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Mass drug administration for malaria (Review)

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Mass drug administration for malaria.
Cochrane Database of Systematic Reviews 2021, Issue 9. Art. No.: CD008846.
DOI: 10.1002/14651858.CD008846.pub3.

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[Intervention Review]

Mass drug administration for malaria

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Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 9, 2021.

Citation: Shah MP, Hwang J, Choi L, Lindblade KA, Kachur SP, Desai M. Mass drug administration for malaria. *Cochrane Database of Systematic Reviews* 2021, Issue 9. Art. No.: CD008846. DOI: 10.1002/14651858.CD008846.pub3.

ABSTRACT

Background

Studies evaluating mass drug administration (MDA) in malarious areas have shown reductions in malaria immediately following the intervention. However, these effects vary by endemicity and are not sustained. Since the 2013 version of this Cochrane Review on this topic, additional studies have been published.

Objectives

Primary objectives

To assess the sustained effect of MDA with antimalarial drugs on:

- the reduction in malaria transmission in moderate- to high-transmission settings;

- the interruption of transmission in very low- to low-transmission settings.

Secondary objective

To summarize the risk of drug-associated adverse effects following MDA.

Search methods

We searched several trial registries, citation databases, conference proceedings, and reference lists for relevant articles up to 11 February 2021. We also communicated with researchers to identify additional published and unpublished studies.

Selection criteria

Randomized controlled trials (RCTs) and non-randomized studies comparing MDA to no MDA with balanced co-interventions across study arms and at least two geographically distinct sites per study arm.

Data collection and analysis

Two review authors independently assessed trials for eligibility and extracted data. We calculated relative risk (RR) and rate ratios with corresponding 95% confidence intervals (CIs) to compare prevalence and incidence, respectively, in MDA compared to no-MDA groups.

We stratified analyses by malaria transmission and by malaria species. For cluster-randomized controlled trials (cRCTs), we adjusted standard errors using the intracluster correlation coefficient. We assessed the certainty of the evidence using the GRADE approach. For non-randomized controlled before-and-after (CBA) studies, we summarized the data using difference-in-differences (DiD) analyses.

Main results

Thirteen studies met our criteria for inclusion. Ten were cRCTs and three were CBAs.

Cluster-randomized controlled trials

Moderate- to high-endemicity areas (prevalence ≥ 10%)

We included data from two studies conducted in The Gambia and Zambia.

At one to three months after MDA, the *Plasmodium falciparum* (hereafter, *P falciparum*) parasitaemia prevalence estimates may be higher compared to control but the CIs included no effect (RR 1.76, 95% CI 0.58 to 5.36; Zambia study; low-certainty evidence); parasitaemia incidence was probably lower (RR 0.61, 95% CI 0.40 to 0.92; The Gambia study; moderate-certainty evidence); and confirmed malaria illness incidence may be substantially lower, but the CIs included no effect (rate ratio 0.41, 95% CI 0.04 to 4.42; Zambia study; low-certainty evidence).

At four to six months after MDA, MDA showed little or no effect on *P falciparum* parasitaemia prevalence (RR 1.18, 95% CI 0.89 to 1.56; The Gambia study; moderate-certainty evidence) and, no persisting effect was demonstrated with parasitaemia incidence (rate ratio 0.91, 95% CI 0.55 to 1.50; The Gambia study).

Very low- to low-endemicity areas (prevalence < 10%)

Seven studies from Cambodia, Laos, Myanmar (two studies), Vietnam, Zambia, and Zanzibar evaluated the effects of multiple rounds of MDA on *P falciparum*. Immediately following MDA (less than one month after MDA), parasitaemia prevalence was reduced (RR 0.12, 95% CI 0.03 to 0.52; one study; low-certainty evidence). At one to three months after MDA, there was a reduction in both parasitaemia incidence (rate ratio 0.37, 95% CI 0.21 to 0.55; 1 study; moderate-certainty evidence) and prevalence (RR 0.25, 95% CI 0.15 to 0.41; 7 studies; low-certainty evidence). For confirmed malaria incidence, absolute rates were low, and it is uncertain whether MDA had an effect on this outcome (rate ratio 0.58, 95% CI 0.12 to 2.73; 2 studies; very low-certainty evidence).

For *P falciparum* prevalence, the relative differences declined over time, from RR 0.63 (95% CI 0.36 to 1.12; 4 studies) at four to six months after MDA, to RR 0.86 (95% CI 0.55 to 1.36; 5 studies) at 7 to 12 months after MDA. Longer-term prevalence estimates showed overall low absolute risks, and relative effect estimates of the effect of MDA on prevalence varied from RR 0.82 (95% CI 0.20 to 3.34) at 13 to 18 months after MDA, to RR 1.25 (95% CI 0.25 to 6.31) at 31 to 36 months after MDA in one study.

Five studies from Cambodia, Laos, Myanmar (2 studies), and Vietnam evaluated the effect of MDA on *Plasmodium vivax* (hereafter, *P vivax*). One month following MDA, *P vivax* prevalence was lower (RR 0.18, 95% CI 0.08 to 0.40; 1 study; low-certainty evidence). At one to three months after MDA, there was a reduction in *P vivax* prevalence (RR 0.15, 95% CI 0.10 to 0.24; 5 studies; low-certainty evidence). The immediate reduction on *P vivax* prevalence was not sustained over time, from RR 0.78 (95% CI 0.63 to 0.95; 4 studies) at four to six months after MDA, to RR 1.12 (95% CI 0.94 to 1.32; 5 studies) at 7 to 12 months after MDA. One of the studies in Myanmar provided estimates of longer-term effects, where overall absolute risks were low, ranging from RR 0.81 (95% CI 0.44 to 1.48) at 13 to 18 months after MDA, to RR 1.20 (95% CI 0.44 to 3.29) at 31 to 36 months after MDA.

Non-randomized studies

Three CBA studies were conducted in moderate- to high-transmission areas in Burkina Faso, Kenya, and Nigeria. There was a reduction in *P falciparum* parasitaemia prevalence in MDA groups compared to control groups during MDA (DiD range: -15.8 to -61.4 percentage points), but the effect varied at one to three months after MDA (DiD range: 14.9 to -41.1 percentage points).

Authors' conclusions

In moderate- to high-transmission settings, no studies reported important effects on *P falciparum* parasitaemia prevalence within six months after MDA. In very low- to low-transmission settings, parasitaemia prevalence and incidence were reduced initially for up to three months for both *P falciparum* and *P vivax*; longer-term data did not demonstrate an effect after four months, but absolute risks in both intervention and control groups were low. No studies provided evidence of interruption of malaria transmission.

PLAIN LANGUAGE SUMMARY

Administration of antimalarial drugs to whole populations for reducing malaria

What is mass drug administration (MDA) for malaria?

MDA for malaria consists of giving a full treatment course of antimalarial medicine (even to persons with no symptoms of malaria and regardless of whether malaria is present) to every member of a defined population or every person living in a defined geographical area (except to those for whom the medicine could be harmful) at approximately the same time and often at repeated intervals.

How can MDA reduce malaria transmission in a population?

The life cycle of the malaria parasite consists of human liver, human blood, and mosquito stages. Malaria infection begins with the bite of an *Anopheles* species mosquito carrying the malaria parasite. During the bite, the infective mosquito injects the malaria parasite into the human host. After initially replicating in the liver, the parasites are released into the bloodstream. During the blood stage, parasites multiply in red blood cells, sometimes causing fever and other symptoms characteristic of malaria. Some of these parasites become a form which is infectious to mosquitoes. When the infected person is bitten again, the mosquito ingests blood containing the parasites, which then restarts the transmission cycle.

MDA with antimalarial drugs temporarily prevents new and clears existing malaria infections in the population. Depending on the characteristics of the antimalarial drug used, MDA targets parasites at different stages, which can lead to reduced disease burden and transmission in the population. Whether MDA can successfully reduce or interrupt malaria transmission may depend on how much malaria there is in the area; the use of other tools to control malaria, including preventing mosquito bites; the proportion of the population who receive at least one round of MDA; population movement; and when MDA rounds occur in relation to the peak malaria transmission season.

What was the aim of the review?

To guide policy-making and future research for malaria control and elimination, the aim of this review was to update the evidence evaluating the effect of MDA compared to no MDA on malaria outcomes in moderate- to high-transmission settings and very low- to low-transmission settings. Our search of relevant published and unpublished literature identified 13 studies that met our inclusion criteria.

What are the main findings of the review?

Malaria burden was compared in people receiving MDA and those who did not receive MDA, at different time points. The findings differed by malaria transmission setting. In areas with malaria prevalence of 10% or higher (moderate- to high-transmission areas), based on one trial, MDA did not reduce malaria in the population (low-certainty evidence). In areas with malaria prevalence under 10% (very low- to low-endemicity areas), evidence from seven trials indicates that MDA reduced malaria in the population immediately after MDA has stopped (low-certainty evidence), but we are uncertain if the decline continues long-term because the number of malaria cases in both intervention and control groups were low (very low-certainty evidence).

In all settings of malaria transmission, the type of antimalarial drug used for MDA, co-interventions such as mosquito control, coverage of MDA, and risk of re-introduction may have an impact on the effect of MDA compared to no MDA. However, we were unable to explore these factors due to the limited number of studies.

How up to date is the review?

We included studies available up to 11 February 2021.

SUMMARY OF FINDINGS

Summary of findings 1. MDA compared to no MDA for *Plasmodium falciparum* malaria (moderate to high endemicity, short-term follow-up)

Patient or population: People of all ages living in an area with moderate to high endemicity of *P falciparum* malaria (≥ 10% prevalence)
Setting: Moderate to high endemicity defined as ≥10% prevalence of *P falciparum*
Intervention: MDA
Comparison: Control (no MDA or placebo)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no MDA	Risk with MDA				
Follow-up: 1 to 3 months						
Parasitaemia prevalence	5 per 100	9 per 100 (3 to 27)	RR 1.76 (0.58 to 5.36)	786 (1 RCT)	⊕⊕⊖⊖ LOW[a,b,c] Due to imprecision	At 1-3 months post-MDA, parasite prevalence may increase in MDA compared no MDA. However, the effects vary and it is possible that MDA makes little or no difference on parasitaemia prevalence.
Parasitaemia incidence	68 events per 100 person-years	42 events per 100 person-years (27 to 63)	Rate ratio 0.61 (0.40 to 0.92)	739 (1 RCT)	⊕⊕⊕⊖ MODERATE[a,b,d] Due to imprecision	At 1-3 months post-MDA, there is probably a reduction in parasitaemia incidence in MDA compared to no MDA.
Confirmed malaria illness incidence	28 per 1000 population	11 per 1000 population (1 to 122)	Rate ratio 0.41 (0.04 to 4.42)	144,422 (1 RCT)	⊕⊕⊖⊖ LOW[a,b,c] Due to imprecision	At 1-3 months post-MDA, there may be a reduction in confirmed malaria illness incidence in MDA compared to no MDA.
Follow-up: 4 to 6 months						
Parasitaemia prevalence	55 per 100	65 per 100 (49 to 86)	RR 1.18 (0.89 to 1.56)	1414 (1 RCT)	⊕⊕⊕⊖ MODERATE[a,b,d] Due to imprecision	At 4-6 months post-MDA, there is probably little or no effect on parasitaemia prevalence in MDA compared to no MDA
Parasitaemia incidence	129 events per 100 person-years	118 events per 100 person-years (71 to 194)	Rate ratio 0.91 (0.55 to 1.50)	1376 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,d,e] Due to risk of bias and imprecision	We do not know if MDA has an effect on parasitaemia incidence at 4-6 months post-MDA

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **cRCT:** cluster-randomized controlled trial; **MDA:** mass drug administration; **RCT:** randomized controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Not downgraded for inconsistency; the comparison presented is reported from a single study.
[b]Not downgraded for indirectness; outcome was evaluated in all ages or assessed in children (considered the most appropriate population to measure malaria transmission in moderate- to high-endemicity areas).
[c]Downgraded 2 levels for imprecision due to very wide CIs.
[d]Downgraded 1 level for imprecision due to wide CIs.
[e]Downgraded 2 levels for risk of bias since malaria cases in outcome were defined as fever plus parasitaemia > 5000, which excludes all afebrile and low density infections and results in an underestimate of the outcome.

Summary of findings 2. MDA compared to no MDA for *Plasmodium falciparum* malaria (very low to low endemicity, short-term follow-up)

Patient or population: People of all ages living in an area with very low to low endemicity of *P falciparum* malaria (< 10% prevalence)
Setting: Very low to low endemicity defined as < 10% prevalence of *P falciparum*
Intervention: MDA
Comparison: Control (no MDA or placebo)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with MDA				
Follow-up: < 1 month						
Parasitaemia prevalence follow up: range < 1 month	12 per 100	1 per 100 (0 to 6)	RR 0.12 (0.03 to 0.52)	1232 (1 RCT)	⊕⊕⊖⊖ LOW[a-d] Due to risk of bias and imprecision	At < 1 month post-MDA, there may a reduction in parasitaemia prevalence in MDA compared to no MDA.
Follow-up: 1 to 3 months						

Parasitaemia prevalence	3 per 100	1 per 100 (0 to 1)	RR: 0.25 (0.15 to 0.41)	17,454 (7 RCTs)[5]	⊕⊕⊖⊖ LOW[e-i] Due to risk of bias	At 1-3 months post-MDA, there may a reduction in parasitaemia prevalence in MDA compared to no MDA.
Parasitaemia incidence	15 events per 100 person-years	5 events per 100 person-years (3 to 10)	Rate ratio 0.37 (0.21 to 0.66)	736 (1 RCT)	⊕⊕⊕⊖ MODERATE[b,d,,j] Due to imprecision	At 1-3 months post-MDA, there is probably a reduction in parasitaemia incidence in MDA compared to no MDA.
Confirmed malaria illness incidence	6 per 1000 population	4 per 1000 population (1 to 17)	Rate ratio: 0.58 (0.12 to 2.73)	130,651 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[a,j-l] Due to risk of bias and imprecision	We do not know if MDA has an effect on confirmed malaria illness incidence at 1-3 months post-MDA compared to no MDA.
Follow-up: 4 to 6 months						
Parasitaemia prevalence	5 per 100	3 per 100 (2 to 6)	RR: 0.63 (0.36 to 1.12)	5670 (4 RCTs)	⊕⊖⊖⊖ VERY LOW[c,d,f,l] Due to risk of bias and imprecision	We do not know if MDA has an effect on parasitaemia prevalence at 4-6 months post-MDA compared to no MDA.
Confirmed malaria illness incidence	4 per 1000 population	4 per 1000 population (0 to 53)	Rate ratio 0.93 (0.07 to 12.43)	23,251 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,k,l] Due to risk of bias and imprecision	We do not know if MDA has an effect on confirmed malaria illness incidence at 4-6 months post-MDA compared to no MDA.
Follow-up: 7 to 12 months						
Parasitaemia prevalence	5 per 100	4 per 100 (3 to 6)	RR: 0.86 (0.55 to 1.36)	7760 (5 RCTs)	⊕⊖⊖⊖ VERY LOW[c,d,l,m] Due to risk of bias and imprecision	We do not know if MDA has an effect on parasitaemia prevalence at 7-12 months post-MDA compared to no MDA.
Confirmed malaria illness incidence	11 per 1000 population	5 per 1000 population (2 to 12)	Rate ratio 0.47 (0.21 to 1.03)	26,576 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[d,f,j,l] Due to risk of bias and imprecision	We do not know if MDA has an effect on confirmed malaria illness incidence at 7-12 months post-MDA compared to no MDA.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **cRCT:** cluster-randomized controlled trial; **MDA:** mass drug administration; **RCT:** randomized controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded 1 level for risk of bias due to several criteria scored as high or unclear risk of bias.
[b]Not downgraded for inconsistency; the comparison presented is reported from a single study.
[c]Not downgraded for indirectness; all ages are at similar risk of malaria transmission, given the local epidemiology of malaria in this study setting and the outcomes were assessed by a highly sensitive diagnostic method (ultrasensitive PCR).
[d]Downgraded 1 level for imprecision due to wide CIs.
[e]Eight included studies reported parasitaemia prevalence during the 1-3 month post-MDA follow-up period; however, one study did not contribute data in the meta-analysis due to no events at baseline before MDA or at any follow-up time points.
[f]Downgraded 2 levels for risk of bias due to several criteria scored as high or unclear risk of bias, including baseline imbalance and high risk of contamination in several studies.
[g]Not downgraded for inconsistency based on I^2 statistic; however, reasons for heterogeneity explored in post-hoc sub-group analysis by continent (sub-Saharan Africa and Southeast Asia; Analysis 4.1).
[h]Not downgraded for indirectness; all ages are at similar risk of malaria transmission, given the local epidemiology of malaria in this study setting so there is no concern with assessing this outcome in different age groups across studies.
[i]Not downgraded for imprecision due to appreciable benefit of pooled effect as reported by seven studies.
[j]Not downgraded for indirectness since outcome was assessed in all ages and by routine detection methods.
[k]Downgraded 2 levels for imprecision due to very wide CIs.
[l]Not downgraded for inconsistency based on I^2 statistic.
[m]Downgraded 2 levels for risk of bias due to several criteria scored as high or unclear risk of bias, including baseline imbalance, high risk of contamination, and a large unexplained increase in sampled population in the MDA group at this time point.

Summary of findings 3. MDA compared to no MDA for *Plasmodium falciparum* malaria (very low to low endemicity, long-term follow-up)

Patient or population: People of all ages living in an area with very low to low endemicity of *P falciparum* malaria (< 10% prevalence)
Setting: Very low to low endemicity defined as < 10% prevalence of *P falciparum*
Intervention: MDA
Comparison: Control (no MDA or placebo)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with MDA				

Follow-up: 13 to 18 months						
Parasitaemia prevalence	4 per 100	4 per 100 (1 to 14)	RR 0.82 (0.20 to 3.34)	1537 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a-d] Due to risk of bias and imprecision	We do not know if MDA has an effect on parasitaemia prevalence at 13-18 months post-MDA compared to no MDA.
Confirmed malaria illness incidence	17 per 1000 population	13 per 1000 population (3 to 51)	Rate ratio 0.77 (0.20 to 3.03)	23,251 (1 RCT)	⊕⊖⊖⊖ VERY LOW[b,d-f] Due to risk of bias and imprecision	We do not know if MDA has an effect on confirmed malaria illness incidence at 13-18 months post-MDA compared to no MDA.
Follow-up: 19 to 24 months						
Parasitaemia prevalence follow-up: range 19 to 24 months	3 per 100	1 per 100 (0 to 6)	RR 0.34 (0.06 to 1.97)	1393 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a-d] Due to risk of bias and imprecision	We do not know if MDA has an effect on parasitaemia prevalence at 19-24 months post-MDA compared to no MDA.
Follow-up: 25 months and above						
Parasitaemia prevalence follow-up: range 25 to 30 months	3 per 100	3 per 100 (1 to 12)	RR 0.89 (0.22 to 3.62)	1521 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a-d] Due to risk of bias and imprecision	We do not know if MDA has an effect on parasitaemia prevalence at 25-30 months post-MDA compared to no MDA.
Parasitaemia prevalence follow-up: range 31 to 36 months	3 per 100	4 per 100 (1 to 19)	RR 1.25 (0.25 to 6.31)	1679 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a-d] Due to risk of bias and imprecision	We do not know if MDA has an effect on parasitaemia prevalence at 31-36 months post-MDA compared to no MDA.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **cRCT:** cluster-randomized controlled trial; **MDA:** mass drug administration; **RCT:** randomized controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded 2 levels for risk of bias due to several criteria scored as high or unclear risk of bias, including baseline imbalance, high risk of contamination, and a large unexplained increase in sampled population in the MDA group at this time point.
[b]Not downgraded for inconsistency; the comparison presented is reported from a single study.
[c]Not downgraded for indirectness; all ages are at similar risk of malaria transmission, given the local epidemiology of malaria in this study setting and the outcomes were assessed by a highly sensitive diagnostic method (ultrasensitive PCR).
[d]Downgraded 2 levels for imprecision due to very wide CIs.
[e]Downgraded 1 level for risk of bias due to several criteria scored as high or unclear risk of bias.
[f]Not downgraded for indirectness since outcome was assessed in all ages and by routine detection methods.

