total of 13,831 mosquitoes were included in the meta-analysis. After combining the trials, the transmission of *P. falciparum* to *Anopheles* mosquitoes were lower in artesunate, artemether-lumefantrine and primaquine groups as compared with their control counterparts with OR of 0.36 (95% confidence interval (CI), 0.14-0.90), 0.49 (95% CI, 0.31-0.79) and 0.09 (95% CI, 0.01-0.73); respectively. In non-comparative longitudinal studies, the use of a single-dose of primaquine was shown to deter the transmission of malaria briefly.

Conclusion: Evidence on the transmission blocking effect of artemisinin derivatives and primaquine is conclusive. Trials evaluating the combined impact of artemisinin derivatives and primaquine on malaria transmission is urgently needed.

Keywords: Malaria transmission blocking, Artesunate, Artemether-lumefantrine, Primaquine, Systematic review, Meta-analysis

Background

Globally, an estimated 3.3 billion people were at risk of malaria in 2011, with populations living in sub-Saharan Africa having the highest risk of malaria infection [1]. Between 2000 and 2010, malaria mortality rates fell by 26% around the world. In the World Health Organization (WHO) African Region the decrease was 33%. During this period, an estimated 1.1 million malaria deaths were

averted globally, primarily as a result of a scale-up of interventions with a proven track record [2,3]. However, malaria transmission still occurs in 99 countries around the world, and the malaria burden continues to cripple health systems in many African countries. In 2010, this entirely preventable and treatable disease caused an estimated 655,000 deaths worldwide [4].

Proven strategies for malaria control include early treatment of the illness with artemisinin-based combination therapies (ACTs) [5], intermittent preventive treatment for pregnant women (IPT_p) [6], and using measures that

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reduce the risk of infection such as indoor residual spraying (IRS) or insecticide-treated nets (ITNs) [7]. These tools and strategies have shown to be effective at contributing to malaria control [8]. Among the drugs used currently in malaria case management, the ACTs and primaquine have an impact on the transmissible stages of *Plasmodium falciparum*. It is assumed that artemisinin derivatives act against young gametocytes, whereas primaquine acts on mature gametocytes, which are usually present in the circulation at the time when the patient presents for treatment [9].

Independent reports and a pooled data analysis study speculated about the malaria transmission reduction by artemisinin derivatives from malaria patients to *Anopheles gambiae*, a major malaria vector in Africa [10]. Similarly, many studies have reflected the impact of primaquine on malaria transmission from patients to *Anopheles stephensi*, a sub-tropical species that predominates in Asia. However, no systematic analysis has been performed on the transmission blocking activity of artemisinin derivatives and primaquine. The present study attempts to make a systematic review and meta-analysis of the impact of artemisinin derivatives and primaquine on malaria transmission to the vector, and to measure whether there are general trends across the different reports on the change in malaria transmission due to artemisinin derivatives and primaquine. The study also explores the reasons for variations across the reports.

Methods

Conduct of systematic review and search strategy

The investigator developed a protocol for this systematic review and conducted it in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Additional file 1: Checklist S1) [11]. A search was conducted to identify studies assessing malaria transmission blocking effect of drugs. PubMed, Google Scholar, Web of Science, ScienceDirect, Medscape and the Cochrane library were systematically searched without language, publication status or date restrictions. Literature references were also scanned manually. The last search was run on July 15, 2013. Search terms included artemisinin derivatives, primaquine, malaria transmission, transmission blocking/reducing drugs and mosquito infection (Additional file 2: Table S1). Studies comprising cases of *P. falciparum* treated with antimalarials (artemisinin derivatives and/or primaquine) and evaluating malaria transmission to *Anopheles* mosquitoes were included. Based on the inclusion criteria, studies for both artemisinin derivative (artesunate and artemether) and primaquine were selected for qualitative and quantitative synthesis. Figure 1 outlines the identification of studies for this systematic review and meta-analysis.

Inclusion and exclusion criteria

Once it was determined that a paper contained a study on malaria transmission after interventions (artemisinin

derivatives or primaquine), the full length article was consulted to check whether studies fulfill the following inclusion criteria for the meta-analysis:

- i. controlled clinical trial on malaria patients;
- ii. study on malaria transmission test from a patient to mosquito after treating the patient with the existing antimalarials; and
- iii. evaluating mosquito mid-gut for oocyst prevalence to measure the extent of malaria transmission.