Summary of findings 4. MDA compared to no MDA for *P vivax* malaria (very low to low endemicity, short-term follow-up)

Patient or population: People of all ages living in an area with very low to low endemicity of *P vivax* malaria (< 10% prevalence)
Setting: Very low to low endemicity defined as < 10% prevalence of *P vivax*
Intervention: MDA
Comparison: Control (no MDA or placebo)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with MDA				
Follow-up: < 1 month						
Parasitaemia prevalence follow up: range < 1 month	27 per 100	5 per 100 (2 to 11)	RR 0.18 (0.08 to 0.40)	1232 (1 RCT)	⊕⊕⊖⊖ LOW[a-d] Due to risk of bias and imprecision	At < 1 month post-MDA, there may a reduction in parasitaemia prevalence in MDA compared to no MDA.
Follow-up: 1 to 3 months						
Parasitaemia prevalence	12 per 100	2 per 100 (1 to 3)	RR: 0.15 (0.10 to 0.24)	6896 (5 RCTs)	⊕⊕⊖⊖ LOW[c,e-g] Due to risk of bias	At 1-3 months post-MDA, there may a reduction in parasitaemia prevalence in MDA compared to no MDA.
Follow-up: 4 to 6 months						

Parasitaemia prevalence	11 per 100	9 per 100 (7 to 10)	RR: 0.78 (0.63 to 0.95)	5670 (4 RCTs)	⊕⊖⊖⊖ VERY LOW[c,d,f,h] Due to risk of bias and imprecision	We do not know if MDA reduces parasitaemia prevalence at 4-6 months post-MDA compared to no MDA.
Follow-up: 7 to 12 months						
Parasitaemia prevalence	9 per 100	11 per 100 (9 to 13)	RR: 1.12 (0.94 to 1.34)	7760 (5 RCTs)	⊕⊖⊖⊖ VERY LOW[c,d,h,i] Due to risk of bias and imprecision	We do not know if MDA has an effect on parasitaemia prevalence at 7-12 months post-MDA compared to no MDA.
Confirmed malaria illness incidence	41 per 1000 population	57 per 1000 population (40 to 80)	Rate ratio: 1.38 (0.97 to 1.95)	3325 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[d,f,h,j] Due to risk of bias and imprecision	We do not know if MDA has an effect on confirmed malaria illness incidence at 7-12 months post-MDA compared to no MDA.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **cRCT:** cluster-randomized controlled trial; **MDA:** mass drug administration; **RCT:** randomized controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded 1 level for risk of bias due to several criteria scored as high or unclear risk of bias.
[b]Not downgraded for inconsistency; the comparison presented is reported from a single study.
[c]Not downgraded for indirectness; all ages are at similar risk of malaria transmission, given the local epidemiology of malaria in this study setting and the outcomes were assessed by a highly sensitive diagnostic method (ultrasensitive PCR).
[d]Downgraded 1 level for imprecision due to wide CIs.
[e]Not downgraded for imprecision due to appreciable benefit of pooled effect as reported by five studies.
[f]Downgraded 2 levels for risk of bias due to several criteria scored as high or unclear risk of bias, including baseline imbalance and high risk of contamination.
[g]Not downgraded for inconsistency despite the large value of the I^2 statistic since the direction of effect was consistent with large imprecision.
[h]Not downgraded for inconsistency based on I^2 statistic.
[i]Downgraded 2 levels for risk of bias due to several criteria scored as high or unclear risk of bias, including a large unexplained increase in sampled population in the MDA group at this time point.
[j]Not downgraded for indirectness since outcome was assessed in all ages and by routine detection methods.

Summary of findings 5. MDA compared to no MDA for *P vivax* malaria (very low to low endemicity, long-term follow-up)

Patient or population: People of all ages living in an area with very low to low endemicity of *P vivax* malaria (< 10% prevalence)
Setting: Very low to low endemicity < 10% prevalence of *P vivax*
Intervention: MDA
Comparison: Control (no MDA or placebo)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with MDA				
Follow-up: 13 to 18 months						
Parasitaemia prevalence	17 per 100	14 per 100 (8 to 25)	RR 0.81 (0.44 to 1.48)	1537 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a-d] Due to risk of bias and imprecision	We do not know if MDA reduces parasitaemia prevalence at 13-18 months post-MDA compared to no MDA.
Follow-up: 19 to 24 months						
Parasitaemia prevalence follow-up: range 19 to 24 months	11 per 100	9 per 100 (4 to 20)	RR 0.84 (0.38 to 1.83)	1393 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a-d] Due to risk of bias and imprecision	We do not know if MDA reduces parasitaemia prevalence at 19-24 months post-MDA compared to no MDA.
Follow-up: 25 months and above						
Parasitaemia prevalence follow-up: range 25 to 30 months	11 per 100	9 per 100 (4 to 21)	RR 0.89 (0.41 to 1.94)	1521 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a-d] Due to risk of bias and imprecision	We do not know if MDA reduces parasitaemia prevalence at 25-30 months post-MDA compared to no MDA.
Parasitaemia prevalence follow-up: range 31 to 36 months	6 per 100	7 per 100 (3 to 20)	RR 1.20 (0.44 to 3.29)	1679 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a-c,e] Due to risk of bias and imprecision	We do not know if MDA reduces parasitaemia prevalence at 31-36 months post-MDA compared to no MDA.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **cRCT:** cluster-randomized controlled trial; **MDA:** mass drug administration; **RCT:** randomized controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded 2 levels for risk of bias due to several criteria scored as high or unclear risk of bias, including a large unexplained increase in sampled population in the MDA group at this time point.
[b]Not downgraded for inconsistency; the comparison presented is reported from a single study.
[c]Not downgraded for indirectness; all ages are at similar risk of malaria transmission, given the local epidemiology of malaria in this study setting and the outcomes were assessed by a highly sensitive diagnostic method (ultrasensitive PCR).
[d]Downgraded 1 level for imprecision due to wide CIs.
[e]Downgraded 2 levels for imprecision due to very wide CIs.

BACKGROUND

Description of the condition

Malaria remains a leading cause of morbidity and mortality, and was responsible for an estimated 229 million clinical cases and 409,000 deaths in 2019, mostly in children under five years of age living in sub-Saharan Africa. Malaria is a parasitic disease that is transmitted to humans by the bite of a female *Anopheles* species mosquito. Among the four *Plasmodium* species of human malaria (*P falciparum*, *P vivax*, *P ovale*, and *P malariae*), *P falciparum* and *P vivax* cause the largest number of malaria cases, while *P falciparum* is responsible for a majority of severe and fatal infections. Without effective treatment, malaria may manifest with severe complications and lead to death (WHO 2020a).

Since 2000, the global burden of malaria has been reduced considerably due to the expansion of effective malaria control strategies such as vector control and case management (Bhatt 2015; WHO 2020a). Currently recommended vector control tools include the use of insecticide-treated bed nets (ITNs), indoor residual spraying (IRS) with insecticides, and larval source management. Case management of malaria, which relies on the prompt diagnosis (parasitological confirmation) and administration of effective antimalarial treatment, has been enhanced by the use of rapid diagnostic tests (RDTs) and artemisinin-based combination therapy (ACTs). Intermittent preventive treatment (IPT) with antimalarial drugs in certain high risk populations, such as pregnant women, children, and infants, is another key malaria control strategy. However, challenges in achieving and maintaining high levels of coverage with these proven interventions, as well as the emergence of insecticide resistance in mosquitos and antimalarial drug resistance in parasites, threaten the success of these interventions. Therefore, additional strategies must be considered to complement existing tools to accelerate progress towards malaria elimination. Recent World Malaria Reports from the World Health Organization (WHO) have noted a stagnation in reductions of malaria cases (WHO 2020a). This finding underscores the need for continued evaluation and improved targeting of malaria control and elimination strategies to identify those activities that will have a positive impact on malaria transmission.

In the past decade, there has been renewed interest in mass drug administration (MDA), which was a component of many malaria elimination programmes during the eradication era in the mid-twentieth century. MDA has been used widely for controlling and eliminating the five most highly prevalent neglected tropical diseases (lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminths, and trachoma) (Hotez 2009). However, the role of MDA for malaria has been less clear due to the fear of rapid emergence of antimalarial drug resistance and the varying success of the intervention in sustaining reductions in malaria burden and interrupting malaria transmission. A Cochrane Review found MDA to be effective in reducing malaria parasitaemia prevalence within one month following the intervention (Poirot 2013), but results on sustaining the impact four to six months after the intervention were mixed or the evidence was of low quality. Since the publication of the previous review, additional studies have been conducted to assess both the immediate- and longer-term effects of MDA in low-transmission and moderate- to high-transmission settings. The additional evidence provides the opportunity to address gaps in knowledge surrounding MDA as a strategy to accelerate progress towards malaria elimination across transmission settings.

Description of the intervention

MDA for malaria consists of administering a full therapeutic course of antimalarial medicine (irrespective of the presence of symptoms or infection) to every member of a defined population or every person living in a defined geographical area (except to those for whom the medicine is contraindicated) at approximately the same time and often at repeated intervals. MDA for malaria is intended to reduce or interrupt transmission, curtail morbidity and mortality, or prevent reoccurrence and resulting malaria transmission (WHO 2015a).

Many early studies of MDA for malaria (dating back to the 1930s) observed a marked decrease in parasite prevalence following MDA, but often MDA did not result in interruption of transmission. Subsequent studies that evaluated MDA in conjunction with other malaria control tools, including the Garki Project conducted in 1969 in Northern Nigeria (Molineaux 1980), often demonstrated substantial decreases in, but not interruption of, malaria transmission (Greenwood 2004; von Seidlein 2003). In Nicaragua, MDA was administered to approximately 8 million people in 1981 and resulted in marked immediate decline in malaria incidence, but rates eventually reverted back to those observed prior to MDA (Garfield 1983). Notably, MDA in conjunction with ITNs on Aneityum Island, Vanuatu in 1991 was an exception, and interruption of transmission was achieved following eight rounds of MDA with chloroquine, sulfadoxine-pyrimethamine, and primaquine (Kaneko 2000 VUT). On another island setting (Anjouan Island, Comoros), two rounds of MDA, with artemisinin-piperaquine or artemisinin-piperaquine with single low dose primaquine, were associated with a rapid 99% decrease in malaria cases (from 7362 before to 47 cases after MDA rounds) (Deng 2018 COM). More recently, the role of MDA to curb malaria morbidity and mortality in complex emergency settings was highlighted during the Ebola outbreak in West Africa (Aregawi 2016 SLE; Kuehne 2016).

How the intervention might work

MDA targets the human parasite reservoir through the administration of a curative antimalarial dose to the entire population, irrespective of symptoms or parasitaemia. MDA provides a prophylactic effect, whereby new infections are temporarily prevented, and a treatment effect, in which parasitaemia is cleared. Unlike case management, in which symptomatic cases are treated, MDA also targets asymptomatic malaria infections, that are believed to contribute to ongoing malaria transmission (Lindblade 2013). Theoretically, in combination with high levels of vector control, clearing the human parasite reservoir could lead to an interruption of transmission in areas of low endemicity or a temporary decline in malaria burden in higher transmission settings. However, MDA effectiveness may be limited by factors such as antimalarial properties and operational considerations including population coverage, risk of re-introduction, and timing.

The *Plasmodium* parasite life cycle includes stages in humans (liver and blood) and mosquitoes. In particular, parasitic infections during the exo-erythrocytic and erythrocytic cycles in humans have important implications for clinical illness, diagnosis, treatment, and prevention. Once *Plasmodium* sporozoites are injected by

mosquitoes in a human host, parasites invade and multiply in liver cells, leading to hepatocytic rupture and the release of parasites into the blood stream. *P vivax* and *P ovale* can persist in a dormant liver stage as hypnozoites, leading to relapsing erythrocytic stage infections months or years after initial infection. During the blood stage, asexual reproduction of merozoites in red blood cells results in a cycle of parasite maturation and erythrocytic destruction, triggering clinical symptoms such as fever, headache, and chills. Some parasites undergo sexual differentiation (gametocytes) in humans, which subsequently leads to malaria transmission once the gametocytes are ingested during a mosquito blood meal.

The life cycle of the *Plasmodium* parasite offers numerous vulnerable stages that could be exploited in a MDA strategy to reduce disease burden and transmission. Most antimalarial drugs are effective schizonticides against asexual blood stage parasites and can eliminate blood stream infections and prevent illness, and may reduce the overall density of asexual parasites, leading to a decline in gametocyte density. Artemisinins and 8-aminoquinolines (e.g. primaquine and tafenoquine) have gametocytocidal properties and act directly on circulating gametocytes. Primaquine has long been the only available drug with unique activity against mature gametocytes of *P falciparum* and the hypnozoite stage of *P vivax* and *P ovale* species, reducing the possibility of transmission and relapse (WHO 2015b). Tafenoquine, another 8-aminoquinoline, recently received regulatory approval for the radical cure of *P vivax* infections in persons older than 16 years (GlaxoSmithKline 2018). The addition of ivermectin, or other endectocides, could potentially reduce malaria transmission by shortening the lifespan of mosquitos, thus preventing parasite development in the mosquito. Although ivermectin is not an antimalarial drug, it is often used to control other parasitic infections in malaria-endemic settings and the effect of MDA with ivermectin on malaria transmission has been summarized in a separate Cochrane Review (Chaccour 2010; Tesh 1990; de Souza 2021).

Operationally, high levels of MDA coverage may not be achieved since a proportion of the population may be excluded from MDA due to contraindications to antimalarials or health conditions, absence during treatment rounds, or refusal. Although conducting multiple rounds of MDA can improve intervention coverage, the same people are often repeatedly excluded from MDA rounds, which reduces the effective coverage, or the proportion of the population receiving at least one round of MDA. High rates of population movement or migration also pose a challenge by increasing the risk of re-introduction. Additionally, mathematical modelling has provided insights into the optimal timing in which rounds should take place in relation to the malaria transmission season. Implementation of MDA prior to the rainy season has been shown to have the greatest effect, due to widespread parasite clearance just prior to the high transmission season (Brady 2017; Okell 2011).

Why it is important to do this review

Despite unprecedented success in malaria control, progress has stalled in recent years (Alonso 2017). In addition to increased financial and political commitment, technical and operational strategies are needed to accelerate progress towards malaria elimination. Given the variable success of MDA, more recent studies have been conducted with consideration of transmission setting, seasonality of malaria, duration of intervention, MDA coverage, antimalarials with longer prophylactic action, and measurement of longer-term effects. Recent mathematical models have suggested that malaria reduction following MDA is more likely to be sustained in lower transmission settings compared to higher, in conjunction with vector control interventions, and when the intervention is continued over two years compared to one (Brady 2017; Okell 2011). Additionally, there has been recent debate within the malaria community on the role of MDA in malaria elimination (Eisele 2019; Mendis 2019).

Currently, the WHO recommends the use of MDA for *P falciparum* in areas approaching elimination, for the elimination of *P falciparum* in areas of multidrug resistance in the Greater Mekong subregion, epidemics, and complex emergency settings (WHO 2015a). At the time the recommendations were released (2015), insufficient evidence was available to provide guidance on the use of MDA for *P vivax*, or for the use of MDA for *P falciparum* in areas of moderate to high transmission. However, use of MDA could be considered in areas approaching interruption of transmission of *P falciparum* with good coverage of vector control, implementation of surveillance, access to treatment, and minimal risk of re-introduction of infection. Since the publication of the previous Cochrane Review (Poirot 2013), and the release of the WHO guidelines, additional studies have been conducted in both very low- to low-transmission settings and moderate- to high-transmission settings, including both *P falciparum* and *P vivax*. Due to renewed interest in MDA as a strategy to accelerate progress towards malaria elimination, an update to the previous review to address whether MDA provides sustained impact in very low- to low-transmission settings and moderate- to high-transmission settings will provide evidence to evaluate the appropriateness of existing recommendations, guide future policies, highlight current knowledge gaps, and direct future research.

OBJECTIVES

Primary objectives

To assess the sustained effect of mass drug administration (MDA) with antimalarial drugs on:

- the reduction in malaria transmission in moderate- to high-transmission settings;
- the interruption of transmission in very low- to low-transmission settings.

Secondary objective

To summarize the risk of drug-associated adverse effects following MDA.

METHODS

Criteria for considering studies for this review

Types of studies

We considered the following study designs.

- Randomized controlled trials (RCTs) with: (a) the unit of randomization being a cluster, and (b) at least two clusters per arm.
- Randomized cross-over trials with: (a) the unit of randomization being a cluster, (b) at least two clusters per arm, and (c) a

suitable washout period during which the intervention is no longer applied.
- Quasi-experimental designs, including stepped wedge where sites are randomly allocated.
- Non-randomized controlled before-and-after studies (CBAs) with: (a) a contemporaneous control group, and (b) at least two sites per arm.
- Interrupted time series (ITS) studies with: (a) a clearly defined point in time when the intervention occurred, and (b) at least three data points collected over one year both before and after MDA.

We excluded studies if we observed any of the following.

- The follow-up periods for the intervention and control periods were not identical.
- The intervention was applied at the individual level.
- There was no control arm for RCTs or CBAs, or insufficient pre- or post-intervention data points for ITS.

Types of participants

Children and adults living in areas of any malaria endemicities were included and analysed by transmission setting according to the objectives. Due to the nature of the intervention, we included only studies that were carried out on entire populations at the same time. We excluded studies in which chemoprevention was delivered in the form of individually-timed, intermittent, preventive treatment in sub-populations (i.e. pregnant women, children or infants) or seasonal malaria chemoprevention. We did not exclude studies in special groups (i.e. refugees and soldiers), but none of these met eligibility criteria.

Types of interventions

Intervention

For the purpose of this review, we defined MDA as the direct administration of a full therapeutic course of antimalarial medicine (irrespective of the presence of symptoms or infection) to every member of a defined population or every person living in a defined geographical area (except for those for whom the medicine was contraindicated) at approximately the same time and often at repeated intervals. We included only studies that provided doses of antimalarials intended for curative purposes.

Control

We included studies in which all other malaria and non-malaria co-interventions were balanced in all arms. These included the use of ITNs, IRS, source reduction activities, environmental management, mass drug campaigns for other neglected tropical diseases, and mass nutritional supplementation activities such as vitamin A distribution.

Types of outcome measures

Studies must have reported at least one primary outcome for inclusion.

Primary outcomes

- Parasitaemia prevalence, as measured by microscopy, malaria RDT, or molecular method, such as polymerase chain reaction (PCR).
- Parasitaemia incidence (e.g. incidence of infection through active surveillance as measured in a cohort).
- Confirmed malaria illness incidence, defined as febrile illness with diagnostically confirmed parasitaemia (WHO 2015c) (e.g. incidence of confirmed clinical infection as measured in passive or routine surveillance data collected at health facilities).

Secondary outcomes

- All-cause and malaria-specific mortality.
- Gametocytaemia prevalence, as measured by microscopy or molecular method.
- Known adverse effects related to MDA drugs using WHO definitions (Edwards 2000).

Search methods for identification of studies

Electronic searches

Search strategy for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, ongoing).

Databases

We searched the following databases on 11 February 2021, using the search terms and strategy described in Appendix 1.

- Cochrane Infectious Diseases Group Specialized Register (searched 11 February 2021).
- Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (Issue 2 of 12, February 2021).
- MEDLINE (PubMed; 1966 to 11 February 2021).
- Embase (Ovid; 1947 to 11 February 2021).
- LILACS (Latin American and Caribbean Health Science Information database, BIREME; 1982 to 11 February 2021).

We also searched the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/en/) and ClinicalTrials.gov (clinicaltrials.gov/ct2/home) for trials in progress, using 'malaria' and 'mass drug administration' as search terms.

Searching other resources

Reference lists

We checked the reference lists of all studies and articles identified by the above methods and of previously published reviews, as well as references listed in review articles (Greenwood 2004; Newby 2015; Poirot 2013; Shanks 2012; von Seidlein 2003).

Conference proceedings

We searched the following recent proceedings for relevant abstracts.

- Sixth Multilateral Initiative on Malaria Pan-African Malaria Conference (Durban, South Africa; October 2013).
- American Society of Tropical Medicine and Hygiene (ASTMH) 62nd Annual Meeting (Washington, DC, USA; November 2013).
- ASTMH 63rd Annual Meeting (New Orleans, LA, USA; November 2014).
- ASTMH 64th Annual Meeting (Philadelphia, PA, USA; October 2015).

- ASTMH 65th Annual Meeting (Atlanta, GA, USA; November 2016).
- ASTMH 66th Annual Meeting (Baltimore, MD, USA; November 2017).
- ASTMH 67th Annual Meeting (New Orleans, Louisiana, USA; October 2018).

Researchers and organizations

In addition to the electronic searches described above, we reached out to the Malaria Elimination Initiative and other relevant groups to identify both published and unpublished studies that might be available from other sources. We also contacted the Malaria Eradication Research Agenda Consortium and the Bill and Melinda Gates Foundation.

Data collection and analysis

Selection of studies

Two review authors (MPS and MD) independently assessed the titles and abstracts of trials identified by the literature searches. We obtained the full-text versions of any potentially relevant articles identified by at least one of the review authors. The same two review authors assessed the full-text articles of potentially relevant studies for inclusion, using an eligibility form based on predetermined inclusion criteria. We resolved any disagreements by discussion and consensus, with arbitration by a third review author (KAL) when necessary. We ensured that multiple publications of the same trial were included only once. We listed studies excluded after full-text assessment, together with their reasons for exclusion, in the Characteristics of excluded studies table. We illustrated the study selection process using a Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) diagram.

Data extraction and management

Two review authors (MPS and MD) independently extracted information from the trials using pre-piloted electronic data extraction forms. In case of differences in extracted data, the two review authors discussed these differences to reach consensus. If unresolved, further discussion involved a third review author (KAL). In case of missing data, we contacted the original study author(s) for clarification.

We extracted the following data.