Similar trials with the aforementioned criteria were also included for the qualitative synthesis. Studies involving laboratory animals or trials without control arms were excluded in the meta-analysis.

Study design and outcome measures

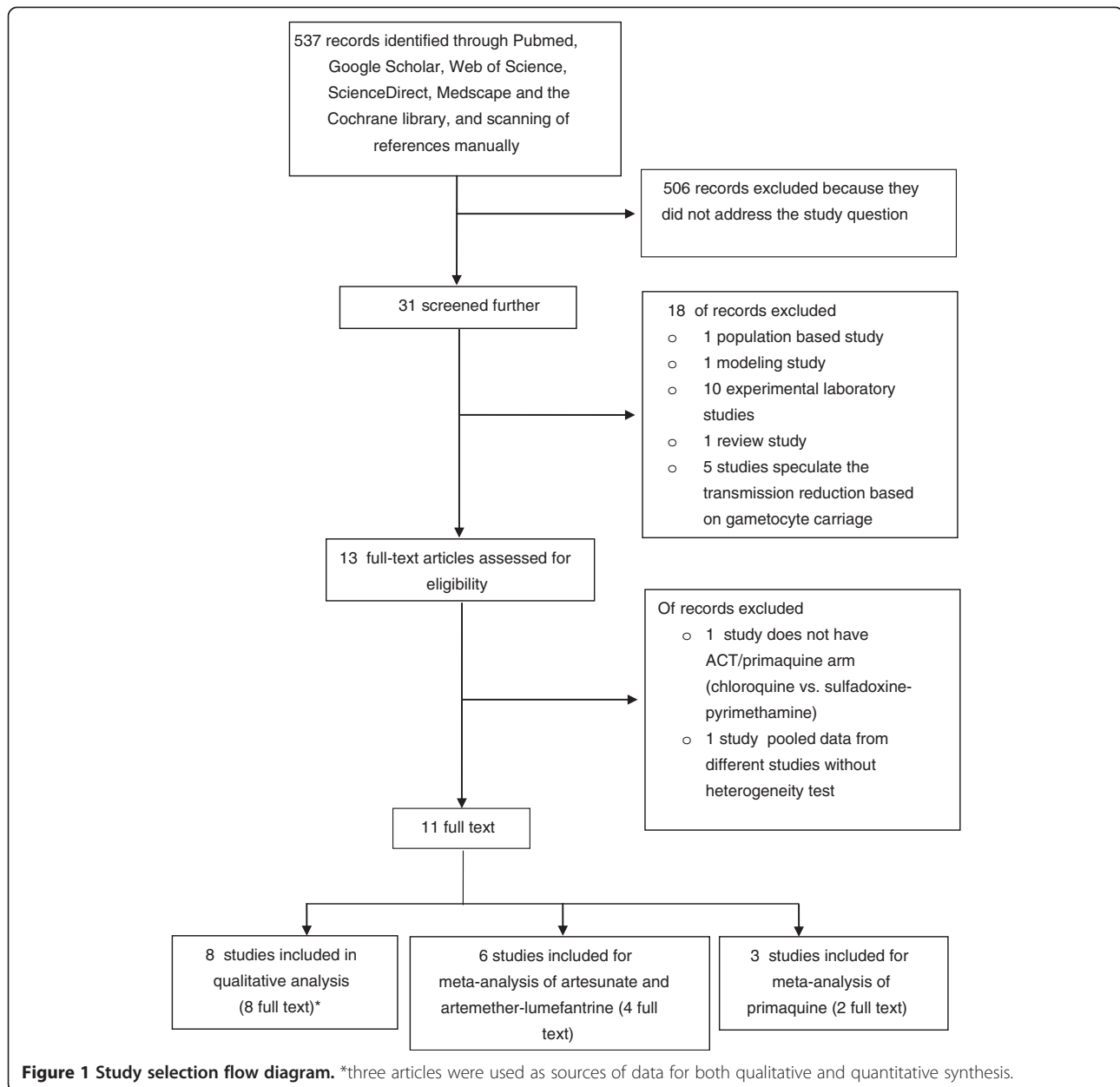
The endpoints were mosquito infection prevalence out of all mosquitoes getting a blood-meal on patients after treatment with antimalarials. The endpoint evaluation was done in mosquitoes following their blood-meal directly on patients and artificial membrane feeding apparatus in primaquine trials and artemisinin derivatives; respectively. A data extraction sheet was used by the investigator to calculate the prevalence of mosquito infection in each trial. Information was extracted from each included trial on characteristics of trial participants, types of intervention (including type, dose, duration and frequency) and trial outcomes (mosquito infection prevalence). The odds of the end points from mosquitoes in the categories of artemisinin derivatives/primaquine and control (standard drugs) were calculated. The odds ratio (OR) and 95% confidence intervals (CI) for the prevalence of mosquito infection was then calculated.

The risk of bias in the studies used for meta-analysis was assessed by the investigator in an un-blinded manner using a tool developed by the Cochrane Collaboration (focusing on specific domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting) [12]. Due to the small number of studies identified, trials were not excluded based on quality assessment. For the same reason, publication bias was not assessed [12].

Statistical analysis

Meta-analysis was performed using Meta-analyst, a software for meta-analysis of binary, continuous and diagnostic data [13]. The random effect method was used to test for differences in binary outcomes between artemisinin derivatives/primaquine and control (standard drug).

Heterogeneity, the variations among study outcomes, was checked by tau^2 statistic, chi-square based Q-test, I^2 statistics and heterogeneity P-value. The author chose the



random effects meta-analytic model (DerSimonian and Laird) [14] to calculate the combined OR and 95% CI, even in a meta-analysis with low level of heterogeneity, in order to accommodate the random variation within the studies and the variation between the different studies.

Results

Description of included studies

The literature search identified the transmission blocking trials at the level of mosquitoes using two artemisinin derivatives (artesunate and artemether) and primaquine. Of 31 potentially relevant publications, only 6 publications

(nine studies) on artemisinin derivatives and primaquine, fulfilled the inclusion criteria for the meta-analysis (Table 1). Eight publications were qualified for the qualitative analysis of transmission blocking property of primaquine and artemisinin derivatives.

Some of the publications, which fulfilled the inclusion criteria, had results of multiple studies; and these were used to generate effect sizes for the transmission blocking property of drugs (artesunate, artemether or primaquine) *vs.* controls. The studies used in the quantitative analysis were from Africa (Gambia and Kenya) and USA dealing with artemisinin derivatives and primaquine; respectively.

Table 1 Characteristics of trials included in the meta-analysis

Location (Study year)	Participants	Treatment arms	Mosquitoes (numbers used)	Mosquito infection method	Ref.
Gambia* (2000)	Children (1–9 yrs)	Artesunate [a] + chloroquine [b]; chloroquine [b]	<i>Anopheles gambiae</i> (1208)	Membrane feeding	[15]
Gambia (1999)	Children	Artesunate [a] + sulfadoxine-pyrimethamine [f]; sulfadoxine-pyrimethamine [f]	<i>Anopheles gambiae</i> (3192)	Membrane feeding	[16]
Gambia (1998)	Children	Artesunate [g] + sulfadoxine-pyrimethamine [f]; sulfadoxine-pyrimethamine [f]	<i>Anopheles gambiae</i> (2688)	Membrane feeding	[16]
Kenya (2003–4)	Children (6 months–10 yrs)	Sulfadoxine-pyrimethamine [h] + placebo [i]; artesunate [a] + sulfadoxine-pyrimethamine [h]; sulfadoxine-pyrimethamine [h] + Amodiaquine [j]; artemether-lumefantrine [k]	<i>Anopheles gambiae</i> (3000)	Membrane feeding	[17]
Gambia (2002)	Children (1-10 yrs)	Artemether-lumefantrine [c]; chloroquine[d] + sulfadoxine-pyrimethamine [e]	<i>Anopheles gambiae</i> (540)	Membrane feeding	[18]
USA**	Adults	Primaquine [l]; Sulfadiazine + pyrimethamine [m]	<i>Anopheles stephensi</i> (30)	Direct skin bite	[19]
USA*** (1968)	Adults (25 to 41 yrs)	Primaquine [l]; pyrimethamine [n]	<i>Anopheles stephensi</i> (163)	Direct skin bite	[20]

a = 4 mg/kg for 3 days.

b = 25 mg/kg over 3 days: 10 mg, 10 mg, 5 mg.

c = Each dose: One half-tablet of co-artemether (20 mg artemether + 120 mg of lumefantrine) per 5 kg body weight up to 24 kg (two tablets).

d = Three daily doses of 10 mg/kg.

e = One half-tablet of SP (12.5 mg of pyrimethamine with 250 mg of sulfadoxine per half-tablet).