- Trial design: type of trial; method of participant selection; adjustment for clustering (for cRCTs); sample size; method of blinding of participants and personnel.
- Participants: trial settings (country, transmission season, endemicity, antimalarial drug resistance context, parasite and vector species of interest) and population characteristics; recruitment rates; withdrawal and loss to follow-up.
- Intervention: MDA regimen, coverage, and timing (number of rounds/campaigns, years of implementation, and timing relative to transmission season).
- Outcomes: definition of outcome; diagnostic or surveillance method; number of events; number of participants or person time; time point at which outcome was assessed in relation to MDA; statistical power; unit of analysis; incomplete outcomes or missing data.

For dichotomous data (parasitaemia prevalence and gametocytaemia prevalence), we extracted the number of participants experiencing each outcome and the number of participants in each treatment group. For count data (parasitaemia incidence, confirmed malaria illness incidence, and mortality), we extracted the number of events in the treatment and control groups, and the total person time at risk in each group or the rate ratio, and a measure of variance (for example, standard error). We did not extract any continuous data.

For cRCTs, we recorded the number of clusters randomized, number of clusters analysed, and the intracluster correlation coefficient (ICC) value.

For non-randomized studies, there were no studies that reported adjusted measures of intervention effects, so we were unable to obtain an effect estimate that controlled for confounding.

We included pre-intervention data up to one year prior to the intervention. We included all post-MDA data, and outcomes were reported according to designated time points of: less than 1 month, 1 to 3 months, 4 to 6 months, 7 to 12 months, 13 to 18 months, 19 to 24 months, 25 to 30 months, and 31 to 36 months after MDA. For studies with multiple rounds of MDA, we defined 'during MDA' as the intervention time period - i.e. the time between the start of the first round and end of the last round of MDA - and the 'post-MDA' follow-up period as the time following the last round of MDA.

Assessment of risk of bias in included studies

Two review authors (MPS and MD) independently assessed the risk of bias for each included cluster-RCT using the Cochrane risk of bias tool and the five additional criteria listed in Section 16.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* that relate specifically to cluster-RCTs (Higgins 2011a; Higgins 2011b). We assessed non-randomized controlled studies for risk of bias using the Cochrane Effective Practice and Organisation of Care (EPOC) risk of bias tool. We resolved any discrepancies through discussion or by consulting a third review author (KAL). We classified judgements of risk of bias as either at low, high, or unclear risk of bias, and we used summary graphs (risk of bias summary and risk of bias graph) to display results.

Measures of treatment effect

We compared intervention and control groups by calculating risk ratios (RR) or rate ratios for incidence data. We presented all results with their corresponding 95% confidence intervals (CIs). At all time periods, a RR less than 1.0 indicates that parasitaemia prevalence was lower in the MDA compared to control arm, while a RR greater than 1.0 indicates that parasitaemia prevalence was higher in the MDA compared to control arm. Similarly, a rate ratio less than 1.0 can be interpreted as a lower rate of malaria infection (incidence) in the MDA compared to control arm, and a rate ratio greater than 1.0 reflects a higher malaria incidence measured in the MDA compared to control arm.

For non-randomized studies, since adjusted effect measures were not provided, we did not present a measure of treatment effect. Instead, we described the effect of MDA compared to no MDA using a difference-in-differences (DiD) analysis in which we calculated the difference in dichotomous outcomes between pre- and during-MDA time periods, and pre- and post-MDA time periods within

intervention and control arms and then took the difference of those values between intervention and control groups.

Unit of analysis issues

Since a variety of analytical methods were used to adjust for clustering in cRCTs, we extracted raw data and estimated effective sample sizes adjusted for clustering using either: (1) the study-provided ICC (as indicated in the Characteristics of included studies tables), or, (2) for studies that did not report an ICC, an estimated ICC calculated as the average of other study-provided ICCs in the same malaria transmission setting (0.02766 for areas of very low to low transmission, and 0.1225 for areas of moderate to high transmission). We only presented results from cRCTs that were adjusted for clustering. No cRCTs included multiple intervention arms so adjustment for multiple comparison in meta-analysis was not required (Richardson 2016).

Dealing with missing data

We attempted to contact study investigators to obtain missing data. We applied no imputation measures for working with missing data.

Assessment of heterogeneity

We inspected forest plots for overlapping CIs and assessed statistical heterogeneity in each meta-analysis using the I^2 statistic and Chi^2 test. We regarded heterogeneity as moderate if the I^2 statistic values were between 30% and 60%; substantial if they were between 50% and 90%; and considerable if they were between 75% and 100%. We regarded a Chi^2 test statistic with a P value of less than or equal to 0.10 as indicative of statistically significant heterogeneity. We explored clinical and methodological heterogeneity through consideration of the trial populations, methods, and interventions, and by visualization of trial results.

If there was considerable heterogeneity (i.e. an I^2 statistic value of 75% to 100%) and inconsistency in the direction of the effect, then we did not perform a meta-analysis.

Assessment of reporting biases

Since there were fewer than 10 trials included in each meta-analysis, we did not investigate reporting biases (such as publication bias) using funnel plots.

Data synthesis

We analysed data using Review Manager 5 (RevMan 5) (Review Manager 5). We used a fixed-effect meta-analysis to combine data if heterogeneity was absent. We pooled estimates where considerable heterogeneity was present if the direction of effect was consistent.

Malaria endemicity was classified as very low to low (prevalence of *P falciparum* or *P vivax* < 10%), or moderate to high (≥ 10%) (WHO 2017). Study-specific endemicity was defined by baseline malaria prevalence by microscopy or RDT or annual parasite incidence in the control group, and preferentially using data from (1) children, or (2) all ages. If only molecular data were available, we used a tool developed by Okell 2012 to estimate microscopy prevalence from PCR data in the control group at baseline.

For the main objective in moderate- to high-transmission settings, we defined a reduction in malaria transmission as a 50% reduction in median malaria parasite prevalence or incidence, or both, at 12 months post-intervention. For the main objective in very low- to low-transmission settings, we considered interruption of transmission as a reduction in number of indigenous malaria infections to zero at six months post-intervention. To evaluate both objectives, we stratified analyses by study design (i.e. cRCTs and non-randomized controlled studies) and post-intervention time periods (i.e. less than 1 month after MDA, 1 to 3 months, 4 to 6 months, 7 to 12 months, 13 to 18 months, 19 to 24 months, 25 to 30 months, and 31 to 36 months after MDA). For studies with data from multiple time points within the same post-intervention time period (Landier 2017 MMRa; Pongvongsa 2018 LAO; Tripura 2018 KHM; von Seidlein 2019 VNM), we used the latest time point for analysis for that category. We did not stratify studies by number of MDA rounds due to few studies after previous stratification. We only conducted a meta-analysis if we identified a sufficient number of studies (> 1) with both an outcome indicator estimate and a measure of precision.

Subgroup analysis and investigation of heterogeneity

We stratified outcomes by malaria transmission setting (very low- to low-transmission and moderate- to high-transmission settings) and *Plasmodium* species (*P falciparum* or *P vivax*). Given the few number of studies after stratification, we did not carry out subgroup analyses to explore causes of heterogeneity. However, for a single outcome where studies conducted in sub-Saharan Africa and Southeast Asia were combined (*P falciparum* prevalence at one to three months after MDA in very low- to low-endemicity settings), we carried out a supplementary post-hoc subgroup analysis by continent (Africa and Asia), to consider whether the geographical differences in malaria epidemiology may explain heterogeneity in effect of MDA.

Sensitivity analysis

Due to an insufficient number of studies, we did not perform sensitivity analyses on the primary outcomes to assess the effect of excluding trials at high risk of bias (for baseline imbalance and incomplete outcome data) on the overall results. We did not undertake sensitivity analyses to investigate the impact of varying the ICC value on meta-analysis results since the ICC values were obtained directly from studies or applied from comparable studies.

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of evidence using the GRADE approach (Guyatt 2011). We rated each important outcome as described by Balshem 2011.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect.
- Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

RCTs started as high quality evidence but could be downgraded if there were valid reasons within the following five categories: risk of

bias, imprecision, inconsistency, indirectness, and publication bias. We summarized our findings in a summary of findings table.

RESULTS

Description of studies

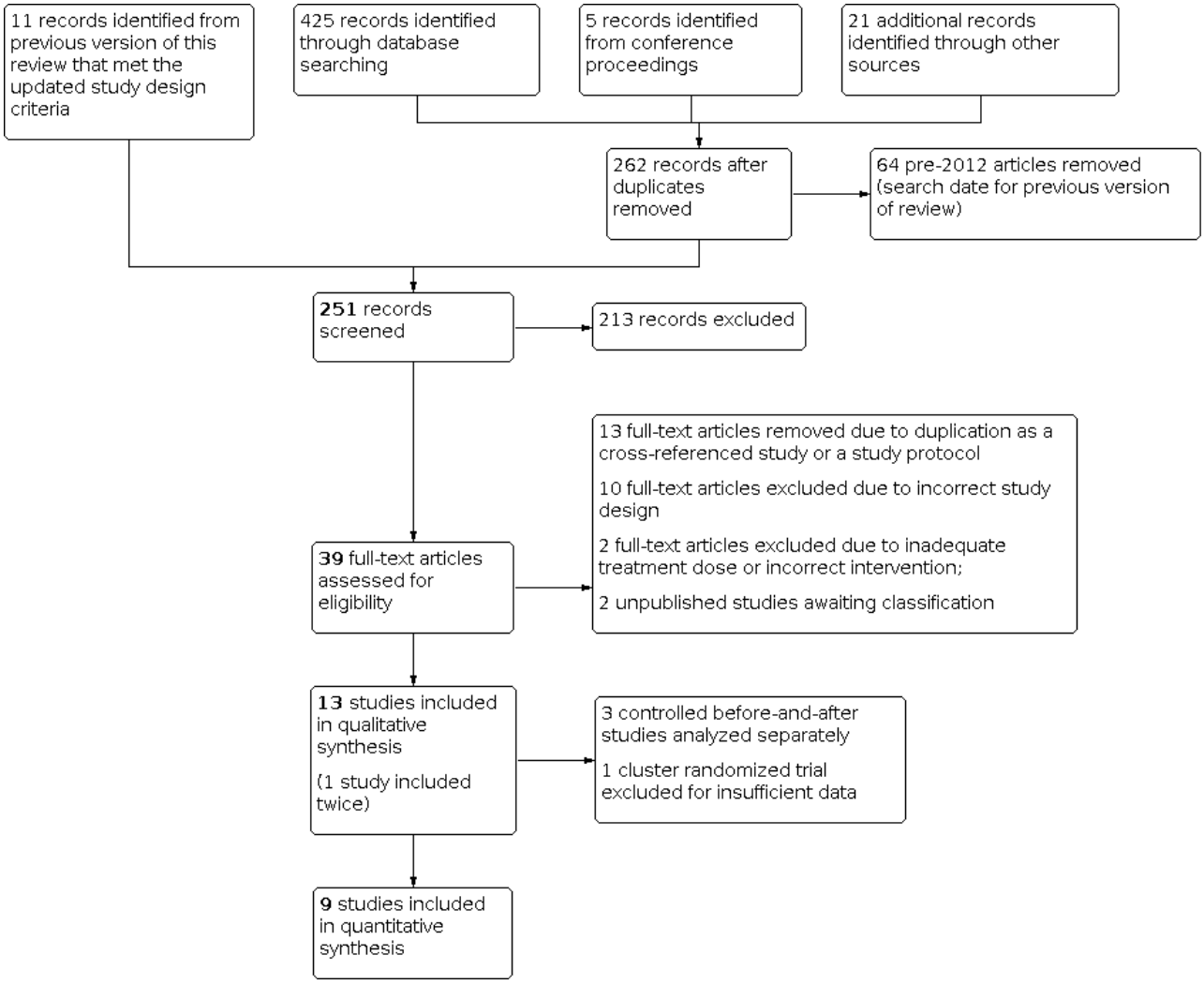
Detailed descriptions of included studies, excluded studies, studies awaiting classification, and ongoing studies are provided in the Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification, and Characteristics of ongoing studies tables, respectively.

Results of the search

The last published version of this review included 32 studies: two cRCTs, eight non-randomized trials, and 22 uncontrolled before-and-after studies (Poirot 2013).

Following the revised inclusion criteria, which restricted the review to more rigorous study designs with a control group and balanced co-interventions across study arms (described in detail in Differences between protocol and review), the updated literature search (to 11 February 2021) identified 462 records. After de-duplication and removal of studies excluded by the previous review's literature search in 2012, we screened 251 titles. Of those, we assessed 39 full-text articles for study eligibility (Figure 1).

Figure 1. Study flow diagram



Included studies

A total of 13 studies met the criteria for inclusion, comprising five studies included in the previous review (Escudie 1962 BFA; Molineaux 1980 NGA; Roberts 1964 KEN; Shekalaghe 2011 TZA; von Seidlein 2003 GMB), and eight new studies (Eisele 2020 ZMBa; Eisele 2020 ZMBb; Landier 2017 MMRa; McLean 2021 MMR; Morris 2018 TZA; Pongvongsa 2018 LAO; Tripura 2018 KHM; von Seidlein 2019 VNM). Since clusters in the Eisele trial were randomized by areas of low and high malaria transmission and the outcomes were stratified by endemicity (specified a priori by design), we considered this trial as two studies (Eisele 2020 ZMBa; Eisele 2020 ZMBb). Four studies were part of a multi-county trial conducted in Southeast Asia (Landier 2017 MMRa; Pongvongsa 2018 LAO; Tripura 2018 KHM; von Seidlein 2019 VNM). We analysed these as separate studies due to differences in study design (differences in antimalarial drug used for MDA, timing of MDA in

relation to the transmission season, and follow-up time periods) and heterogeneity of effects.

Cluster-randomized trials

Ten cRCTs were included in the qualitative syntheses: two from moderate- to high-endemicity areas (high: Eisele 2020 ZMBb; von Seidlein 2003 GMB), and eight from very low- to low-endemicity areas (very low: Morris 2018 TZA; Shekalaghe 2011 TZA; Tripura 2018 KHM; von Seidlein 2019 VNM; low: Eisele 2020 ZMBa; Landier 2017 MMRa; McLean 2021 MMR; Pongvongsa 2018 LAO).

Five studies were conducted in sub-Saharan Africa and five studies were conducted in Southeast Asia. Trial locations in sub-Saharan Africa were Southern Province, Zambia (Eisele 2020 ZMBa; Eisele 2020 ZMBb), Unguja Island, Tanzania (Morris 2018 TZA), Lower Moshi, Tanzania (Shekalaghe 2011 TZA), and Farafenni, The Gambia (von Seidlein 2003 GMB). Study locations in Southeast Asia included Kayin (Karen) state, Myanmar (Landier 2017 MMRa), Southeast Myanmar (McLean 2021 MMR), Savannakhet province, Laos (Pongvongsa 2018 LAO), Battambang province, Cambodia (Tripura 2018 KHM), and Binh Phuoc and Ninh Thuan provinces, Vietnam (von Seidlein 2019 VNM).

One cRCT conducted in an area of very low malaria transmission of Tanzania reported zero events at both baseline and follow-up time points for several outcomes and was excluded from quantitative syntheses (Shekalaghe 2011 TZA). The nine remaining cRCTs provided data for comparison of MDA versus no MDA in this review: three studies compared MDA to placebo or no MDA (McLean 2021 MMR; Morris 2018 TZA; von Seidlein 2003 GMB), four studies compared MDA to delayed MDA (Landier 2017 MMRa; Pongvongsa 2018 LAO; Tripura 2018 KHM; von Seidlein 2019 VNM), while two studies (Eisele 2020 ZMBa; Eisele 2020 ZMBb) compared MDA and focal MDA (household-level MDA where a member tested positive by RDT) separately to no MDA and we included only the MDA arm for comparison.

Interventions

Characteristics of the intervention have been summarized in Table 1.

Moderate- to high-transmission areas

One study administered four rounds of MDA with dihydroartemisinin piperaquine (DHAp) to all persons older than three months, except for pregnant women in the first trimester (Eisele 2020 ZMBb). The four MDA rounds occurred at the start of the rainy season, during the rainy season, during the dry season, and again at the start of the rainy season. MDA coverage was 88.1% in round one and 72.0% in round two. Both study arms received LLINs and IRS with Actellic (an insecticide) at baseline before MDA. The second trial administered a single round of MDA with sulfadoxine-pyrimethamine plus artesunate at the start of the rainy season to all persons six months of age or older, except for pregnant women (von Seidlein 2003 GMB). MDA coverage among the target population was 89% and no co-interventions were provided.

Very low- to low-transmission areas

Seven studies administered multiple rounds of MDA with dihydroartemisinin piperaquine (Eisele 2020 ZMBa; Landier 2017 MMRa; McLean 2021 MMR; Morris 2018 TZA; Pongvongsa 2018 LAO; Tripura 2018 KHM; von Seidlein 2019 VNM). Five of these studies also added a single dose of primaquine at each round (Landier 2017 MMRa; McLean 2021 MMR; Morris 2018 TZA; Pongvongsa 2018 LAO; von Seidlein 2019 VNM). The interval between rounds varied across studies. In Eisele 2020 ZMBa, MDA was administered at the start of the rainy season, during the rainy season, during the dry season, and at the start of the rainy season. In McLean 2021 MMR, three rounds of MDA were administered one month apart during the dry season. The two rounds of MDA in Morris 2018 TZA were administered two months apart. The three rounds of MDA in Landier 2017 MMRa and Pongvongsa 2018 LAO, conducted one month apart, were administered at the start and during rainy season. Three rounds of MDA in Tripura 2018 KHM were administered during rainy season, while three rounds of MDA took place at the end of the transmission season in von Seidlein 2019 VNM.

Most studies administering MDA with dihydroartemisinin piperaquine excluded pregnant women in their first trimester, with the exception of Tripura 2018 KHM, which excluded all pregnant women from MDA. Studies administering a single dose of primaquine excluded all pregnant women from primaquine. After these exclusions, MDA was administered to all persons three months of age and older (Eisele 2020 ZMBa), six months of age and older (Landier 2017 MMRa; Morris 2018 TZA; Pongvongsa 2018 LAO; Tripura 2018 KHM; von Seidlein 2019 VNM), or 12 months of age and older (McLean 2021 MMR). MDA coverage ranged from 66% to 95% in the first round and was generally lower (56% to 99%) in subsequent rounds for all studies except von Seidlein 2019 VNM, in which coverage increased in subsequent rounds. All studies provided ITNs to all study arms. In addition, Eisele 2020 ZMBa and Morris 2018 TZA included a single round of IRS at baseline; Landier 2017 MMRa, Pongvongsa 2018 LAO, Tripura 2018 KHM, and von Seidlein 2019 VNM provided uninterrupted access to case management in study villages; and Shekalaghe 2011 TZA included a single treatment campaign for trachoma with azithromycin.

One study administered a single round of sulfadoxine-pyrimethamine plus artesunate with a single dose of primaquine three to five weeks prior to the start of the rainy season (Shekalaghe 2011 TZA). All persons older than 12 months received MDA. However, pregnant women or individuals who were anaemic did not receive primaquine.

Outcomes

Outcome data are summarized in Table 2.

Moderate- to high-transmission areas

All outcomes reported were for *P falciparum.* In Eisele 2020 ZMBb, parasitaemia prevalence was measured by RDT prior to MDA, during MDA (following the first two rounds), and one to three months after MDA. In von Seidlein 2003 GMB, parasitaemia prevalence was measured by microscopy prior to MDA and four to six months after MDA. Both studies also reported parasitaemia incidence, but measured the outcome differently. Eisele 2020 ZMBb measured parasitaemia incidence by RDT through active surveillance in a cohort of persons three months of age and older, for two months following the fourth round of MDA. In von Seidlein 2003 GMB, parasitaemia incidence was captured through weekly surveillance in children under 11 years for cases with temperatures of 37.5 °C and higher, and *P falciparum* parasitaemia above 5000 parasites per µL by microscopy for five months following MDA. Eisele

2020 ZMBb reported confirmed malaria illness incidence prior to MDA and one to three months after MDA. Only von Seidlein 2003 GMB reported the secondary outcomes of gametocytaemia prevalence (pre-MDA and four to six months after MDA) and malaria-specific mortality. Both studies monitored adverse effects in the MDA study arm.

Very low- to low-transmission areas

All studies reported *P falciparum* parasitaemia prevalence, but the measurement of outcomes differed across studies with respect to follow-up time points, population sampled, and detection method. Eisele 2020 ZMBa, Landier 2017 MMRa, McLean 2021 MMR, Pongvongsa 2018 LAO, Tripura 2018 KHM, and von Seidlein 2019 VNM reported prevalence at baseline before MDA. The timing of the first prevalence measure reported by Morris 2018 TZA started and extended past the first round of MDA and, therefore, was classified as during MDA. Eisele 2020 ZMBa also reported parasitaemia prevalence during MDA following the first two MDA rounds. All studies reported the outcome at one to three months after MDA. Four studies reported prevalence at four to six months after MDA (Landier 2017 MMRa; Pongvongsa 2018 LAO; Tripura 2018 KHM; von Seidlein 2019 VNM). Five studies provided prevalence at 7 to 12 months after MDA (Landier 2017 MMRa; McLean 2021 MMR; Pongvongsa 2018 LAO; Tripura 2018 KHM; von Seidlein 2019 VNM). Additionally, McLean 2021 MMR reported outcomes at 13 to 18 months after MDA and at all additional follow-up intervals through to 31 to 36 months after MDA.