f = One-half tablet of pyrimethamine-sulfadoxine (12.5 mg pyrimethamine + 250 mg sulfadoxine) for a body weight of 10 kg & a further one-quarter tablet for each 5 kg increase.

g = 4 mg/kg immediate dose of artesunate.

h = 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine as a single dose plus.

i = placebo once daily for 3 days.

j = 10 mg/kg for once daily for 3 days.

k = administered as half a tablet (20 mg of artemether and 120 mg of lumefantrine) per 5 kg of body weight in a 6-dose.

l = single dose of 45 mg of primaquine base.

m = 500 mg of sulfadiazine every 6 hours for 5 days and 50 mg of pyrimethamine daily for 3 days.

n = Pyrimethamine 50 mg daily for 3 days.

*two parallel studies involving autologous plasma and control serum.

**the study year is not mentioned in the article.

***two parallel studies involving two strains of *P. falciparum*. Ref. = References.

Study quality assessment

A summary of the risk of bias assessment of the controlled trials can be found in Table 2. The extent of risk of bias varied across the studies. In general, trials done using artemisinin derivatives had a low risk of bias in most areas, whereas the trials on primaquine had an unclear risk of bias in most areas.

Heterogeneity assessment

Heterogeneity among the selected published studies was examined and the outcomes are presented in Table 3. A moderate to substantial heterogeneity was observed in the trials used for the two meta-analyses (with artesunate *vs.* without artesunate, primaquine *vs.* other antimalarials). The pooled ORs were calculated by the random-effects model, which assumes that the estimated effect size in different trials follow some distribution [21].

Artesunate-based combinations *versus* antimalarials without artesunate

The transmission blocking property of artesunate in combination with other antimalarials (chloroquine, sulfadoxine-

pyrimethamine alone, sulfadoxine-pyrimethamine with amodiaquine or with placebo) were compared with the respective standard treatments (controls) without artesunate. The total number of mosquitoes checked for oocyst were 4,013 in the artesunate group and 6,075 in the control group. The OR was 0.36 (95% CI, 0.14-0.90), which favours artesunate-based combination therapy in reducing the transmission of *P. falciparum* parasite from patients to mosquitoes (Figure 2).

Artemether-lumefantrine *versus* other antimalarials

The association between the use of artemether-lumefantrine and the reduction of malaria transmission was investigated. The total number of mosquitoes evaluated for oocyst was 1,695 in artemether-lumefantrine group and 1,845 in control group. The OR was 0.49 (95% CI, 0.31-0.79), which favours artemether-lumefantrine therapy in reducing the transmission of malaria from patients to mosquitoes (Figure 3).

The meta-analysis was in favour of artemisinin derivatives in reducing malaria transmission (Figures 2 and 3). In two randomised trials, the transmission blocking

Table 2 Risk of bias assessment within the trials

Study location (year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants & personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other	Ref.
Gambia (2000)	low	low	low	low	low	low	unclear	[15]
Gambia (1999)	low	unclear	low	low	low	low	unclear	[16]
Gambia (1998)	low	unclear	low	low	low	low	unclear	[16]
Kenya (2003–4)	low	unclear	low	low	low	low	unclear	[17]
Gambia (2002)	low	low	low	low	low	low	unclear	[18]
USA*	high	high	low	low	unclear	unclear	unclear	[19]
USA (1968)	high	high	low	low	unclear	unclear	unclear	[20]

*The study year is not mentioned in the publication. Ref = references.

activity of ACTs were compared. In the first study, treatment with artemether-lumefantrine was associated with a lower proportion of infected mosquitoes as compared with dihydroartemisinin-piperaquine (OR 0.53; 95% CI, 0.37- 0.77) [22]. The second study comparing artemether-lumefantrine and artesunate in combination with sulfadoxine-pyrimethamine did not show any difference in the proportion of infected mosquitoes (OR 1.60; 95% CI, 0.87-2.98) [17].

Primaquine single dose versus other antimalarials

The association between single-dose primaquine (45 mg) and malaria transmission blocking from patients to mosquitoes was assessed. Overall, 65 mosquitoes in the primaquine group and 138 mosquitoes in the comparative group were used. The OR was 0.09 (95% CI, 0.01-0.73), which favours single-dose primaquine therapy in reducing the transmission of malaria from patients to mosquitoes (Figure 4).