Eisele 2020 ZMBa measured parasitaemia prevalence by RDT in children aged 5 years and older. Five studies evaluated the outcome by ultrasensitive PCR (uPCR) in either adults aged 18 to 55 years (McLean 2021 MMR), or persons six months of age and older (Landier 2017 MMRa; Pongvongsa 2018 LAO; Tripura 2018 KHM; von Seidlein 2019 VNM). Morris 2018 TZA measured prevalence by 18s-quantitative PCR (qPCR) in persons of all ages. *P falciparum* parasitaemia incidence was only reported in Eisele 2020 ZMBa and measured by RDT through active surveillance in a cohort of persons three months of age and older, for two months following MDA. Confirmed malaria illness incidence was reported prior to MDA and at: one to three months after MDA in Eisele 2020 ZMBa, Morris 2018 TZA, and Tripura 2018 KHM; four to six months after MDA in Morris 2018 TZA; 7 to 12 months after MDA in Landier 2017 MMRa, Morris 2018 TZA, and Tripura 2018 KHM; and 13 to 18 months after MDA only in Morris 2018 TZA. All studies monitored adverse effects.

Shekalaghe 2011 TZA reported parasitaemia prevalence by microscopy and quantitative nucleic acid sequence-based amplification (QT-NASBA), confirmed malaria illness incidence, and gametocytaemia prevalence by microscopy in all ages prior to and after MDA up to four months, but these data were omitted from quantitative synthesis at all time points due to either zero events pre-MDA (outcomes by microscopy) or unclear timing of post-MDA events (outcomes by QT-NASBA).

P vivax parasitaemia prevalence was reported by Landier 2017 MMRa, McLean 2021 MMR, Pongvongsa 2018 LAO, Tripura 2018 KHM, and von Seidlein 2019 VNM, and included the same pre-MDA and post-MDA follow-up time points, detection method, and population sampled as *P falciparum* parasitaemia. Confirmed malaria illness incidence for *P vivax* was reported prior to MDA in Tripura 2018 KHM, and at 7 to 12 months after MDA in Landier 2017 MMRa; and Tripura 2018 KHM.

Non-randomized controlled studies

We included three CBA studies in qualitative syntheses. All studies were conducted in areas of moderate to high endemicity (moderate: Roberts 1964 KEN; high: Escudie 1962 BFA; Molineaux 1980 NGA). All studies were conducted in sub-Saharan Africa in the countries of Burkina Faso (Escudie 1962 BFA), Kenya (Roberts 1964 KEN), and Nigeria (Molineaux 1980 NGA).

Escudie 1962 BFA included six arms (chloroquine plus primaquine or amodiaquine plus primaquine every four weeks; chloroquine plus primaquine or amodiaquine plus primaquine every two weeks; chloroquine plus primaquine or amodiaquine plus primaquine every four weeks with IRS; chloroquine plus primaquine or amodiaquine plus primaquine every two weeks with IRS; IRS only; non-IRS control). Of these six arms, three arms with two comparisons contributed to this review: chloroquine plus primaquine or amodiaquine plus primaquine every four weeks ('low frequency'); chloroquine plus primaquine or amodiaquine plus primaquine every two weeks ('high frequency'); and non-IRS control. Given similar mechanisms of antimalarial action for chloroquine and amodiaquine, and the combined reporting of outcomes at post-MDA time points, these drugs were not analysed as separate groups within the six arms described. Of the four arms included in Molineaux 1980 NGA (low frequency MDA plus IRS, high frequency MDA plus IRS, IRS only, and no intervention), we included three arms with two comparisons in this review: low frequency MDA plus IRS, high frequency MDA plus IRS, and IRS only). Roberts 1964 KEN compared MDA to no MDA and all data provided comparisons for this review.

Interventions

Characteristics of the intervention have been summarized in Table 1.

All studies administered multiple rounds of MDA using different antimalarials and at different frequencies of MDA rounds. Escudie 1962 BFA administered MDA with a single dose of chloroquine plus primaquine or amodiaquine plus primaquine every four weeks for seven rounds, or every two weeks for 15 rounds to the entire population (all ages). MDA coverage ranged from 75% to 91% per round in the four-week low frequency MDA arm and 84% to 97% per round in the two-week high frequency MDA arm. Molineaux 1980 NGA administered MDA with sulfalene-pyrimethamine either every 10 weeks ('low frequency MDA') or every 2 weeks during the wet season and every 10 weeks during the dry season ('high frequency MDA') to all ages except infants prior to their first malaria episode. MDA coverage was similar across arms, ranging from 73% to 92% per round in the low frequency MDA arm and 72% to 91% in the high frequency MDA arm. In Roberts 1964 KEN, two rounds of MDA with pyrimethamine were administered once a year (at the start of the rainy season) to all ages with coverage of 95% in round one and 93% in round two.

Molineaux 1980 NGA administered IRS using propoxur for three to four rounds per year in all arms, but there were no co-interventions in the other two studies.

Outcomes

Outcome data are summarized in Table 2.

All outcomes reported were for *P falciparum.* All studies reported parasitaemia prevalence by microscopy at pre-MDA and during-

MDA time points, but outcomes were assessed for different lengths of post-MDA follow-up and in different age groups. Molineaux 1980 NGA provided no post-MDA data, Escudie 1962 BFA reported parasitaemia prevalence at one to three months after MDA, and Roberts 1964 KEN provided parasitaemia prevalence at time points up to 7 to 12 months after MDA. Two studies assessed parasitaemia prevalence in all age groups (Molineaux 1980 NGA; Roberts 1964 KEN), and Escudie 1962 BFA assessed parasitaemia prevalence only in children aged two to nine years. Gametocytaemia prevalence was reported by Escudie 1962 BFA in children aged two to nine years prior to MDA, during MDA, and one to three months after MDA, and by Molineaux 1980 NGA in all ages, prior to MDA and during MDA (no post-MDA time points). No other outcomes, including adverse effects, were reported by these studies.

Excluded studies

We excluded 25 articles for the following reasons: 13 were duplicates (cross-referenced articles of another study); 10 failed to meet the study design inclusion criteria; and two were the incorrect intervention or inadequate treatment dose. We have provided detailed reasons in the Characteristics of excluded studies.

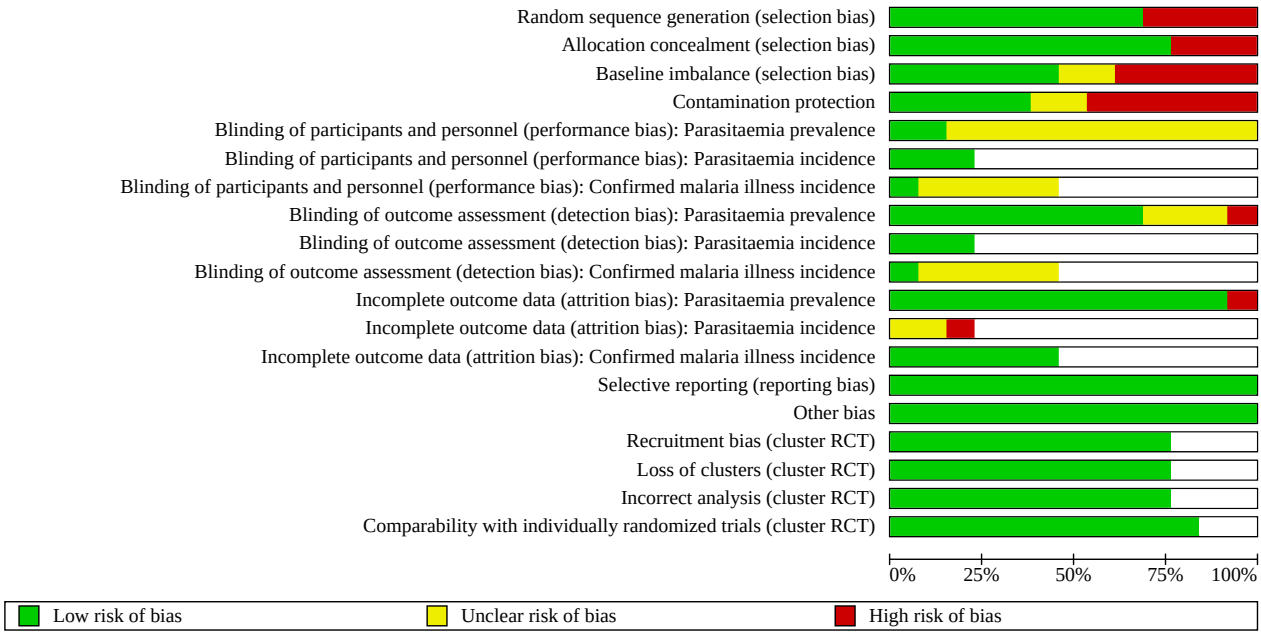
Two additional excluded studies were unpublished trials that are awaiting classification (Characteristics of studies awaiting classification). We made several attempts to contact Song TGO, but did not receive a response. We were unable to obtain sufficient information from authors of El-Sayed SDN to assess the trial for eligibility. However, we plan to screen the study should the authors publish the results.

Risk of bias in included studies

Our summary assessment for risks of bias are shown in Figure 2 and Figure 3, and details are provided for each study in the Characteristics of included studies tables.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

We assessed nine studies as low risk of bias for random sequence generation due to the use of a computerized randomization algorithm (Eisele 2020 ZMBa; Eisele 2020 ZMBb; Landier 2017 MMRa; Morris 2018 TZA; Pongvongsa 2018 LAO; Shekalaghe 2011 TZA; Tripura 2018 KHM; von Seidlein 2003 GMB; von Seidlein 2019 VNM). We assessed the remaining four studies as high risk of bias, due to lack of randomization (Escudie 1962 BFA; Molineaux 1980 NGA; Roberts 1964 KEN), or the use of a non-computerized randomization method (McLean 2021 MMR). We judged all 10 cRCTs to be at low risk for bias related to allocation concealment since allocation was performed by an institution, and all non-randomized studies to be at high risk of bias for allocation concealment.

Blinding

Parasitaemia prevalence

We assessed two placebo-controlled studies as low risk for performance bias since participants and study staff were blinded (Shekalaghe 2011 TZA; von Seidlein 2003 GMB). We judged all other studies, which included non-MDA control groups, as unclear risk for performance bias since participants were not blinded and it was unclear whether or how this could affect this outcome.

Outcome assessment by laboratory staff was blinded to study arm in nine studies, and we judged these as low risk (Landier 2017 MMRa; McLean 2021 MMR; Molineaux 1980 NGA; Morris 2018 TZA; Pongvongsa 2018 LAO; Shekalaghe 2011 TZA; Tripura 2018 KHM; von Seidlein 2003 GMB; von Seidlein 2019 VNM). Three studies did not describe blinding of laboratory staff, and we judged these as unclear risk of detection bias (Eisele 2020 ZMBa; Eisele 2020 ZMBb; Roberts 1964 KEN). Outcome assessment in one study was clearly unblinded, and we considered this study as high risk of detection bias (Escudie 1962 BFA).

Parasitaemia incidence

We judged all three studies reporting parasitaemia incidence as low risk of both performance and detection bias since this outcome was evaluated through active surveillance, so lack of blinding of participants and study staff was presumed to minimally affect the outcome (Eisele 2020 ZMBa; Eisele 2020 ZMBb), or the trial was placebo-controlled (von Seidlein 2003 GMB).

Confirmed malaria illness incidence

We judged one placebo-controlled trial as having low risk of performance and detection bias due to blinding of participants, study staff, and outcome assessment (Shekalaghe 2011 TZA). We judged five studies as having unclear risk since it was unclear how lack of blinding would affect care-seeking behaviours by participants, or outcome assessment (Eisele 2020 ZMBa; Eisele 2020 ZMBb; Landier 2017 MMRa; Morris 2018 TZA; Tripura 2018 KHM).

Incomplete outcome data

Parasitaemia prevalence

We judged one trial that reported large variations in the size of the population evaluated for parasitaemia prevalence outcomes at different time points as having high risk of bias since, based on the described methodology, the population evaluated should have remained consistent (McLean 2021 MMR). The remaining eight studies had a low risk of attrition bias.

Parasitaemia incidence

We judged one study as high risk of bias due to a large proportion of missed malaria infections (particularly, afebrile or low parasite density malaria infections) due to outcome definitions (von Seidlein 2003 GMB). We judged two studies as unclear risk of bias

since loss to follow-up was not provided by baseline endemicity strata (Eisele 2020 ZMBa, Eisele 2020 ZMBb).

Confirmed malaria illness incidence

We judged all six studies reporting this outcome as having low risk of bias (Eisele 2020 ZMBa; Eisele 2020 ZMBb; Landier 2017 MMRa; Morris 2018 TZA; Tripura 2018 KHM; Shekalaghe 2011 TZA).

Selective reporting

All studies reported the outcomes that were pre-specified and were judged as having low risk of reporting bias.

Other potential sources of bias

No cRCTs were judged to have a high or unclear risk of bias from recruitment, loss of clusters, incorrect analyses, or comparability with individually randomized trials. All studies were judged to be at low risk for other biases.

Baseline imbalance

We judged five studies to have high risk of bias due to unbalanced baseline malaria prevalence in intervention and control arms (Landier 2017 MMRa; Morris 2018 TZA; Pongvongsa 2018 LAO; Roberts 1964 KEN; Tripura 2018 KHM). Two studies did not report baseline demographic characteristics (other risk factors for malaria), and we judged these to have unclear risk of bias (Escudie 1962 BFA; Molineaux 1980 NGA). The remaining studies were balanced for malaria and demographic characteristics across arms at baseline.

Contamination protection

The study arms for six studies were either paired by geographic proximity or located in close geographic proximity with a high potential for population movement. We judged these studies as having a high risk of contamination bias (Landier 2017 MMRa; McLean 2021 MMR; Pongvongsa 2018 LAO; Roberts 1964 KEN; Tripura 2018 KHM; von Seidlein 2019 VNM). Two studies did not describe methods for contamination protection, and we judged these as unclear risk (Escudie 1962 BFA; Morris 2018 TZA). The remaining four studies included buffer zones to minimize contamination of outcome assessment, and we judged these as low risk (Eisele 2020 ZMBa; Eisele 2020 ZMBb; Shekalaghe 2011 TZA; von Seidlein 2003 GMB).

Effects of interventions

See: **Summary of findings 1** MDA compared to no MDA for *Plasmodium falciparum* malaria (moderate to high endemicity, short-term follow-up); **Summary of findings 2** MDA compared to no MDA for *Plasmodium falciparum* malaria (very low to low endemicity, short-term follow-up); **Summary of findings 3** MDA compared to no MDA for *Plasmodium falciparum* malaria (very low to low endemicity, long-term follow-up); **Summary of findings 4** MDA compared to no MDA for *P vivax* malaria (very low to low endemicity, short-term follow-up); **Summary of findings 5** MDA compared to no MDA for *P vivax* malaria (very low to low endemicity, long-term follow-up)

Cluster-randomized trials

Moderate- to high-transmission areas

Effects reported on *P falciparum* outcomes

At one to three months after MDA

Eisele 2020 ZMBb found a non-significant increase in *P falciparum* parasitaemia prevalence (RR 1.76, 95% CI 0.58 to 5.36; 1 study; Analysis 1.1), a significant reduction in parasitaemia incidence by 39% (rate ratio 0.61, 95% CI 0.40 to 0.92; 1 study; Analysis 1.2), and a non-significant reduction in confirmed malaria illness incidence by 59% (RR 0.41, 95% CI 0.04 to 4.51; 1 study; Analysis 1.3) in MDA compared to non-MDA clusters at one to three months after MDA.

At four to six months after MDA

As reported by von Seidlein 2003 GMB, at four to six months after MDA, MDA did not reduce *P falciparum* parasitaemia prevalence (RR 1.18, 95% CI 0.89 to 1.56; 1 study; Analysis 1.1), and also did not reduce the secondary outcomes of *P falciparum* gametocytaemia prevalence (RR 1.13, 95% CI 0.20 to 6.54; 1 study; Analysis 1.4), and malaria-specific mortality (RR 1.42, 95% CI 0.12 to 17.15; 1 study; Analysis 1.5).

Very low- to low-transmission areas

Effects reported on *P falciparum* outcomes

At less than one month after MDA

McLean 2021 MMR reported that MDA reduced *P falciparum* parasitaemia prevalence by 88% immediately (less than one month) after MDA (RR 0.12, 95% CI 0.03 to 0.52; 1 study; Analysis 2.1).

At one to three months after MDA

Based on results from seven studies, MDA significantly reduced *P falciparum* parasitaemia prevalence by 75% one to three months after MDA (RR 0.25, 95% 0.15 to 0.41; 7 studies; Analysis 2.1). The largest reduction was observed by Landier 2017 MMRa in Myanmar (RR 0.06, 95% CI 0.01 to 0.45; 1 study; Analysis 2.1), while the opposite effect was found by Morris 2018 TZA in Zanzibar (RR 1.34, 95% CI 0.30 to 5.92; Analysis 2.1). Although the I^2 value(31%) did not indicate inconsistency in the results, we explored differences in malaria epidemiology by continent as a cause of heterogeneity in this effect. When the effects were sub-grouped by continent (Africa and Asia) in post-hoc analysis (Analysis 4.1), there was no effect of MDA in two studies in sub-Saharan Africa (pooled RR 0.97, 95% CI 0.32 to 2.98; Eisele 2020 ZMBa; Morris 2018 TZA), but a larger reduction in the five studies in Southeast Asia (RR 0.19, 95% CI 0.11 to 0.33; Landier 2017 MMRa; McLean 2021 MMR; Pongvongsa 2018 LAO; Tripura 2018 KHM; von Seidlein 2019 VNM).

Eisele 2020 ZMBa measured the effect of MDA compared to no MDA on *P falciparum* parasitaemia incidence in very low- to low-endemicity areas, and found a statistically significant 63% reduction one to three months after MDA (rate ratio 0.37, 95% CI 0.21 to 0.66; 1 study; Analysis 2.2).

MDA also reduced confirmed malaria illness incidence (rate ratio 0.58, 95% CI 0.12 to 2.73, 2 studies; Analysis 2.3). However, the effect was imprecise and not statistically significant.

At four to six months after MDA

Based on findings from four studies in Southeast Asia, at four to six months after MDA, there was a non-significant reduction in *P falciparum* parasitaemia prevalence by 37% (RR 0.63, 95% CI 0.36 to 1.12; 4 studies; Analysis 2.1) in MDA compared to non-MDA clusters. Effects across studies included few malaria cases and were therefore very imprecise. The strongest reduction was observed by Pongvongsa 2018 LAO in Laos (RR 0.07, 95% CI 0 to 1.31; Analysis 2.1), while the weakest effect was found by Landier 2017 MMRa in Myanmar (RR 0.89, 95% CI 0.27 to 2.95; Analysis 2.1).

There was no effect of MDA on confirmed malaria illness incidence four to six months after MDA as reported by a single study, Morris 2018 TZA (rate ratio 0.93, 95% CI 0.07 to 12.43; Analysis 2.3).

At 7 to 12 months after MDA

At 7 to 12 months after MDA, there was a small but non-significant reduction in *P falciparum* parasitaemia prevalence (RR 0.86, 95% CI 0.55 to 1.36; 5 studies; Analysis 2.1) in MDA compared to non-MDA clusters. Due to few malaria cases, the effect estimates across studies were very imprecise. Additionally, the direction of effect was inconsistent across studies, with two studies showing a non-significant increase in *P falciparum* parasitaemia prevalence in the MDA compared to no-MDA arm (Landier 2017 MMRa; von Seidlein 2019 VNM), while three studies found that MDA reduced parasitaemia prevalence (McLean 2021 MMR; Pongvongsa 2018 LAO; Tripura 2018 KHM).

MDA reduced confirmed malaria illness incidence 7 to 12 months after MDA (rate ratio 0.47, 95% CI 0.21 to 1.03; 3 studies; Analysis 2.3). However, the effect was not statistically significant and there was substantial heterogeneity (I^2=72%, Analysis 2.3).

At longer time periods (> 12 months) after MDA

At 13 to 18 months after MDA, MDA did not significantly reduce *P falciparum* parasitaemia prevalence in McLean 2021 MMR (RR 0.82, 95% CI 0.20 to 3.34; 1 study; Analysis 2.1) or confirmed malaria illness incidence in Morris 2018 TZA (rate ratio 0.77, 95% CI 0.2 to 3.03; 1 study; Analysis 2.3). McLean 2021 MMR reported no effect on parasitaemia prevalence at 19 to 24 months, 25 to 30 months and 31 to 36 months after MDA (Analysis 2.1).

Effects reported on *P vivax* outcomes

At less than one month after MDA

McLean 2021 MMR showed that MDA had an immediate and large reduction on *P vivax* parasitaemia prevalence at less than one month after MDA (RR 0.18, 95% CI 0.08-0.40; 1 study; Analysis 3.1).

At one to three months after MDA

Although there was considerable heterogeneity across five studies (I^2 = 84%) in the effect of MDA on *P vivax* parasitaemia prevalence one to three months after MDA, we meta-analysed the results since the direction of effect was consistent and all reported effect estimates were very imprecise due to a small number of malaria events. At one to three months after MDA, MDA significantly reduced *P vivax* parasitaemia prevalence by 85% (RR 0.15, 95% CI 0.10 to 0.24; 5 studies; Analysis 3.1).