Single-dose of primaquine and malaria transmission at different points in time

Single-dose primaquine from 15 mg to 45 mg were given to individuals diagnosed with *P. falciparum*, and the patients were exposed to mosquito bites at different days, i.e. before and after treatment. The data of mosquito infection rate versus time (treatment days) from 16 patients, reported by multiple studies, is presented in Figure 5.

In more than 93% of all the patients, the *Plasmodium* transmission to the mosquitoes had been blocked within the third day of administration of a single dose of

primaquine. However, mosquitoes feeding on patients after 10 days of treatment became oocyst-positive. Briefly, this has been revealed in a study that followed patients for two weeks. Mosquitoes, fed on one patient on the 14th day and a second patient on the 11th and 15th days after primaquine treatment, became oocyst-positive (Figure 5).

Addition of primaquine to antimalarials and malaria transmission: the mefloquine case

Chen and his colleague studied the impact of single-dose mefloquine with and without primaquine (45 mg) on the transmission rate of *Plasmodium* from patients to mosquitoes [26]. Before treatment, the mosquito infection prevalence was similar in mefloquine alone and mefloquine plus primaquine arms. Mosquitoes, fed on membrane feeding apparatus containing blood from patients treated with mefloquine plus primaquine on later days, were not infected unlike the group treated with mefloquine alone that showed a sluggish reduction in infection rate through time (Figure 6).

In the mefloquine plus primaquine group, the transmission of malaria was blocked throughout the duration of follow-up, i.e. 3 weeks (Figure 6). This duration of transmission blockade was longer than the duration (about 10 days) reported in those studies, which used only primaquine (Figure 5).

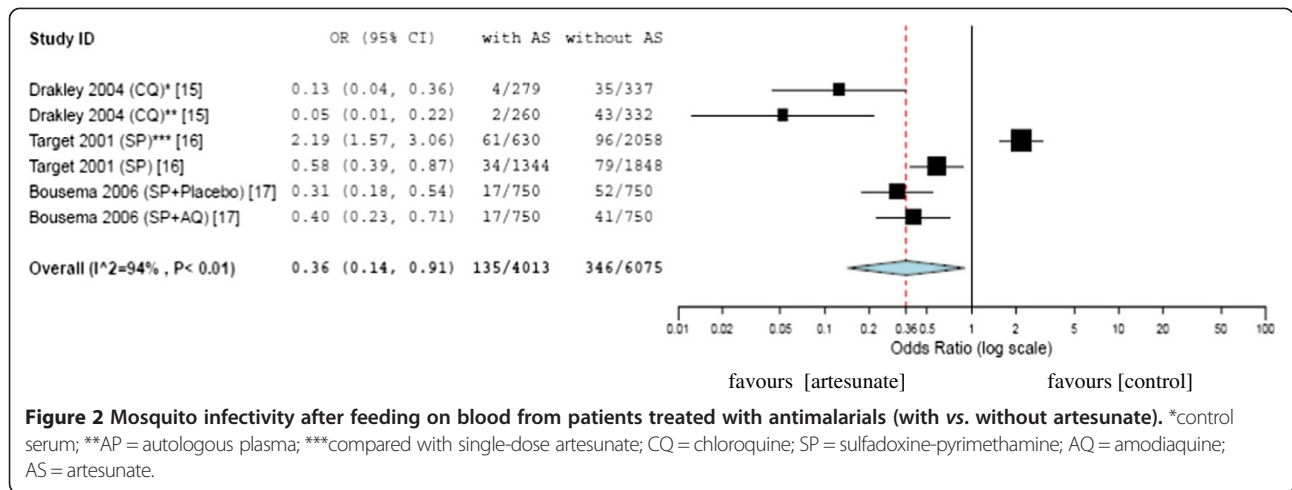
Discussion

Preventing mosquitoes from biting by the existing tools (e.g. ITNs and IRS) and blocking the transmission of

Table 3 Statistics to test heterogeneity in the meta-analysis

Comparison	Heterogeneity				Model used for meta-analysis*
	Tau ²	Q-value	P heterogeneity	I ² (%)	
With artesunate vs. without artesunate	1.18	79.7 (df = 5)	<0.01	94	Random
Artemether-lumefantrine vs. other antimalarials	0.05	2.77 (df = 2)	0.25	28	Random
Primaquine vs. other antimalarial	1.95	5.15 (df = 3)	0.16	42	Random

*For the reasons mentioned in the method (statistical analysis section), random effects model was chosen for all comparison.



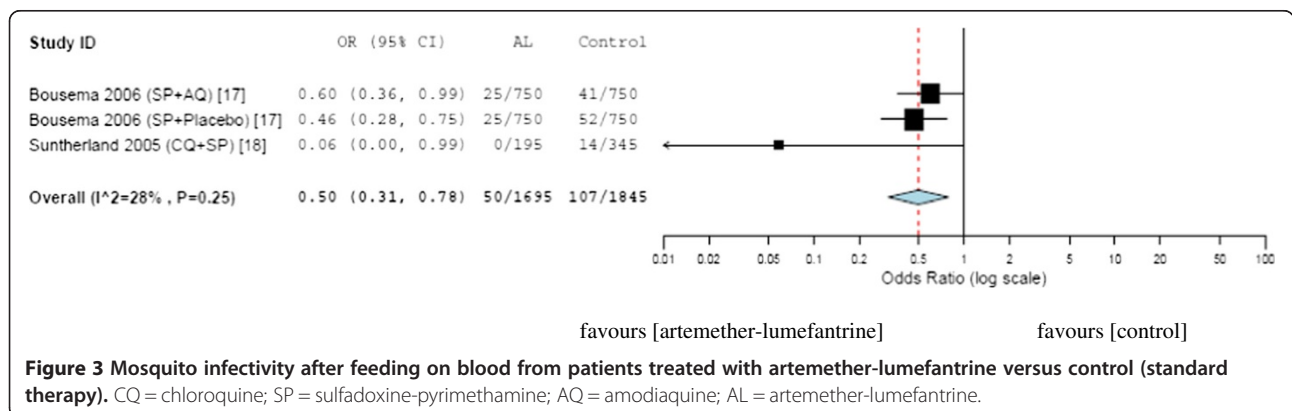
Plasmodium parasites from patients to mosquitoes using agents (vaccine or drugs) may substantially improve public health through reducing the burden of malaria [27]. In areas of stable malaria, a meta-analysis of ITNs on malaria transmission revealed a reduction by 50% [28]. However, a meta-analysis on existing antimalarials to block the transmission of the parasite from patients to mosquitoes has not yet been done to the author's knowledge.

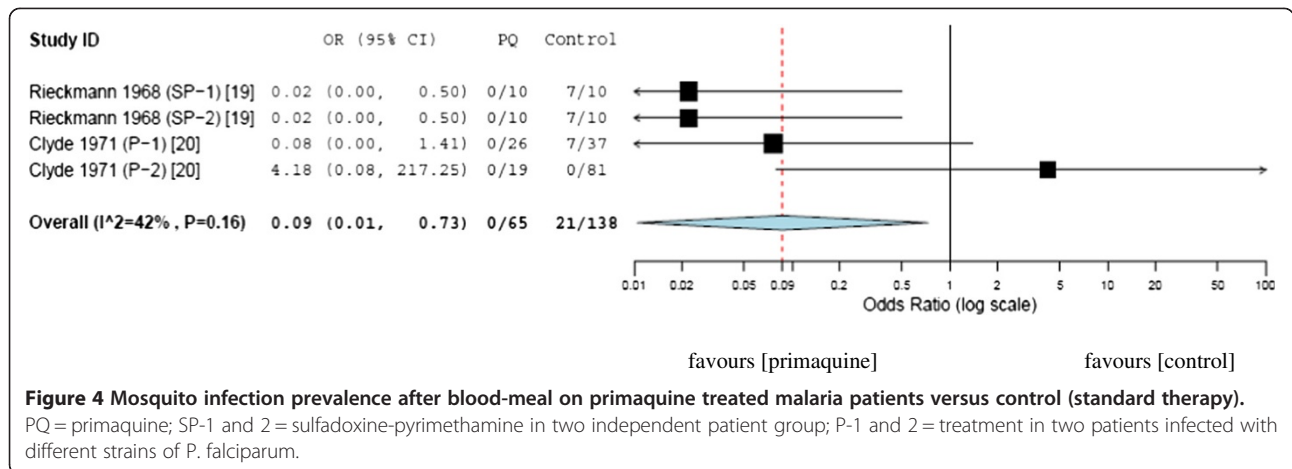
The current meta-analysis re-affirmed the advantage of ACTs in reducing transmission of *Plasmodium* to the mosquitoes. In the overall analysis, the odds of transmission of malaria in artesunate-based combination treatment group was 2.78 times less than the odds of transmission of malaria in antimalarials without artesunate (Figure 2). Similarly, the odds of malaria transmission to mosquitoes in artemether-lumefantrine treated group was 2 times less than the odds on other antimalarials used in the studies (Figure 3). Exceptionally, in one trial [16], the odds of parasite transmission was higher in artesunate-based combination therapy than the standard therapy without artesunate. This difference might be attributed to the use of only one dose of artesunate in the trial.