At four to six months after MDA

MDA significantly reduced *P vivax* parasitaemia prevalence by 22% at four to six months after MDA (RR 0.78, 95% CI 0.63 to 0.95; 4 studies; Analysis 3.1).

At 7 to 12 months after MDA

At 7 to 12 months after MDA, MDA did not reduce *P vivax* parasitaemia prevalence (RR 1.12, 95% CI 0.94 to 1.34; 5 studies; Analysis 3.1). There was a non-significant increase in confirmed malaria illness incidence (pooled rate ratio 1.38, 95% CI 0.97 to 1.95; 2 studies; Analysis 3.2) in MDA compared to non-MDA clusters.

At longer time periods (> 12 months) after MDA

McLean 2021 MMR reported that MDA did not reduce parasitaemia prevalence at 13 to 18 months, 19 to 24 months, 25 to 30 months, and 31 to 36 months after MDA (Analysis 3.1).

Adverse effects

Adverse effects (AEs) of MDA were reported by all ten cRCTs included in qualitative synthesis (Eisele 2020 ZMBa; Eisele 2020 ZMBb; Landier 2017 MMRa; McLean 2021 MMR; Morris 2018 TZA; Pongvongsa 2018 LAO; Shekalaghe 2011 TZA; Tripura 2018 KHM; von Seidlein 2003 GMB; von Seidlein 2019 VNM). We have provided details by study in the Characteristics of included studies tables. McLean 2021 MMR reported AEs by relatedness to MDA drug, but did not provide diagnoses of AEs. Eisele 2020 ZMBa and Eisele 2020 ZMBb reported AEs by MDA and fMDA arms combined and in aggregate across low- and high-transmission strata clusters.

Two studies reported one serious AE with MDA using dihydroartemisinin piperaquine (Eisele 2020 ZMBa or Eisele 2020 ZMBb), or dihydroartemisinin piperaquine plus primaquine (McLean 2021 MMR). One study reported that 0.5% of all AEs reported after MDA with dihydroartemisinin piperaquine plus primaquine were perceived as serious by participants (Morris 2018 TZA). Two studies administering dihydroartemisinin piperaquine plus primaquine reported multiple serious AEs that were not drug-related (Landier 2017 MMRa; von Seidlein 2019 VNM). Landier 2017 MMRa also reported three cases of black urine. One study reported a possibly drug-related severe skin reaction following administration of MDA using sulfadoxine-pyrimethamine plus artesunate with primaquine (Shekalaghe 2011 TZA).

Four studies indicated stomach pains or diarrhoea and vomiting as commonly reported AEs to MDA with dihydroartemisinin piperaquine (Eisele 2020 ZMBa; Eisele 2020 ZMBb), dihydroartemisinin piperaquine plus primaquine (Morris 2018 TZA, Pongvongsa 2018 LAO, von Seidlein 2019 VNM), and sulfadoxine-pyrimethamine plus artesunate (von Seidlein 2003 GMB). Dizziness and fever were mentioned as minor AEs to MDA with dihydroartemisinin piperaquine (Morris 2018 TZA, Tripura 2018 KHM) and sulfadoxine-pyrimethamine plus artesunate (von Seidlein 2003 GMB). Dizziness was also a common AE in two studies with MDA using dihydroartemisinin piperaquine plus primaquine (Landier 2017 MMRa, Pongvongsa 2018 LAO). Three studies also indicated complaints of nausea, headache, and fatigue in relation to MDA with dihydroartemisinin piperaquine plus primaquine (Morris 2018 TZA, von Seidlein 2019 VNM), or dihydroartemisinin piperaquine alone (Tripura 2018 KHM). Pruritis or itching were

reported by studies administering dihydroartemisinin piperaquine plus primaquine (Landier 2017 MMRa; Pongvongsa 2018 LAO) and a study administering MDA with sulfadoxine-pyrimethamine plus amodiaquine (von Seidlein 2003 GMB). Common cold or dry cough was reported as a common minor AE in two studies using MDA with dihydroartemisinin piperaquine (Eisele 2020 ZMBa; Eisele 2020 ZMBb), or MDA with dihydroartemisinin piperaquine plus primaquine (Pongvongsa 2018 LAO).

Among the four studies that reported the distribution of AEs (as either percentage of participants or percentage of doses with an AE), the frequency of at least one AE report was highest in MDA with sulfadoxine-pyrimethamine plus amodiaquine (33% of participants, von Seidlein 2003 GMB), and lower in MDA with dihydroartemisinin piperaquine (0.24% (Eisele 2020 ZMBa or Eisele 2020 ZMBb) to 11.6% (Morris 2018 TZA) of participants) or dihydroartemisinin piperaquine plus primaquine (3.6% of participants in McLean 2021 MMR).

Non-randomized studies

P falciparum parasitaemia prevalence

In the three non-randomized trials, we summarized changes in parasitaemia prevalence from baseline to during-MDA or post-MDA, in MDA compared to no-MDA groups, using a DiD analysis (Table 3).

MDA appeared to reduce parasitaemia prevalence in all studies during MDA compared to pre-MDA, with a wide range of DiD percentage point reductions from -15.8 (Roberts 1964 KEN), to -61.4 (Escudie 1962 BFA). The smallest reduction was observed in Roberts 1964 KEN, in which two rounds of MDA using pyrimethamine were administered one year apart and, therefore, the during-MDA time period included multiple surveys between the two rounds. Similar percentage point reductions from baseline were observed between both the low-frequency MDA plus IRS (-23.2 percentage points) and high frequency MDA plus IRS (-20.9 percentage points) compared to the control (IRS only) group in Molineaux 1980 NGA during the period that MDA was administered with sulfalene-pyrimethamine. In Escudie 1962 BFA, there was a substantially greater DiD reduction in parasitaemia prevalence in the low-frequency MDA group (amodiaquine plus primaquine or chloroquine plus primaquine every four weeks, -61.4 percentage points) compared to the high-frequency MDA group (amodiaquine plus primaquine or chloroquine plus primaquine every two weeks; -36.3 percentage points) at during-MDA compared to pre-MDA time periods.

At one to three months after MDA, parasitaemia prevalence was reduced in the low-frequency MDA arm of Escudie 1962 BFA by -42.1 percentage points, but there was an increase in parasitaemia prevalence in the high-frequency MDA arm compared to control, as reflected by a +14.9 percentage point DiD. There was an initial reduction in parasitaemia prevalence (-28.1 percentage points) found in Roberts 1964 KEN at one to three months after MDA, which decreased over time to -22.8 percentage points at four to six months after MDA, and to -11.3 percentage points at 7 to 12 months after MDA. Given the introduction of new interventions in Molineaux 1980 NGA immediately following MDA, there were no post-MDA data available.

P falciparum gametocytaemia prevalence

In the two non-randomized trials reporting gametocytaemia prevalence, we summarized changes in the effect of MDA from baseline to during-MDA or post-MDA using DiD analysis (Table 4).

From pre-MDA to during-MDA, with the exception of the low-frequency MDA arm in Escudie 1962 BFA, there was a small DiD reduction on gametocytaemia prevalence, ranging from -1 percentage point (Escudie 1962 BFA high-frequency MDA) to -5.0 percentage points in both arms of Molineaux 1980 NGA. A large reduction from pre-MDA (-14.1 percentage points) was observed in the low-frequency MDA arm of Escudie 1962 BFA during MDA. However, compared to the pre-MDA period, gametocytaemia prevalence at one to three months after MDA was increased in both the low-frequency MDA arm (18.3 percentage points) and high-frequency MDA arm (53.4 percentage points) in Escudie 1962 BFA compared to no MDA.

DISCUSSION

Summary of main results

We included 13 studies in this review: 10 cRCTs, of which two were from areas of moderate to high transmission, and eight were from areas of very low to low endemicity; and three CBAs, all from settings of moderate to high transmission.

Areas of moderate- to high-endemicity (cRCTs)

The two included studies were both conducted in sub-Saharan Africa. We included MDA versus no-MDA comparisons from von Seidlein 2003 GMB, which examined the effect of one round of MDA with sulfadoxine-pyrimethamine plus artesunate, and from Eisele 2020 ZMBb, which examined the effect of four rounds of MDA with dihydroartemisinin piperaquine. No co-interventions were implemented in the von Seidlein 2003 GMB study, but IRS, ITNs, and enhanced community case management practices were included in all arms of Eisele 2020 ZMBb.

Based on these data, in comparison to no-MDA:

- at one to three months after MDA, *P falciparum* parasitaemia prevalence may be higher (low-certainty evidence), parasitaemia incidence is probably lower (moderate-certainty evidence), and confirmed malaria illness incidence may be lower (low-certainty evidence) in MDA compared to no-MDA, as reported by a single study (Eisele 2020 ZMBb);
- at four to six months after MDA, MDA probably leads to little or no effect on *P falciparum* parasitaemia prevalence (moderate-certainty evidence) and we do not know the effect on parasitaemia incidence (very low-certainty evidence) as reported by a single study (von Seidlein 2003 GMB).

Longer-term effects of MDA on outcomes were not reported by any included studies in moderate- to high-transmission settings.

Areas of very low- to low-endemicity (cRCTs)

Of the eight studies included in qualitative synthesis, three were carried out in sub-Saharan Africa and five were conducted in Southeast Asia. One study that administered one round of MDA with sulfadoxine-pyrimethamine plus artesunate plus primaquine was excluded from quantitative synthesis due to insufficient data (Shekalaghe 2011 TZA). Of the remaining

seven trials, we included one comparison (multiple rounds of MDA with dihydroartemisinin piperaquine plus primaquine) each from Landier 2017 MMRa, McLean 2021 MMR, Morris 2018 TZA, Pongvongsa 2018 LAO, and von Seidlein 2019 VNM; and one comparison (multiple rounds of MDA with dihydroartemisinin piperaquine) each from Eisele 2020 ZMBa and Tripura 2018 KHM. All studies implemented ITNs, while Morris 2018 TZA and Eisele 2020 ZMBa also included IRS in both intervention and control arms.

Based on these data, in comparison to no-MDA:

- at less than one month after MDA, *P falciparum* parasitaemia prevalence may be lower in MDA compared to no-MDA (low-certainty evidence*);*
- at one to three months after MDA, MDA probably reduces *P falciparum* parasitaemia incidence (moderate-certainty evidence) and may reduce *P falciparum* parasitaemia prevalence (low-certainty evidence), but we do not know if MDA has an effect on confirmed malaria illness incidence (very low-certainty evidence);
- at 4 to 6 months and 7 to 12 months after MDA, we do not know the effect of MDA on *P falciparum* parasitaemia prevalence and confirmed malaria illness incidence (very low-certainty evidence);
- as reported by a single study (McLean 2021 MMR), we do not know if MDA has an effect on *P falciparum* parasitaemia prevalence at longer-term follow-up periods (13 to 36 months, very low-certainty evidence).

Despite the very low-certainty evidence available for outcomes after four months post-MDA, there was a general trend of a substantial reduction in *P falciparum* parasitaemia prevalence immediately following MDA and the strength of the reduction declined over time.

Five studies provided data for comparison of *P vivax* outcomes:

- at less than one month after MDA, *P vivax* parasitaemia prevalence may be lower in MDA compared to no-MDA (low-certainty evidence);
- at one to three months after MDA, *P vivax* parasitaemia prevalence may be lower in MDA compared to no-MDA (low-certainty evidence);
- at four to six months after MDA, we do not know if MDA reduces *P vivax* parasitaemia prevalence (very low-certainty evidence);
- at 7 to 12 months after MDA, we do not know the effect of MDA on *P vivax* parasitaemia prevalence and confirmed malaria illness incidence (very low-certainty evidence);
- as reported by a single study (McLean 2021 MMR), we do not know if MDA has an effect on *P vivax* parasitaemia prevalence at longer-term follow-up periods (13 to 36 months, very low-certainty evidence).

Very low-certainty evidence was available for multiple outcomes. However, similar to *P falciparum* outcomes in this setting, there was a general trend of a large and immediate reduction in *P vivax* parasitaemia prevalence following MDA that waned over time.

In relation to the Objectives of this review:

- in moderate- to high-transmission settings, no studies provided data at longer-term time periods to observe a 50% reduction in median malaria parasite prevalence or incidence, or both, at 12 months after MDA. However, the available studies showed a reduction in parasitaemia incidence, but not parasitaemia prevalence, at time periods prior to six months after MDA;
- in very low- to low-transmission settings, there was a strong reduction in *P falciparum* and *P vivax* parasitaemia prevalence immediately following MDA, that decreased over time. However, there was no evidence of interruption of transmission, defined as a reduction in number of indigenous malaria infections to zero at six months after MDA.

Overall completeness and applicability of evidence

This review highlights a renewed interest in MDA as a strategy to accelerate progress towards malaria elimination, given the more recent studies conducted since the previous review on this topic (Poirot 2013). In areas of moderate to high transmission, no studies reported outcomes under six months after MDA, but available evidence from earlier post-MDA time periods showed that MDA decreased parasitaemia incidence, but not parasitaemia prevalence. In very low- to low-transmission areas, several studies found substantial short-term reductions in parasitaemia prevalence following MDA that were not sustained longer-term. None of these studies found a reduction to zero indigenous malaria cases at any post-MDA time period.

In both malaria transmission settings, we found that MDA compared to no MDA led to significant reductions in *P falciparum* parasitaemia incidence at one to three months after MDA, and in very low- to low-transmission settings, correspondingly large and statistically significant reductions in parasitaemia prevalence at less than one month after MDA (one study) and at one to three months after MDA (seven studies). However, in moderate- to high-transmission settings, this trend was not mirrored by a reduction in parasitaemia prevalence, based on a single study reporting at one to three months and four to six months after MDA. We believe one explanation for this counterintuitive finding of a reduction in incidence but not prevalence is due to differences in the study design and populations used to measure these outcomes. Studies measured incidence in a fixed cohort and prevalence in a random sample of the population in cross-sectional surveys. Since the inclusion criteria for cohort studies typically requires establishment of a period of residency in the study area, cohort participants may also be more likely to receive at least one round of MDA compared to a cross-section of the population that can include individuals who recently moved to the study area after the MDA round (i.e. did not receive the intervention) but prior to the survey. This distinction also raises the concern about risk of re-introduction of malaria. It is possible that we found no effect of MDA on several outcomes due to the high risk of re-introduction in the study areas of included studies, possibly due to a combination of high levels of migration and low effective MDA coverage (i.e. the proportion of the population that received at least one round of MDA).

In an area of moderate to high transmission, Eisele 2020 ZMBb found an unexpected increase in parasitaemia prevalence in the MDA arm compared to no-MDA control at one to three months, following four rounds of MDA. Although the effect estimate was very imprecise, it is worth noting that parasitaemia prevalence decreased overall in the entire study area (both the lower- and higher-transmission strata) and specifically in the moderate- to high-transmission control clusters, from above 50% at baseline to below 10% following four rounds of MDA. Other

interventions such as ITNs, IRS and enhanced community case management were implemented at high coverage in intervention and control arms at the start of the study and may have contributed to the overall decline in malaria transmission in the study area. This finding may also highlight the importance of implementing MDA as a component of a package of malaria control interventions to achieve reductions in malaria transmission.

Although not an important cause of heterogeneity in our analysis, the short-term effects of MDA in studies conducted in very low- to low- transmission settings differed by geography. Trials conducted in Southeast Asia generally found a large reduction in parasitaemia prevalence at one to three months after MDA (Landier 2017 MMRa; McLean 2021 MMR; Pongvongsa 2018 LAO; Tripura 2018 KHM; von Seidlein 2019 VNM), while the two studies in Africa showed a smaller or no reduction (Eisele 2020 ZMBa; Morris 2018 TZA). All studies administered MDA with dihydroartemisinin piperaquine (primaquine was included in most Southeast Asia trials and the Zanzibar study), implemented multiple rounds of MDA, and had similar levels of coverage. Trials in Africa included substantially larger MDA target populations (> 10,000 in Zanzibar; > 37,000 in Zambia) compared to Southeast Asia (< 5000) and implemented additional co-interventions (mainly, IRS) across arms. Although not measured directly, differences in underlying malaria epidemiology, population movement and risk of re-introduction, and implementation of the intervention (more resource-intensive in larger trials) could have contributed to variations in the short-term effects by geography.

Of note, the certainty of evidence for outcomes in this review was based on a small number of included studies that, after stratification by endemicity and post-MDA time period, often resulted in limited evidence. We assessed studies from very low- to low-endemicity settings as high risk of bias for several criteria, and the certainty of evidence from studies from all endemicities was affected by imprecision. This highlights the need for additional studies with high-quality evidence (both randomized and non-randomized designs) and with sufficient sample sizes to account for the correlation due to clustering. Finally, we excluded many studies due to reasons such as imbalanced co-interventions across arms or insufficient time points before and after MDA to conduct interrupted time series (ITS) analyses. Although these studies did not meet our criteria for inclusion, they may provide information useful for policymakers.

Quality of the evidence

In settings of moderate to high transmission, we judged the two trials as having low risk of bias (Figure 2), and Summary of findings 1 describes our assessment of the certainty of evidence available. No pooled effect estimates were provided for outcomes in moderate- to high-transmission settings due to a single study reporting after stratification by post-MDA time period.

We judged most studies from very low- to low-endemicity settings to be at high risk or unclear risk of bias for some criteria (Figure 2), and our assessment of the certainty of evidence available for important short-term outcomes is provided in Summary of findings 2, Summary of findings 3, Summary of findings 4, and Summary of findings 5. Studies in this setting were generally underpowered and there were only a few malaria events across arms, resulting in imprecise estimates of effect. Many outcomes were downgraded by one or two levels due to imprecision after adjustment for clustering. All parasitaemia prevalence outcomes at longer-term post-MDA time periods were downgraded by one or two levels due to risk of bias, mainly due to baseline imbalance or biased sampling approaches for cross-sectional parasitaemia surveys.

Potential biases in the review process

Although we sought to examine short- and longer-term effects of MDA over a range of follow-up time periods, there were few studies available within each follow-up time period. Therefore, we were unable to examine whether variables, such as type of antimalarial drug, MDA coverage or number of rounds, and co-interventions, modified the effect of MDA compared to no MDA.

Agreements and disagreements with other studies or reviews

Previous reviews on this topic described substantial but temporary reductions in malaria burden immediately following MDA (in both low- and high-transmission settings) (Greenwood 2004; Newby 2015; Poirot 2013; von Seidlein 2003). Our review provides evidence of short-term reductions in parasitaemia incidence in both transmission settings and evidence of short-term reductions in parasitaemia prevalence in very low- to low-endemicity areas, but not in moderate- to high-endemicity areas. This difference is possibly due to the limited number of studies in moderate- to high-transmission settings included in this review (two trials), different study design, or differences in malaria context between older and newer studies. Many older studies included in previous reviews were conducted in settings prior to scale-up of vector control measures (e.g. ITNs), improvements in case management (i.e. RDTs and ACTs), and potentially less population movement to limit risk of re-introduction. This may have resulted in a larger effect of MDA, which is supported by our results from non-randomized studies that showed large short-term reductions in parasitaemia prevalence in older studies conducted in settings of moderate to high endemicity. Additionally, it is possible that our inclusion of more rigorous study designs provided less biased comparisons for evaluating the effect of MDA.

The 2013 Cochrane Review on this topic highlighted a few studies on small islands or in highland settings in which malaria transmission was interrupted by MDA (Poirot 2013), but these studies did not meet inclusion criteria for our updated review. Although MDA has been attributed to successful elimination of malaria in Vanuatu (Kaneko 2000 VUT), we excluded this study due to an imbalance in co-interventions, since MDA was administered in combination with ITNs and larvivorous fish, while the no-MDA control arm received delayed ITNs and no additional interventions. Additionally, more recent studies from island settings did not meet our inclusion criteria: ITNs were introduced concurrently with MDA in a recent study conducted in Grande Comore, Comoros (Affane 2012 COM), and there were insufficient data points collected to adequately account for trends in malaria seasonality using the ITS design in a study conducted on Anjouan island, Comoros (Deng 2018 COM).

Finally, the previous Cochrane Review also highlighted a paucity of data to assess whether a reduction by MDA was sustained (Poirot 2013). Our findings address some of the knowledge gaps from the previous review with the availability of longer-term follow-up data post-MDA for parasitaemia prevalence, and confirmed

malaria illness incidence from several studies in very low- to low-transmission settings.

AUTHORS' CONCLUSIONS

Implications for practice

In moderate- to high-transmission settings, only two studies contributed data to assess the effect of MDA on outcomes. Based on results from a single trial, MDA probably reduces parasitaemia incidence, but does not reduce parasitaemia prevalence at one to three months after MDA. However, it is worth noting that there was a large overall reduction in parasitaemia prevalence in both the intervention and control arms from baseline to post-MDA. The second trial showed no effect of a single round of MDA at four to six months after MDA. Given the absence of data in moderate- to high-transmission settings at time points after six months, we were unable to determine the longer-term effects of MDA on malaria transmission.

In very low- to low-transmission settings, MDA probably reduces *P falciparum* parasitaemia incidence at under one month, and *P falciparum* and *P vivax* prevalence at one to three months after MDA. The short- and long-term effects of MDA on *P falciparum* and *P vivax* parasitaemia prevalence at time periods after four months is uncertain due to very low-certainty evidence, but the immediate large reduction in parasitaemia prevalence is not sustained over time. Based on data provided in studies conducted in very low- to low-transmission settings, we did not find evidence in any study of interruption of transmission as measured by a reduction to zero indigenous cases following MDA.

Other variables, such as type of antimalarial drug, MDA coverage, number of rounds, and co-interventions, may affect the impact of MDA on malaria outcomes and should be considered when conducting MDA. Additionally, the degree of population mobility and potential for importation of parasites also plays an important role in the effect of MDA. These considerations should be weighed carefully in recommendations surrounding MDA.

Our findings in very low- to low-transmission settings support the existing WHO Malaria Policy Advisory Committee's (MPAC) 2015 recommendations on the use of MDA in areas approaching elimination with high coverage of vector control and surveillance, good access to treatment, and limited risk of re-introduction of infection (WHO 2015a). These recommendations are currently being updated through a revised guideline development process at WHO (WHO 2020b).

Implications for research

Given the addition of several cRCTs since the publication of the previous review on this topic (Poirot 2013), this updated review provides additional information about MDA in the context of a renewed interest in MDA as a strategy to accelerate progress towards malaria elimination. Although several studies, conducted more recently in very low- to low-endemicity settings, attempted to collect data on outcomes at longer time points following MDA, the certainty of the evidence on the sustained effect of MDA was very low due to high risk of bias and large imprecision. Although of higher certainty evidence compared to trials conducted in very low- to low-endemicity settings, none of the included studies in moderate- to high-endemicity settings measured the effect of MDA after four to six months. Future studies should measure the longer-term effect of MDA and ensure that outcomes from a sufficient number and representative sample of participants are collected to obtain more precise estimates of effect. In relation to study design, cRCTs should be designed with a sufficient number of clusters to help to ensure that measured and unmeasured confounders are balanced across randomized arms, studies designed for interrupted time series analysis should include sufficient pre- and post-intervention data to adequately capture seasonal malaria trends, and co-interventions should be balanced across study arms.

ACKNOWLEDGEMENTS

The Academic Editor is Dr Joseph Okebe.

The editorial base of the Cochrane Infectious Diseases Group is funded by UK aid from the UK government for the benefit of low- and middle-income countries (project number 300342-104). The views expressed do not necessarily reflect the UK government's official policies.

We thank Marty Chaplin, Statistical Editor with the Cochrane Infectious Diseases Group (CIDG), for the statistical advice provided in this review. We also appreciate the assistance of Vittoria Lutje, CIDG Information Specialist, for running the literature search strategy.

Leslie Choi is supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed in this review do not necessarily reflect the UK government's official policies.

Jimee Hwang receives salary support from the US President's Malaria Initiative.

We acknowledge Dr Thom Eisele, Dr Alistair McLean, and Dr Ulrika Morris for sharing unpublished data from their trials and also for their permission to include these data in the review in preparation for the WHO Evidence Review Group meeting on MDA for malaria in September 2018. We also received assistance from Dr Lorenz von Seidlein regarding study clarifications.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Eisele 2020 ZMBa

Study characteristics	
Methods	Dates of study: 2014-2017 Location of study: Zambia Malaria endemicity (prevalence): Clusters stratified by ≤ 10% and > 10% parasite prevalence prior to randomization. This study includes the low transmission strata [Low]. Transmission season: January to May Malaria species: *Plasmodium falciparum* Vector species: *Anopheles funestus* (hereafter *An funestus*) and *Anopheles gambiae* (hereafter *An gambiae*) Antimalarial drug resistance context: Widespread resistance to chloroquine and sulfadoxine-pyrimethamine, but no evidence of resistance to artemisinin. Study design: Cluster-randomized trial (3 arms: MDA, fMDA, and a no fMDA or MDA control; only MDA and control arms included in this review) Statistical power: 80% power (alpha = 0.05) to detect a 50% reduction in parasite prevalence accounting for clustering, and 80% power (alpha = 0.05) to detect a 50% reduction in parasite incidence accounting for clustering For cluster-RCTs Unit of randomization: Health facility catchment area (HFCA) Adjusted analyses for clustering: Yes; however, in this review, we performed cluster adjustment of the raw data using the study-provided ICC to calculate effective sample sizes Adjustment method: Random intercept for HFCA ICC (estimated at the HFCA level in the low transmission strata): 0.06517 (in 2014); 0.01753 (in 2015); 0.01515 (in 2016); 0.04184 (in 2017) Number of clusters randomized: 20 Number of clusters analysed: 20 Number of people: 82,866 (low), 184,928 (total) Average cluster size: 9246 Features**:** Stratified by low vs high (below and above 10%) transmission strata and HFCA population size prior to randomization of clusters
Participants	Age groups included: All ages above 3 months. Children < 3 months and pregnant women in first trimester excluded from MDA with dihyrdroartemisinin piperaquine, but offered appropriate dose of antimalarial treatment in accordance with national policy if found to be RDT positive (note: testing was performed in fMDA and MDA arms, but all eligible persons were treated in the MDA arm, irrespective of RDT result).

Eisele 2020 ZMBa *(Continued)*

	Population targeted Intervention: 37,694 Comparison: 45,172
Interventions	Intervention: Drug/dose: • Ages ≥ 14 years (> 45 kg): Dihydroartemisinin plus piperaquine (120 mg/960 mg as 3 tablets) given for three days • Ages 8-13 years (25 to 40 kg): Dihydroartemisinin plus piperaquine (80 mg/640 mg as 2 tablets) given for three days • Ages 1-7 years (10 to 23 kg): Dihydroartemisinin plus piperaquine (40 mg/320 mg as 1 tablet) given for three days • Ages 3 months to 1 year (8 kg): Dihydroartemisinin plus piperaquine (20 mg/160 mg as ½ tablet) given for three days Number of rounds (timing/dates): 4 (December 2014 at the end of the dry season, February-March 2015 at the start of the rainy season, September-October 2015 during dry season, and February-March 2016 at start of the rainy season) Interval: Variable Duration implemented: 15 months Coverage (%): 79% in round 1, 63% in round 2, 76% in round 3, and 66% in round 4 Co-interventions: Baseline IRS household coverage in the preceding 12 months was 6.9%; Baseline household LLIN coverage of at least 1 net was 70.3%; Enhanced standard of care was scaled up in the study area, which consisted of RDT or microscopic confirmation of all suspected cases presenting to health facility and treating positives with artemether-lumefantrine and reactive case detection in areas with manageable case counts. Comparison: Type: No MDA and no placebo Co-interventions: Baseline IRS household coverage in the preceding 12 months was 16.9%; Baseline household LLIN coverage of at least 1 net was 75.3%; Enhanced standard of care was scaled up in the study area, which consisted of RDT or microscopic confirmation of all suspected cases presenting to health facility and treating positives with artemether-lumefantrine and reactive case detection in areas with manageable case counts.
Outcomes	Parasitaemia prevalence Measurement: Cross-sectional surveys of *P falciparum* prevalence by RDT in children ≥ 3 months and < 6 years Time points: Pre-MDA (April-May 2014), During MDA (April-May 2015), and Post-MDA 1-3 months (April-May 2016) Sample size (range): 372-545 (intervention); 361-453 (comparison) Parasitaemia incidence Measurement: Prospective cohort of persons ≥ 3 months of age to capture *P falciparum* incidence by RDT Time points: Followed through 2 months post-MDA (January 2015 - May 2016) Sample size: 410 (intervention); 326 (comparison)

Eisele 2020 ZMBa *(Continued)*

	Confirmed malaria illness incidence Measurement: Passive surveillance as measured by outpatient department confirmed malaria cases (by microscopy or RDT) reported through routine health management information systems data Time points: Pre-MDA (January-May 2013 combined with January-May 2014) and Post-MDA 1-3 months (January 2015 - May 2016) Adverse effects (AEs) (reported in both MDA and fMDA arms) A total of 687 AEs (0.24% of participants and 0.43% of treatments) were reported and one was a serious AE. The most common AEs reported were stomach pains, dry cough, and vomiting.
Notes	ClinicalTrials.gov: NCT02329301 Outcomes stratified by low and high transmission strata as specified a priori by study design (defined as above and below 10% parasite prevalence) Two out of ten low transmission strata clusters received two additional rounds of programmatic MDA (for a total of six rounds) at 10 and 12 months following the fourth round of trial MDA, however no outcomes were analysed following the first round of programmatic MDA. Abbreviations: ICC = intracluster correlation coefficient, fMDA = focal mass drug administration, IRS = indoor residual spraying, LLIN = long-lasting insecticide-treated bed net, MDA = mass drug administration, RDT = rapid diagnostic test

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Following stratification by transmission setting and health facility catchment area population size, clusters were randomly allocated to study arms using random allocation rule.
Allocation concealment (selection bias)	Low risk	Allocation was conducted by an institution.
Baseline imbalance (selection bias)	Low risk	The proportion of households that received IRS in the previous 12 months was higher at baseline in control (17%) compared to MDA (7%) clusters, but other baseline characteristics were balanced. Analysis adjusted for baseline differences.
Contamination protection	Low risk	Households within a 3 km buffer around HFCA borders were excluded from the sampling frame for parasite prevalence and incidence.
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Unclear risk	Participants were not blinded to allocation, but access to antimalarials through enhanced standard of care was comparable across arms.
Blinding of participants and personnel (performance bias) Parasitaemia incidence	Low risk	Participants were not blinded to allocation, but parasitaemia incidence was assessed through active follow-up in a prospective cohort cleared of parasitaemia at baseline.
Blinding of participants and personnel (performance bias)	Unclear risk	Participants were not blinded to allocation, which may have impacted care-seeking.

Eisele 2020 ZMBa *(Continued)*

Confirmed malaria illness incidence		
Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Unclear risk	Outcome assessment by microscopy not described.
Blinding of outcome assessment (detection bias) Parasitaemia incidence	Low risk	Blood samples for malaria testing collected from all individuals, irrespective of study arm at follow-up visits.
Blinding of outcome assessment (detection bias) Confirmed malaria illness incidence	Unclear risk	Blinding of health facility staff to allocation arm was not described.
Incomplete outcome data (attrition bias) Parasitaemia prevalence	Low risk	Simple random sample of children at baseline and follow-up.
Incomplete outcome data (attrition bias) Parasitaemia incidence	Unclear risk	"No statistically significant differences in primary outcomes or covariates between individuals" included in analysis and those lost to follow-up, "although fewer individuals were lost to follow up in high transmission areas than in low transmission areas". Based on this information provided, it is unclear whether attrition bias was a concern once lost to follow-up is stratified by baseline endemicity.
Incomplete outcome data (attrition bias) Confirmed malaria illness incidence	Low risk	Based on routine data from health management information system with established reporting from January 2011 onwards.
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes of interest were reported.
Other bias	Low risk	No other bias detected.
Recruitment bias (cluster RCT)	Low risk	No recruitment following randomization.
Loss of clusters (cluster RCT)	Low risk	No clusters were lost.
Incorrect analysis (cluster RCT)	Low risk	Mixed models were used to adjust for clustering by investigators; however, in this review, we performed cluster adjustment of the raw data using a study-provided ICC to calculate effective sample sizes
Comparability with individually randomized trials (cluster RCT)	Low risk	MDA, by definition, is applied at the population level, so this criteria is irrelevant for the intervention evaluated in this review.

Eisele 2020 ZMBb

Study characteristics	
Methods	Dates of study: 2014 to 2017

Eisele 2020 ZMBb *(Continued)*

	Location of study: Zambia Malaria endemicity (prevalence): Clusters stratified by ≤ 10% and > 10% parasite prevalence prior to randomization. This study includes the high transmission strata [High]. Transmission season: January to May Malaria species: *Plasmodium falciparum* Vector species: *An funestus* and *An gambiae* Antimalarial drug resistance context: Widespread resistance to chloroquine and sulfadoxine-pyrimethamine, but no evidence of resistance to artemisinin. Study design: Cluster-randomized trial (3 arms: MDA, fMDA, and a no fMDA or MDA control; only MDA and control arms included in this review) Statistical power: 80% power (alpha = 0.05) to detect a 50% reduction in parasite prevalence accounting for clustering, and 80% power (alpha = 0.05) to detect a 50% reduction in parasite incidence accounting for clustering For cluster RCTs Unit of randomization: Health facility catchment area (HFCA) Adjusted analyses for clustering: Yes; however, in this review, we performed cluster adjustment of the raw data using the study-provided ICC to calculate effective sample sizes Adjustment method: Random intercept for HFCA ICC (estimated at the HFCA level for the high transmission strata): 0.16142 (in 2014); 0.11301 (in 2015); 0.08066 (in 2016); 0.13479 (in 2017) Number of clusters randomized: 20 Number of clusters analysed: 20 Number of people: 102,062 (high), 184,928 (total) Average cluster size: 9246 Features**:** Stratified by low vs high (below and above 10%) transmission strata and HFCA population size prior to randomization of clusters
Participants	Age groups included: All ages above 3 months. Children < 3 months and pregnant women in first trimester excluded from MDA with dihydroartemisinin piperaquine, but offered appropriate dose of antimalarial treatment in accordance with national policy if found to be RDT positive (note: testing was performed in fMDA and MDA arms, but all eligible persons were treated in the MDA arm, irrespective of RDT result). Population targeted Intervention: 45,442 Comparison: 56,620
Interventions	Intervention: Drug/dose: • Ages ≥ 14 years (> 45 kg): Dihydroartemisinin plus piperaquine (120 mg/960 mg as 3 tablets) given for three days • Ages 8-13 years (25 to 40 kg): Dihydroartemisinin plus piperaquine (80 mg/640 mg as 2 tablets) given for three days

Eisele 2020 ZMBb *(Continued)*

- Ages 1-7 years (10 to 23 kg): Dihydroartemisinin plus piperaquine (40 mg/320 mg as 1 tablet) given for three days
- Ages 3 months to 1 year (8 kg): Dihydroartemisinin plus piperaquine (20 mg/160 mg as ½ tablet) given for three days

Number of rounds (timing/dates): 4 (December 2014 at the end of the dry season, February to March 2015 at the start of the rainy season, September to October 2015 during dry season, and February to March 2016 at start of the rainy season)

Interval: Variable

Duration implemented: 15 months

Coverage (%): 79% in round 1, 63% in round 2, 76% in round 3, and 66% in round 4

Co-interventions: Baseline IRS household coverage in the preceding 12 months was 6.9%; Baseline household LLIN coverage of at least 1 net was 70.3%; Enhanced standard of care was scaled up in the study area, which consisted of RDT or microscopic confirmation of all suspected cases presenting to health facility and treating positives with artemether-lumefantrine and reactive case detection in areas with manageable case counts.

Comparison:

Type: No MDA and no placebo

Co-interventions: Baseline IRS household coverage in the preceding 12 months was 16.9%; Baseline household LLIN coverage of at least 1 net was 75.3%; Enhanced standard of care was scaled up in the study area, which consisted of RDT or microscopic confirmation of all suspected cases presenting to health facility and treating positives with artemether-lumefantrine and reactive case detection in areas with manageable case counts.

Outcomes	Parasitaemia prevalence Measurement: Cross-sectional surveys of *P falciparum* prevalence by RDT in children ≥ 3 months and < 6 years Time points: Pre-MDA (April to May 2014), During MDA (April to May 2015), and Post-MDA 1 to 3 months (April to May 2016) Sample size (range): 348 to 490 (intervention); 332 to 505 (comparison) Parasitaemia incidence Measurement: Prospective cohort of persons ≥ 3 months of age to capture *P falciparum* incidence by RDT Time points: Followed through 2 months post-MDA (January 2015 to May 2016) Sample size: 371 (intervention); 368 (comparison) Confirmed malaria illness incidence Measurement: Passive surveillance as measured by outpatient department confirmed malaria cases (by microscopy or RDT) reported through routine health management information systems data Time points: Pre-MDA (January to May 2013 combined with January to May 2014) and Post-MDA 1 to 3 months (January to May 2015) Adverse effects (AEs) (reported in both MDA and fMDA arms) A total of 687 AEs (0.24% of participants and 0.43% of treatments) were reported and one was a serious AE. The most common AEs reported were stomach pains, dry cough, and vomiting.
Notes	ClinicalTrials.gov: NCT02329301

Eisele 2020 ZMBb *(Continued)*

Outcomes stratified by low and high transmission strata as specified a priori by study design (defined as above and below 10% parasite prevalence)

Abbreviations:

ICC = intracluster correlation coefficient, fMDA = focal mass drug administration, IRS = indoor residual spraying, LLIN = long-lasting insecticide-treated bed net, MDA = mass drug administration, RDT = rapid diagnostic test

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Following stratification by transmission setting and health facility catchment area population size, clusters were randomly allocated to study arms using random allocation rule.
Allocation concealment (selection bias)	Low risk	Allocation was conducted by an institution.
Baseline imbalance (selection bias)	Low risk	The proportion of households that received IRS in the previous 12 months was higher at baseline in control (17%) compared to MDA (7%) clusters, but other baseline characteristics were balanced. Analysis adjusted for baseline differences.
Contamination protection	Low risk	Households within a 3 km buffer around HFCA borders were excluded from the sampling frame for parasite prevalence and incidence.
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Unclear risk	Participants were not blinded to allocation, but access to antimalarials through enhanced standard of care was comparable across arms.
Blinding of participants and personnel (performance bias) Parasitaemia incidence	Low risk	Participants were not blinded to allocation, but parasitaemia incidence was assessed through active follow-up in a prospective cohort cleared of parasitaemia at baseline.
Blinding of participants and personnel (performance bias) Confirmed malaria illness incidence	Unclear risk	Participants were not blinded to allocation, which may have impacted care-seeking.
Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Unclear risk	Outcome assessment by microscopy not described.
Blinding of outcome assessment (detection bias) Parasitaemia incidence	Low risk	Blood samples for malaria testing collected from all individuals, irrespective of study arm at follow-up visits.
Blinding of outcome assessment (detection bias) Confirmed malaria illness incidence	Unclear risk	Blinding of health facility staff to allocation arm was not described.
Incomplete outcome data (attrition bias)	Low risk	Simple random sample of children at baseline and follow-up.

Eisele 2020 ZMBb *(Continued)*

Parasitaemia prevalence		
Incomplete outcome data (attrition bias) Parasitaemia incidence	Unclear risk	"No statistically significant differences in primary outcomes or covariates between individuals" included in analysis and those lost to follow-up, "although fewer individuals were lost to follow up in high transmission areas than in low transmission areas". Based on this information provided, it is unclear whether attrition bias was a concern once lost to follow-up is stratified by baseline endemicity.
Incomplete outcome data (attrition bias) Confirmed malaria illness incidence	Low risk	Based on routine data from health management information system with established reporting from January 2011 onwards.
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes of interest were reported.
Other bias	Low risk	No other bias detected.
Recruitment bias (cluster RCT)	Low risk	No recruitment following randomization.
Loss of clusters (cluster RCT)	Low risk	No clusters were lost.
Incorrect analysis (cluster RCT)	Low risk	Mixed models were used to adjust for clustering by investigators. However, in this review, we performed cluster adjustment of the raw data using a study-provided ICC to calculate effective sample sizes
Comparability with individually randomized trials (cluster RCT)	Low risk	MDA, by definition, is applied at the population level, so this criteria is irrelevant for the intervention evaluated in this review.