From the current analysis of the published articles, artesunate- and artemether-based therapy could reduce the transmission of the parasite to the mosquitoes. Thus, these medications, in addition to their role in the clinical case management of malaria, can have an impact on the overall transmission rate of malaria and play a role in controlling malaria.

Primaquine, the old antimalarial drug mainly used in terminal cure of *P. vivax* infection, was also tested for its impact on the transmission of *Plasmodium* to mosquitoes. Trials compared the transmission blocking effect of single-dose primaquine with the conventional antimalarials: sulfadoxine-pyrimethamine and pyrimethamine. The current analysis showed that odds of mosquito infection rate was 11 times less for single-dose primaquine relative to the comparative medicine (Figure 4).

In non-comparative longitudinal trials of single-dose primaquine, the current systematic review presented the trends of mosquito infection rate across successive post-treatment days (Figure 5). There was a rapid drop in mosquito infection rate as illustrated in those mosquitoes feeding on the first and second days post-treatment.



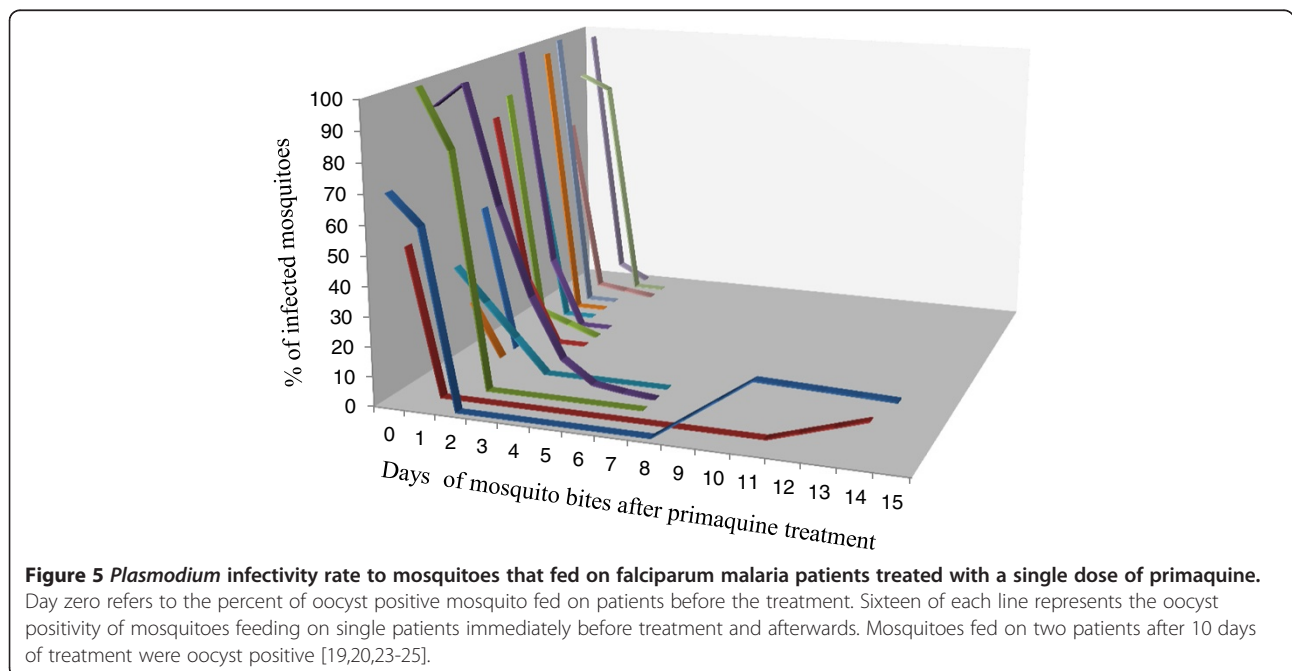


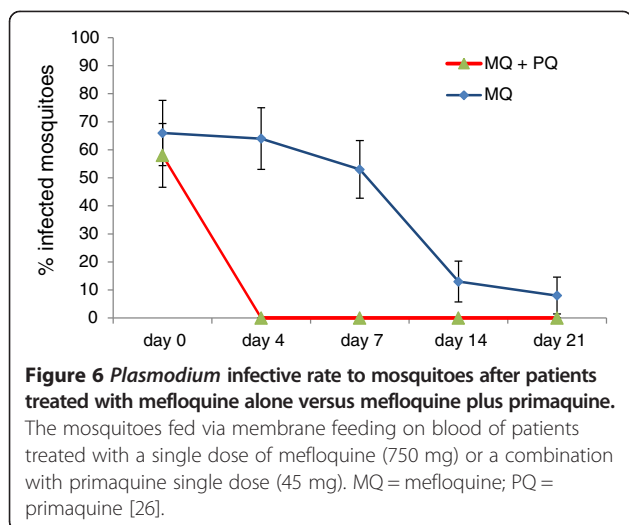
However, the effect was maintained only for a short period as evidenced by the positivity of mosquitoes biting on some patients after the 10 days of single-dose primaquine therapy. As the trials employed single-dose primaquine therapy, which might target only the mature gametocyte [9], the continuity of transmission blockade by a single dose of primaquine fails against the new wave of mature gametocytes that appear after primaquine has been washed out [29].

The use of single-dose primaquine blocks the transmission of malaria temporarily (Figure 5). However, combining it with effective antimalarials - like mefloquine used in the trial conducted by Chen and his colleague - results in a disruption of *Plasmodium* transmission to the vector for a longer period (Figure 6). This might be explained by the fact that the effective schizonticide (mefloquine), by

clearing the parasite, dries out the potential source for a new wave of gametocytes.

Following the introduction of ACTs in malaria case management, many researchers report the additional benefit of ACTs on the partial gametocytocidal effect compared with the non-ACTs regimens [30-34]. Recently, there is also interest of combining ACTs with single-dose primaquine, particularly in areas with a resistant *Plasmodium* to ACTs or in the phase of malaria elimination. The addition of primaquine to ACTs results in a further reduction in gametocyte carriage rate that can have implications on the extent of malaria transmission [35-39]. However, the optimal time of administration, treatment duration and dose of primaquine needs to be understood for improved outcomes. Further studies are also required to





understand the transmission blocking effect upon the addition of primaquine to ACT regimens at the mosquito level, which is a gold standard approach to evaluate malaria transmission.

The present paper analysed the transmission blocking activity of artemisinin derivatives and primaquine. The clinical trials of artemisinin derivatives and primaquine focused on *An. gambiae* and *An. stephensi*; respectively. None of the identified literatures pertained to other dominant malaria vectors such as *An. funestus* and *An. arabiensis* [40-42]. In all of the trials included for meta-analysis, similar colonies of mosquitoes in both intervention and control groups were used. By so doing, confounding bias related to the variable infection success in the different species of vectors could be avoided. Of course, if the variability in susceptibility of the vectors to *P. falciparum* infection modified the transmission blocking activity of drugs, trials with different species of malaria vectors having a range of infection success would be required; then systematic reviews should consider subgroup analysis.

Like any retrospective study, this systematic review has a number of limitations. The literature search might have missed some trials. The author assumed that missing reports is unlikely for two reasons. Firstly, a proper search strategy was followed to identify literatures. Secondly, the research groups working on transmission blocking trials at the level of mosquitoes are few. Another concern is the comparison of the reference drugs (artemisinin derivatives and primaquine) with a heterogeneous array of antimalarials probably with different gametocytocidal activity, which in turn might obscure some systematic differences between drugs. To minimize these risk, random analytic method was followed in all data analysis, including in those with little heterogeneity.

Conclusions

Based on the data reviewed, artemisinin derivatives (artesunate and artemether) and primaquine reduce the transmission of *P. falciparum* from the patient to the mosquitoes. Combining the two medications, after a proper optimization study, might further reduce the transmission of malaria.

Additional files

Additional file 1: Checklist S1 PRISMA 2009 checklist.

Additional file 2: Table S1. Search strategies for the databases.

Competing interests

The author declares that he has no competing interests.

Author contribution

SMA conceived the idea and designed the study, made both qualitative and quantitative synthesis of reported trials, wrote and revised the manuscript.

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