Escudie 1962 BFA

Study characteristics	
Methods	Dates of study: 1960 to 1961 Location of study: Burkina Faso Malaria endemicity (prevalence): 56.1% prevalence in children 0 to 10 years at baseline in control [High] Transmission season: June to December Malaria species: *P falciparum, P ovale, P malariae* Vector species: *An gambiae, An funestus, Anopheles nili* (hereafter *An nili*) Antimalarial drug resistance context: Not described Study design: Controlled before-and-after study (6 arm study: CQ+PQ or AQ+PQ every 4 weeks, CQ+PQ or AQ+PQ every 2 weeks, CQ+PQ or AQ+PQ every 4 weeks with IRS, CQ+PQ or AQ+PQ every 2 weeks with IRS, IRS only, non-IRS control; the 3 arms with IRS are excluded in this review since the population size and number of villages for the IRS only control were not reported) Statistical power: Not described
Participants	Age groups included: All ages

Escudie 1962 BFA *(Continued)*

	Population targeted Intervention (CQ+PQ or AQ+PQ every 4 weeks): 1890 in 5 villages Intervention (CQ+PQ or AQ+PQ every 2 weeks): 2560 in 3 villages Comparison (non-IRS control): 6 villages, population size not described
Interventions	Drug/dose (*for all intervention arms receiving MDA*): • Ages ≥10 years: Chloroquine-primaquine (600 mg/15 mg) or amodiaquine-primaquine (600 mg/15 mg) as a single dose • Ages 5 to 9 years: Chloroquine-primaquine (400 mg/10 mg) or amodiaquine-primaquine (400 mg/10 mg) as a single dose • Ages 0 to 4 years: Chloroquine-primaquine (200 mg/5 mg) or amodiaquine-primaquine (200 mg/5 mg) as a single dose Intervention (CQ+PQ or AQ-PQ every 4 weeks, "low frequency"): Number of rounds (timing/dates): 8 (June, July, August, September, October, November, December 1960) Interval: Every 28 days Duration implemented: 7 months (June to December 1960) Coverage (%): 75% to 91% per round Co-interventions: None Intervention (CQ+PQ or AQ+PQ every 2 weeks, "high frequency"): Number of rounds (timing/dates): 15 (June to December 1960) Interval: Every 14 days Duration implemented: 7 months (June to December 1960) Coverage (%): 84% to 97% per round Co-interventions: None Comparison (non-IRS control): Type: No MDA and no placebo Co-interventions: None
Outcomes	Parasitaemia prevalence Measurement: Cross-sectional surveys in all children ages 2 to 9 years every 4 months (microscopy) Time points: Pre-MDA (June 1960), During-MDA (October 1960), and at 3 months post-MDA (March 1961) Sample size (range): 274 to 348 (intervention: CQ+PQ or AQ+PQ every 4 weeks); 390 to 467 (intervention: CQ+PQ or AQ+PQ every 2 weeks); 217 to 691 (comparison: non-IRS control) Gametocytaemia prevalence Measurement: Cross-sectional surveys in all children ages 2 to 9 years every 4 months (microscopy) Time points: Pre-MDA (June 1960), During MDA (October 1960), and at 3 months post-MDA (March 1961) Sample size (range): 274 to 348 (intervention: CQ+PQ or AQ+PQ every 4 weeks); 390 to 467 (intervention: CQ+PQ or AQ+PQ every 2 weeks); 217 to 691 (comparison: non-IRS control)

Escudie 1962 BFA *(Continued)*

Notes	Samples for outcome assessment in June 1960 were collected prior to MDA distribution; therefore the survey in June 1960 was considered as "pre-MDA". Abbreviations: AQ = amodiaquine, CQ = chloroquine, IRS = indoor residual spraying, MDA = mass drug administration, PQ = primaquine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Assignment to intervention or control was not randomized although drug assignment within intervention was randomized in arms with more than one drug.
Allocation concealment (selection bias)	High risk	Non-randomized controlled study (controlled before-and-after study)
Baseline imbalance (selection bias)	Unclear risk	Baseline characteristics were not described.
Contamination protection	Unclear risk	No information is provided to assess the risk of contamination.
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Unclear risk	Participants were not blinded to allocation.
Blinding of outcome assessment (detection bias) Parasitaemia prevalence	High risk	Microscopists were not blinded to study arm.
Incomplete outcome data (attrition bias) Parasitaemia prevalence	Low risk	Outcomes were assessed in all children ages 2 to 9 years in the study area.
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes were reported.
Other bias	Low risk	No other bias detected.

Landier 2017 MMRa

Study characteristics

Methods	Dates of study: 2013 to 2015 Location of study: Kayin (Karen) state, Myanmar Malaria endemicity (prevalence): *Plasmodium falciparum* prevalence 11.0% in MDA villages and 5.4% in control villages at baseline by ultrasensitive polymerase chain reaction (uPCR); *P vivax* prevalence 18.9% in MDA villages and 17.5% in control villages at baseline by uPCR [Low - estimated *P falciparum* slide prevalence 1.2%] Transmission season: June to October

Landier 2017 MMRa *(Continued)*

	Malaria species: *P falciparum* and *P vivax* Vector species: *Anopheles minimus s.l.*, *An maculatus s.l.*, and *An dirus s.l.* Antimalarial drug resistance context: "Area where artemisinin resistance is firmly established" Statistical power: For the multi-country trial (Landier 2017 MMRa; Tripura 2018 KHM; Pongvongsa 2018 LAO; von Seidlein 2019 VNM), 80% power (alpha = 0.05) to detect a 95% reduction in parasite prevalence from a baseline prevalence of 10% For cluster RCTs Unit of randomization: Village Adjusted analyses for clustering: Yes; however, in this review, we performed cluster adjustment of the raw data using ICC values estimated from the study data to calculate effective sample sizes Adjustment method: Generalized estimating equations ICC: 0.03512 (*P falciparum* outcomes at baseline before MDA), 0 (*P falciparum* outcomes at post-MDA 1 to 3, 4 to 6, and 7 to 12 months); 0 (*P vivax* outcomes at baseline before MDA, post-MDA 4 to 6 months and 7 to 12 months), 0.000798 (*P vivax* outcomes at post-MDA 1 to 3 months) Number of clusters randomized: 4 Number of clusters analysed: 4 Number of people: 3238 Average cluster size: 810 Features: Two village pairs (4 villages) were established by geographical proximity, population size, and parasite prevalence. Within each pair, one village was randomly selected to receive early MDA, while the other village received deferred MDA
Participants	Age groups included: All ages ≥ 6 months. All pregnant women in their first trimester were excluded from MDA and pregnant women in any trimester were excluded from primaquine. Population targeted Intervention: 1434 Comparison: 1804
Interventions	Intervention: Drug/dose: Dihydroartemisinin (7 mg/kg) plus piperaquine (55 mg/kg) administered once a day for 3 days with a single dose of primaquine (0.25 mg/kg) Number of rounds (timing/dates): 3 (May, June, July 2013 or June, July, August 2013) Interval: Every 1 month Duration implemented: 3 months Coverage (%): 66% in round 1, 56% in round 2, and 65% in round 3 Co-interventions: LLITNs, uninterrupted access to diagnosis and treatment in study villages Comparison: Type: Deferred MDA administered in control villages in January, February, and March 2014 Co-interventions: LLITNs, uninterrupted access to diagnosis and treatment in study villages
Outcomes	Parasitaemia prevalence (*P falciparum* and *P vivax*)

Landier 2017 MMRa *(Continued)*

	Measurement: Cross-sectional surveys in all ages every 3 months by uPCR; all individuals present at the time of the survey in the study villages were sampled. Time points: Pre-MDA (May 2013) and at 1 (Aug 2013), 4 (Nov 2013), and 7 (Jan 2014) months post-MDA Sample size (range): 419 to 689 (intervention) and 750 to 848 (control) Confirmed malaria illness incidence (*P falciparum* and *P vivax*) Measurement: Passive case detection at malaria posts for measured or self-reported fever (≥ 37.5C) and confirmed *P falciparum* or *P vivax* infection by RDT or microscopy. Time points: 7 (May 2013 to January 2014) months post-MDA Adverse effects (AEs) AEs monitored by active surveillance through structured interviews on the second, third, and seventh day of MDA treatment course and by passive surveillance via reporting to medical assistants in mobile clinics located in study villages during MDA rounds. From interviews, no serious AEs were reported. The most common AEs were dizziness (n=192) and pruritus (n=17). There were three reports of black urine, from glucose 6-phosphate dehydrogenase (G6PD) deficient (report prior to PQ), G6PD-normal (48 hours after PQ), and G6PD-heterozygous individuals. Among participants reporting passively to mobile clinics, there were 23 serious AEs and 15 deaths that were not drug-related, 9 moderate AEs of which 4 were possibly related to the study drug, and 191 mild AEs of which 1 was highly likely related and 7 were possibly related to the study drug.
Notes	One of four sites from a multi-country trial in Southeast Asia (ClinicalTrials.gov: NCT01872702) Abbreviations: ICC = intracluster correlation coefficient, LLITN = long-lasting insecticide-treated bed net, MDA = mass drug administration, uPCR = ultrasensitive polymerase chain reaction

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation was based on computer-generated random numbers provided by the trial statistician"
Allocation concealment (selection bias)	Low risk	Allocation was conducted by an institution.
Baseline imbalance (selection bias)	High risk	Small number of clusters (4 villages) randomized.
Contamination protection	High risk	Intervention and control clusters were pair-matched by geographical proximity, which likely led to a high risk of contamination due to population movement.
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Unclear risk	Participants were not blinded to allocation.
Blinding of participants and personnel (performance bias) Confirmed malaria illness incidence	Unclear risk	Participants were not blinded to allocation, which may have impacted care-seeking.

Landier 2017 MMRa *(Continued)*

Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Low risk	Laboratory staff performing PCR were unaware of the study arm allocation of samples.
Blinding of outcome assessment (detection bias) Confirmed malaria illness incidence	Unclear risk	Unclear if the health facility staff performing malaria testing were aware of which study arm participants were assigned to.
Incomplete outcome data (attrition bias) Parasitaemia prevalence	Low risk	Parasitaemia surveys were performed in all individuals aged six months or older residing in the study villages.
Incomplete outcome data (attrition bias) Confirmed malaria illness incidence	Low risk	Data collected at malaria health posts with dedicated study staff.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Low risk	No other bias detected.
Recruitment bias (cluster RCT)	Low risk	No recruitment following randomization.
Loss of clusters (cluster RCT)	Low risk	No clusters were lost.
Incorrect analysis (cluster RCT)	Low risk	Although no adjustment for clustering was performed by investigators, in this review, we performed cluster adjustment of the raw data using a study-provided ICC to calculate effective sample sizes.
Comparability with individually randomized trials (cluster RCT)	Low risk	MDA, by definition, is applied at the population level, so this criteria is irrelevant for the intervention evaluated in this review.

McLean 2021 MMR

Study characteristics	
Methods	Dates of study: 2014 to 2017 Location of study: Myanmar Malaria endemicity (prevalence): *P falciparum* < 20 cases per 1000 population per year and *P falciparum/P vivax* 2.7% at baseline by rapid diagnostic test (RDT) [Low] Transmission season: June to August Malaria species: *P falciparum, P vivax, P ovale, P malariae* Vector species: Not described Antimalarial drug resistance context: Artemisinin resistance reported; Kelch 13 in 57% (54/94) of samples at baseline. Study design: Cluster-randomized trial

McLean 2021 MMR *(Continued)*

	Statistical power: Not statistically powered for outcomes For cluster RCTs Unit of randomization: Village Adjusted analyses for clustering: No; however, in this review, we performed cluster adjustment of the raw data using the study-provided ICC to calculate effective sample sizes Adjustment method: Not applicable ICC: 0.056 Number of clusters randomized: 16 Number of clusters analysed: 16 Number of people: 8721 Average cluster size: 554 Features**:** Intervention and control clusters were pair-matched based on *P falciparum* prevalence (+/- 8%), geographical proximity and distance to main road
Participants	Age groups included: All ages ≥ 1 year and pregnant women in first trimester excluded. No primaquine administered to pregnant women in other trimesters. Population targeted Intervention: 5481 Comparison: 3240
Interventions	Intervention: Drug/dose: Dihydroartemisinin (7 mg/kg) plus piperaquine (55 mg/kg) administered once a day for three days with a single dose of primaquine (0.25 mg/kg) Number of rounds (timing/dates): 3 (March, April, May 2015, during dry season) Interval: Every 1 month Duration implemented: 3 months Coverage (%): 90% completed at least one round; Round 1: 86%, Round 2: 86%, Round 3: 88% Co-interventions: LLITNs distributed at the start of study; routine malaria control by village health workers. Comparison: Type: No MDA and no placebo Co-interventions: LLITNs distributed at the start of study; routine malaria control by village health workers.
Outcomes	Parasitaemia prevalence (*P falciparum* and *P vivax*) Measurement: Cross-sectional surveys of *P falciparum* and *P vivax* prevalence by ultrasensitive PCR in adults 18 to 55 years; up to 2 participants sampled from randomly selected households at baseline and the same participants were sampled at follow-up surveys. Time points: Pre-MDA (January 2015) and at < 1 (3-8 June 2015), 3 (24-29 August 2015), 8 (15-26 January 2016), 13 (7-14 June 2016), 19 (2-19 December 2016), 25 (13-18 June 2017), and 31 (1-13 December 2017) months post-MDA

McLean 2021 MMR *(Continued)*

	Sample size (range): 620 to 1106 (intervention); 412 to 543 (comparison) Adverse effects (AEs) A total of 151 (1.4% of all doses, 3.6% of treated individuals) adverse effects reported: 12 (7.9%) not related to drug, 40 (26.5%) unlikely related to drug, 81 (53.6%) possibly related to drug, and 18 (11.9%) probably related to drug. 6 serious AEs: 1 possibly related, 5 unrelated
Notes	Prior to randomization, villages selected based on baseline PCR prevalence survey conducted in 58 villages in study area. Selected villages: (1) had a population between 75 to 1200 people (excluded 15 villages), and (2) were a hotspot village defined as > 30% parasite prevalence (all types) or > 10% *P falciparum* prevalence by PCR (excluded 27 non-hotspot villages) Abbreviations: ICC = intracluster correlation coefficient, LLITN = long-lasting insecticide-treated bed net, MDA = mass drug administration, PCR = polymerase chain reaction

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomization of clusters was performed by flipping a coin.
Allocation concealment (selection bias)	Low risk	Allocation was conducted by an institution.
Baseline imbalance (selection bias)	Low risk	Baseline malaria risk and co-intervention coverage were similar across intervention arms.
Contamination protection	High risk	Intervention and control clusters were pair-matched by geographical proximity, which likely led to a high risk of contamination due to population movement.
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Unclear risk	Participants were not blinded to allocation.
Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Low risk	Laboratory staff performing PCR were unaware of the study arm allocation of samples.
Incomplete outcome data (attrition bias) Parasitaemia prevalence	High risk	Outcome data was assessed only in participants aged 18 to 55 years. Up to 2 participants from randomly selected households at baseline were surveyed at each time point and alternative participants (similarly matched by gender, age, and occupation) were surveyed if selected participants were unavailable during follow-up. Substantial variation in denominators suggesting different participants sampled (non-randomly) during each survey.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Low risk	No other bias detected.
Recruitment bias (cluster RCT)	Low risk	No recruitment following randomization.

McLean 2021 MMR *(Continued)*

Loss of clusters (cluster RCT)	Low risk	No clusters were lost.
Incorrect analysis (cluster RCT)	Low risk	Although no adjustment for clustering was performed by investigators, in this review, we performed cluster adjustment of the raw data using a study-provided ICC to calculate effective sample sizes
Comparability with individually randomized trials (cluster RCT)	Low risk	MDA, by definition, is applied at the population level, so this criteria is irrelevant for the intervention evaluated in this review.

Molineaux 1980 NGA

Study characteristics	
Methods	Dates of study: 1970 to 1976 (included data from 1970 to 1973 in this review) Location of study: Nigeria Malaria endemicity (prevalence): 46% in all ages [High] Transmission season: April to October Malaria species: *Plasmodium falciparum, P malariae, P ovale* Vector species: *Anopheles gambiae, An funestus* Antimalarial drug resistance context: Not described Study design: Controlled before-and-after study (4 arms: no intervention, IRS only, low frequency MDA+IRS, and high frequency MDA+IRS; IRS only, low frequency+IRS, and high frequency+IRS arms included in this review) Statistical power: Consideration of statistical power was mentioned, but the parameters were not described.
Participants	Age groups included: All ages, but infants not included in MDA until their first malaria episode. Population targeted Intervention (low frequency MDA+IRS): 14,129 Intervention (high frequency MDA+IRS): 1810 Comparison (IRS only): 32,828
Interventions	Drug/dose (*for all intervention arms receiving MDA*): • Ages ≥10 years: Sulfalene-pyrimethamine (500 mg/25 mg as 1 tablet) as a single dose • Ages 5 to 9 years: Sulfalene-pyrimethamine (250 mg/12.5 mg as ½ tablet) as a single dose • Ages 1 to 4 years: Sulfalene-pyrimethamine (230 mg/12.0 mg as 30 drops syrup) as a single dose • Ages 6 to 11 months: Sulfalene-pyrimethamine (150 mg/7.5 mg as 20 drops syrup) as a single dose • Ages < 6 months: Sulfalene-pyrimethamine (90 mg/4.5 mg as 12 drops syrup) as a single dose Intervention (Low frequency MDA+IRS group): Number of rounds (timing/dates): 9 (April 1972 - October 1973) Interval: Every 10 weeks

Molineaux 1980 NGA *(Continued)*

	Duration implemented: 18 months Coverage (%): 73% to 92% Co-interventions: IRS using propoxur 3 to 4 rounds per year Intervention (High frequency MDA+IRS group): Number of rounds (timing/dates): 23 (April 1972 - October 1973) Interval: Every two weeks during the wet season (May-October 1972 and May-October 1973) and every 10 weeks during the dry season (December 1972, March 1973, and October-November 1973) Duration implemented: 18 months Coverage (%): 72% to 91% Co-interventions: IRS using propoxur 3 to 4 rounds per year Comparison (IRS only) Type: No MDA and no placebo Co-interventions: IRS using propoxur 3 to 4 rounds per year
Outcomes	Parasitaemia prevalence Measurement: Cross-sectional surveys in selected village clusters (all ages) (microscopy) Time points: Pre-MDA (8 surveys), During MDA (8 surveys) Sample size (range): 1257 to 2099 (intervention: low frequency MDA+IRS); 1486 to 1679 (intervention: high frequency MDA+IRS); 1104 to 1171 (comparison: IRS only) Gametocytaemia prevalence Measurement: Cross- sectional surveys in selected villages clusters (all ages) (microscopy) Time points: Pre-MDA (8 surveys), During MDA (8 surveys) Sample size (range): 1257 to 2099 (intervention: low frequency MDA+IRS); 1486 to 1679 (intervention: high frequency MDA+IRS); 1104 to 1171 (comparison: IRS only)
Notes	Abbreviations: IRS = indoor residual spraying, MDA = mass drug administration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomized controlled study
Allocation concealment (selection bias)	High risk	Non-randomized controlled study
Baseline imbalance (selection bias)	Unclear risk	Similar malaria characteristics between groups at baseline, but unclear if other demographic factors were balanced.
Contamination protection	Low risk	Evaluation villages in both arms were surrounded by similarly treated buffer zones to mitigate possible contamination due to migration.

Molineaux 1980 NGA *(Continued)*

Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Unclear risk	Participants were not blinded to allocation, but there was limited access to antimalarials outside of MDA.
Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Low risk	Microscopists were blinded to study arm allocation through the use of a numeric identification code. Slides were read independently by two microscopists.
Incomplete outcome data (attrition bias) Parasitaemia prevalence	Low risk	Parasitaemia surveys were performed in all ages in selected study villages.
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes were reported.
Other bias	Low risk	No other bias detected.
Comparability with individually randomized trials (cluster RCT)	Low risk	MDA, by definition, is applied at the population level, so this criteria is irrelevant for the intervention evaluated in this review.

Morris 2018 TZA

Study characteristics	
Methods	Dates of study: 2016 to 2017 Location of study: Zanzibar (three districts in Unguja, Central, South, and West districts) Malaria endemicity (prevalence): 2.5% (range between clusters 0.7-4.5%) in control group at baseline by quantitative polymerase chain reaction (qPCR) [Very low - estimated *Plasmodium falciparum* slide prevalence 0.2%] Transmission season: April to August Malaria species: *P falciparum* (predominant), *P malaria, P ovale,* and *P vivax* (rare) Vector species: *Anopheles gambiae s.l.*, *An arabiensis, An merus* and *An funestus* Antimalarial drug resistance context: No evidence of resistance to first line treatment artesunate-amodiaquine, with 100% efficacy in clinical trial conducted in 2017. Study design: Cluster-randomized trial (allocation of shehias, or administrative wards, within the trial arms conducted using computerized block randomization based on shehia population size) Statistical power: Assuming a coefficient of variation of 0.35 and baseline malaria incidence of 12 per 1000, there was 80% power (alpha = 0.05) to detect a 50% reduction in confirmed malaria illness incidence in the intervention group. Study was not powered for parasitaemia prevalence. For cluster-RCTs Unit of randomization: Shehia (hotspot *shehia*, defined as a shehia with an with an annual parasite index of greater than 8 confirmed malaria cases per 1000 population) Adjusted analyses for clustering: Yes; however, in this review, we performed cluster adjustment of the raw data using an estimated ICC to calculate effective sample sizes Adjustment method: Generalized estimating equations

Morris 2018 TZA *(Continued)*

	ICC: Not determined Number of clusters randomized: 16 Number of clusters analysed: 16 Number of people: 23,251 Average cluster size: 1453
Participants	Age groups included: All ages > 6 months. Pregnant women in their first trimester and anyone on concurrent antimalarial treatment at the time of MDA were excluded from MDA with dihydroartemisinin piperaquine. Pregnant women (all trimesters) or women breast feeding infants < 6 months were excluded from receiving low dose primaquine. Population targeted Intervention: 10,944 Comparison: 12,307
Interventions	Intervention: Drug/dose: • Ages ≥ 14 years (> 40 kg): Dihydroartemisinin plus piperaquine (120 mg/960 mg as 3 tablets) given for three days with a single dose of primaquine (15 mg as 2 tablets) • Ages 8 to 13 years (21 to 40 kg): Dihydroartemisinin plus piperaquine (80 mg/640 mg as 2 tablets) given for three days with a single dose of primaquine (7.5 mg as 1 tablet) • Ages 2 to 7 years (10 to 20 kg): Dihydroartemisinin plus piperaquine (40 mg/320 mg as 1 tablet) given for three days with a single dose of primaquine (4 mg as 4 cc solution) • Ages 6 months to 1 year (5 to 9.9 kg): Dihydroartemisinin plus piperaquine (20 mg/160 mg as ½ tablet) given for three days with a single dose of primaquine (2 mg as 2 cc solution) Number of rounds (timing/dates): 2 (30 April to 7 May 2016 at the start of high transmission season, and 28 May to 4 June 4 2016 during the peak of high transmission season) Interval: Every 4 weeks Duration implemented: 6 weeks Coverage (%): 91% in round 1 and 88% in round 2 (dihydroartemisinin piperaquine (DHAp)); 86% in round 1 and 80% in round 2 (low dose primaquine). Co-interventions: IRS (single round in March 2016 with pirimiphos methyl; 85% of households sprayed at baseline) and ITNs (universal distribution campaign in 2015-2016; self-reported ITN use among all ages 75% at baseline). Comparison: Type: No MDA and no placebo Co-interventions: IRS (single round in March 2016 with pirimiphos methyl; 85% of households sprayed at baseline) and ITNs (universal distribution campaign in 2015-2016; self-reported ITN use among all ages 71% at baseline).
Outcomes	Parasitaemia prevalence Measurement: Cross-sectional surveys of *P falciparum* (and *Plasmodium*) prevalence by two-step pooled 18s-quantitative PCR (qPCR) with first step screening by cytochrome b (Cytb) qPCR and 18s-qPCR in participants of all ages from households randomly selected (50% of households randomly selected at each time point).

Morris 2018 TZA *(Continued)*

Time points: During MDA (30 April to 7 May 2016) and 3 months post-MDA (30 August to 9 September 2016)

Sample size (range): 4402 to 4896 (intervention); 3875 to 4905 (comparison)

Confirmed malaria illness incidence

Measurement: Passive case detection at health facilities via malaria case notification system which captures confirmed malaria infections in real time.

Time points: Pre-MDA (May - November 2015) and at 2 (May-August 2016), 5 (May-November 2016), 10 (May 2016 - April 2017), and 14 (May 2016 - August 2017) months post-MDA

Adverse effects (AEs)

Among participants receiving MDA, 11.6% and 3.2% reported at least one AE after the first and second round, respectively. An additional 85 and 29 AE reports were passively identified at health facilities after rounds 1 and 2, respectively. The most commonly reported AEs were: nausea and vomiting (33.1%), stomach pain and diarrhoea (18.9%), and dizziness, headache, and fatigue (23.5%). Across all AEs, 44.1% were considered mild, 52.0% as moderate, and 0.5% as severe. There were no MDA-associated deaths or other serious AEs.

Notes

ClinicalTrials.gov: NCT02721186

The timing of the first parasitaemia survey coincided with the first round of MDA and continued for 10 days following the end of the first MDA distribution; therefore, the first parasitaemia survey was considered as "during MDA".

Abbreviations:

ICC = intracluster correlation coefficient, IRS = indoor residual spraying, ITN = insecticide-treated bed net, MDA = mass drug administration, PCR = polymerase chain reaction

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation of shehias to trial arms was conducted using computerized block randomization based on shehia population size.
Allocation concealment (selection bias)	Low risk	Allocation was conducted by an institution.
Baseline imbalance (selection bias)	High risk	Baseline malaria prevalence was higher in control (2.5%) compared to intervention (0.8%) shehias. Baseline vector control interventions and demographic characteristics were balanced across arms.
Contamination protection	Unclear risk	Distance between hotspot shehias was not described and there was no mention of buffer zones.
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Unclear risk	Allocation concealment was not described.
Blinding of participants and personnel (performance bias) Confirmed malaria illness incidence	Unclear risk	Participants were not blinded to allocation, which may have impacted care-seeking.

Morris 2018 TZA *(Continued)*

Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Low risk	Laboratory staff performing PCR were unaware of the study arm allocation of samples.
Blinding of outcome assessment (detection bias) Confirmed malaria illness incidence	Unclear risk	Unclear if the health facility staff performing malaria testing were aware of which study arm participants were assigned to.
Incomplete outcome data (attrition bias) Parasitaemia prevalence	Low risk	Outcomes were assessed in participants of all ages residing in randomly sampled households. 50% of households randomly selected at each survey
Incomplete outcome data (attrition bias) Confirmed malaria illness incidence	Low risk	Malaria cases reported in real time at health facilities through the malaria case notification system (MCN).
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	No other bias detected.
Recruitment bias (cluster RCT)	Low risk	No recruitment following randomization.
Loss of clusters (cluster RCT)	Low risk	No clusters were lost.
Incorrect analysis (cluster RCT)	Low risk	Clustering accounted for using generalized estimating equations; however, in this review, we performed cluster adjustment of the raw data using an estimated ICC to calculate effective sample sizes.
Comparability with individually randomized trials (cluster RCT)	Low risk	MDA, by definition, is applied at the population level, so this criteria is irrelevant for the intervention evaluated in this review.

Pongvongsa 2018 LAO

Study characteristics	
Methods	Dates of study: 2016 to 2017 Location of study: Savannakhet Province, Laos Malaria endemicity (prevalence): *Plasmodium falciparum* prevalence 4.8% in MDA villages and 17.5% in control villages at baseline by ultrasensitive polymerase chain reaction (uPCR); *P vivax* prevalence 2.3% in MDA villages and 14.7% in control villages at baseline by uPCR [Low - estimated *P falciparum* slide prevalence 5.3%] Transmission season: May to October Malaria species: *P falciparum* and *P vivax* Vector species: Not described Antimalarial drug resistance context: Not described

Pongvongsa 2018 LAO *(Continued)*

	Statistical power: For the multi-country trial (Landier 2017 MMRa; Tripura 2018 KHM; Pongvongsa 2018 LAO; von Seidlein 2019 VNM), 80% power (alpha = 0.05) to detect a 95% reduction in parasite prevalence from a baseline prevalence of 10% For cluster-RCTs Unit of randomization: Village Adjusted analyses for clustering: Yes; however, in this review, we performed cluster adjustment of the raw data using ICC values estimated from the study data to calculate effective sample sizes Adjustment method: Generalized estimating equations ICC: 0.1416 (*P falciparum* outcomes at baseline before MDA), 0.0944 (*P falciparum* outcomes at post-MDA 1-3 months), 0.05406 (*P falciparum* outcomes at post-MDA 4-6 months), 0.04319 (*P falciparum* outcomes at post-MDA 7-12 months); 0.1438 (*P vivax* outcomes at baseline before MDA), 0.0913 (*P vivax* outcomes at post-MDA 1-3 months), 0.02963 (*P vivax* outcomes at post-MDA 4-6 months), 0.01452 (*P vivax* outcomes at post-MDA 7-12 months) Number of clusters randomized: 4 Number of clusters analysed: 4 Number of people: 1889 Average cluster size: 472 Features: Two village pairs (4 villages) were established by geographical proximity, population size and parasite prevalence. Within each pair, one village was randomly selected to receive early MDA, while the other village received deferred MDA.
Participants	Age groups included: All ages ≥ 6 months. All pregnant women were excluded from MDA. Population targeted Intervention: 1006 Comparison: 883
Interventions	Intervention: Drug/dose: Dihydroartemisinin (7 mg/kg) plus piperaquine (55 mg/kg) administered once a day for 3 days with a single dose of primaquine (0.25 mg/kg). Number of rounds (timing/dates): 3 (April, June, and July 2016) Interval: Every 1 month Duration implemented: 3 months Coverage (%): 81% in round 1, 80% in round 2, and 82% in round 3 Co-interventions: LLITNs, uninterrupted access to diagnosis and treatment in study villages Comparison: Type: Deferred MDA administered in control villages in April, June, and July 2017 Co-interventions: LLITNs, uninterrupted access to diagnosis and treatment in study villages
Outcomes	Parasitaemia prevalence (*P falciparum* and *P vivax*) Measurement: Cross-sectional surveys in all ages every 3 months by uPCR; all individuals present at the time of the survey in the study villages were sampled.

Pongvongsa 2018 LAO *(Continued)*

	Time points: Pre-MDA (April 2016, just prior to first MDA round) and at 1 (August 2016), 4 (late October 2016), 7 (January 2017), and 10* (April 2017) months post-MDA Sample size (range): 745 to 859 (intervention) and 618 to 802 (control) Adverse effects (AEs) AEs were assessed by home visits from village volunteers and clinicians following a report of an AE. Following MDA rounds, 282 individuals reported 295 AEs: 291 (99%) were mild, 3 (1%) were moderate, and 1 (< 1%) was severe (case of pneumonia requiring hospitalization). The most common AEs were common cold (17%), gastritis (8%), diarrhoea (8%), vomiting (7%), dizziness (6%), pruritus (6%), watery stool (4%), nausea (3%), and headache (3%).
Notes	One of four sites from a multi-country trial in Southeast Asia (ClinicalTrials.gov: NCT01872702) Abbreviations: ICC = intracluster correlation coefficient, LLITN = long-lasting insecticide-treated bed net, MDA = mass drug administration, uPCR = ultrasensitive polymerase chain reaction * Data from this survey was analysed as post-MDA 7 to 12 month time period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation was based on computer-generated random numbers provided by the trial statistician"
Allocation concealment (selection bias)	Low risk	Allocation was conducted by an institution.
Baseline imbalance (selection bias)	High risk	Baseline prevalence of both *P falciparum* and *P vivax* substantially higher in control compared to intervention villages. Small number of clusters (4 villages) randomized.
Contamination protection	High risk	Intervention and control clusters were pair-matched by geographical proximity, which likely led to a high risk of contamination due to population movement.
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Unclear risk	Participants were not blinded to allocation.
Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Low risk	Laboratory staff performing PCR were unaware of the study arm allocation of samples.
Incomplete outcome data (attrition bias) Parasitaemia prevalence	Low risk	Parasitaemia surveys were performed in all individuals aged six months or older residing in the study villages.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Low risk	No other bias detected.
Recruitment bias (cluster RCT)	Low risk	No recruitment following randomization.

Pongvongsa 2018 LAO *(Continued)*

Loss of clusters (cluster RCT)	Low risk	No clusters were lost.
Incorrect analysis (cluster RCT)	Low risk	Although no adjustment for clustering was performed by investigators, in this review, we performed cluster adjustment of the raw data using a study-provided ICC to calculate effective sample sizes
Comparability with individually randomized trials (cluster RCT)	Low risk	MDA, by definition, is applied at the population level, so this criteria is irrelevant for the intervention evaluated in this review.

Roberts 1964 KEN

Study characteristics	
Methods	Dates of study: 1953 to 1954 Location of study: Kenya Malaria endemicity (prevalence): 37.6% (control) or 23% (intervention) at baseline in all ages by microscopy [Moderate] Transmission season: May to July Malaria species: *P falciparum, P malariae* Vector species: *Anopheles gambiae, An funestus* Antimalarial drug resistance context: Not described Study design: Controlled before-and-after study Statistical power: Not described
Participants	Age groups included: All ages Population targeted Intervention (mean): 101,000 Comparison (mean): population not specified, but control area spans an entire district (Tiriki)
Interventions	Intervention: Drug/dose: • Ages > 12 years: Pyrimethamine (50 mg as 2 tablets) as a single dose • Ages 1 to 12 years: Pyrimethamine (25 mg as 1 tablet) as a single dose • Ages < 1 years: Pyrimethamine (12.5 mg as ½ tablet) as a single dose Number of rounds (timing/dates): 2 (May 1953 and May 1954, just prior to the start of the rainy season) Interval: Every 1 year Duration implemented: 13 months Coverage (%): 95% in round 1 and 93% in round 2 Co-interventions: None Comparison:

Roberts 1964 KEN *(Continued)*

	Type: No MDA and no placebo Co-interventions: None
Outcomes	Parasitaemia prevalence Measurement: Cross-sectional surveys conducted in a sub-sample of study population (see notes); 14 surveys in total (microscopy) Time points: Pre-MDA, During MDA, and at 1, 2, 3, 4, 6, and 7 months post-MDA Sample size (range): 300 to 2100 (intervention); 300 to 2100 (comparison)
Notes	Roberts 1964 KEN (1956 article) states: "Three hundred blood films were taken at each of the two places from people in the following age groups: 0-10 years (100 films), 11-20 years (100 films), 21 years and over (100 films)". Therefore, we assumed that the total participants examined at each survey was 300 in intervention and 300 in comparison groups in order to calculate number of events (malaria cases) for parasitaemia prevalence. We also assumed that samples at each survey time point were independent and aggregated data within follow-up time point categories. Abbreviations: MDA = mass drug administration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomized controlled study
Allocation concealment (selection bias)	High risk	Non-randomized controlled study
Baseline imbalance (selection bias)	High risk	Baseline parasitaemia in the control group was much higher than the intervention group. No other baseline characteristics are described.
Contamination protection	High risk	The control area was located 10 miles from the centre of the intervention area with several major roads connecting both areas. No buffer zone.
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Unclear risk	Participants were not blinded to allocation and unclear if this affected outcomes since the sampling methodology at each parasitaemia survey was not described.
Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Unclear risk	Examination of slides not described. Unclear if multiple reads were taken or if microscopists were blinded.
Incomplete outcome data (attrition bias) Parasitaemia prevalence	Low risk	Data from three hundred slides at each survey sampled in 3 age groups are presented as described.
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes were reported.
Other bias	Low risk	No other bias detected.

Shekalaghe 2011 TZA

Study characteristics	
Methods	Dates of study: 2008 Location of study: Tanzania Malaria endemicity (prevalence): 0% in all ages at baseline by microscopy [Very low] Transmission season: March to May, October to November Malaria species: *Plasmodium falciparum* Vector species: Not described Antimalarial drug resistance context: Not described Study design: Cluster-randomized trial Statistical power: 80% power (alpha = 0.05) to detect a 10-fold lower malaria incidence in the intervention arm vs control (assuming 0.5 episodes per child) accounting for repeated measures and clustering. For cluster-RCTs Unit of randomization: Geographical clusters of households Adjusted analyses for clustering: Yes; however, in this review, we performed cluster adjustment of the raw data using an estimated ICC to calculate effective sample sizes Adjustment method: Generalized estimating equations ICC: Not described Number of clusters randomized: 16 Number of clusters analysed: 16 Number of people: 3457 Average cluster size: 216
Participants	Age groups included: Ages > 1 year, but individuals who had received a full dose of artemisinin-based combination therapy in the two weeks before the intervention were excluded. Pregnant women and individuals who were anaemic did not receive primaquine. Population targeted Intervention: 1110 Comparison: 2347
Interventions	Intervention: Drug/dose: • Ages ≥ 1 year: Sulfadoxine-pyrimethamine (25 mg + 1.25 mg/kg as a single dose on the first day) plus artesunate (4 mg/kg/day for three days) with primaquine (0.75 mg/kg as a single dose on the third day) • Anaemic individuals: No primaquine. Sulfadoxine-pyrimethamine plus artesunate as described above. • Pregnant women: No primaquine. Sulfadoxine-pyrimethamine as described above plus amodiaquine (10 mg/kg once daily for three days) instead of artesunate. Number of rounds (timing/dates): 1 (February-March 2008)

Shekalaghe 2011 TZA *(Continued)*

	Interval: Not applicable Duration implemented: 16 days Coverage (%): 94.6% received at least one dose and 93% received a complete dose of an efficacious anti-malarial drug prior to the transmission season or immediately upon arrival to the area Co-interventions: Reported ITN use 36.1% (2007) and a single treatment campaign for trachoma with azithromycin was undertaken by a non-governmental organization. Comparison: Type: Placebo administered to all persons in eight clusters once daily over three days. Co-interventions: Reported ITN use 36.1% (2007) and a single treatment campaign for trachoma with azithromycin was undertaken by a non-governmental organization. *If Placebo:* Number of rounds (timing/dates): 1 (February-March 2008) Interval: Not applicable Duration implemented: 16 days Coverage (%): Not described
Outcomes	Parasitaemia prevalence Measurement: Cross-sectional surveys of *P falciparum* prevalence by microscopy and QT-NASBA in 50 randomly-selected individuals per cluster Time points: Pre-MDA (January-February 2008) and at < 1 (April 2008), 2 (May 2008), 3 (June 2008), and 4 (July 2008) months post-MDA Sample size (range): 261 to 399 (intervention); 212 to 395 (comparison) Confirmed malaria illness incidence Measurement: Active case surveillance of 150 randomly-selected children (ages 1 to 10 years) from each arm, visited every 2 weeks to monitor symptoms and test by RDT if febrile. Passive surveillance in entire population. Time points: Followed every 2 weeks for 6 months (February-July 2008) Gametocytaemia prevalence Measurement: Cross-sectional surveys of gametocytaemia prevalence by microscopy and QT-NASBA in 50 randomly selected individuals per cluster Time points: Pre-MDA (January-February 2008) and at < 1 (April 2008), 2 (May 2008), 3 (June 2008), and 4 (July 2008) months post-MDA Sample size (range): 261-399 (intervention); 212-395 (comparison) Adverse effects One individual was diagnosed with possibly-drug related severe skin reaction in the week following MDA. A second individual presented with non-drug related skin hyperpigmentation on the face. Both individuals were treated with steroids and monitored until symptoms disappeared. In those given primaquine, moderate anaemia (Hb level of < 8 g/dL) was observed in 40% (6/15 individuals) of the G6PD A-, 11.1% (3/27 individuals) of the G6PD A, and 4.5% (18/399 individuals) of the G6PD B individuals; one case of severe anaemia (haemoglobin level of < 5 g/dL) was observed.
Notes	ClinicalTrials.gov: NCT00509015

Shekalaghe 2011 TZA *(Continued)*

Due to the following reasons, we excluded this study from quantitative synthesis in this review: outcome evaluation by 18S QT-NASBA ended prematurely during the follow-up period; we were unable to classify events in microscopy outcomes by post-MDA time point (reported in aggregate in the publication); and the baseline before MDA number of events for multiple outcomes was zero.

Abbreviations:

ICC = intracluster correlation coefficient, ITN = insecticide-treated bed net, MDA = mass drug administration, QT-NASBA = real-time quantitative nucleic acid sequence based amplification, RDT = rapid diagnostic test

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Clusters were randomized to the intervention or control arm using computer generated randomization tables using excel."
Allocation concealment (selection bias)	Low risk	Placebo-controlled trial, therefore allocation was concealed.
Baseline imbalance (selection bias)	Low risk	Baseline demographic and malaria characteristics were similar across arms.
Contamination protection	Low risk	"Households that were located between clusters (i.e. within 1 km distance from the boundary of intervention and/or control clusters) were considered as buffer zones. Members of these households received the intervention in order to minimize contamination."
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Low risk	Placebo-controlled trial and, at each cross-sectional survey, individuals were randomly selected from computer-generated random tables. However, placebo tablets appear different from intervention drug.
Blinding of participants and personnel (performance bias) Confirmed malaria illness incidence	Low risk	Placebo-controlled trial.
Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Low risk	Placebo-controlled trial; slides were read independently by two microscopists.
Blinding of outcome assessment (detection bias) Confirmed malaria illness incidence	Low risk	Placebo-controlled trial.
Incomplete outcome data (attrition bias) Parasitaemia prevalence	Low risk	Random sample of individuals surveyed at baseline and follow-up.
Incomplete outcome data (attrition bias) Confirmed malaria illness incidence	Low risk	Active (visit by trained fieldworker every 2 weeks) and passive case detection.

Shekalaghe 2011 TZA *(Continued)*

Selective reporting (reporting bias)	Low risk	All pre-specified outcome measures were reported.
Other bias	Low risk	No other bias detected.
Recruitment bias (cluster RCT)	Low risk	No recruitment following randomization.
Loss of clusters (cluster RCT)	Low risk	No clusters were lost.
Incorrect analysis (cluster RCT)	Low risk	Clustering accounted for using generalized estimating equations; however, in this review, we performed cluster adjustment of the raw data using an estimated ICC to calculate effective sample sizes.
Comparability with individually randomized trials (cluster RCT)	Low risk	MDA, by definition, is applied at the population level, so this criteria is irrelevant for the intervention evaluated in this review.

Tripura 2018 KHM

Study characteristics	
Methods	Dates of study: 2014-2016 Location of study: Battambang province, Cambodia Malaria endemicity (prevalence): *Plasmodium falciparum* prevalence 0.9% in MDA villages and 2.4% in control villages at baseline by ultrasensitive polymerase chain reaction (uPCR); *P vivax* prevalence 10.7% in MDA villages and 8.8% in control villages at baseline by uPCR [Very low - estimated *P falciparum* slide prevalence 0.5%] Transmission season: May to October Malaria species: *P falciparum* and *P vivax* Vector species: Not described Antimalarial drug resistance context: Reduced susceptibility to artemisinins and ACT partner drug resistance Study design: Pair-matched cluster-randomized trial Statistical power: For the multi-country trial (Landier 2017 MMRa; Tripura 2018 KHM; Pongvongsa 2018 LAO; von Seidlein 2019 VNM), 80% power (alpha = 0.05) to detect a 95% reduction in parasite prevalence from a baseline prevalence of 10% For cluster-RCTs Unit of randomization: Village Adjusted analyses for clustering: Yes; however, in this review, we performed cluster adjustment of the raw data using ICC values estimated from the study data to calculate effective sample sizes Adjustment method: Generalized estimating equations ICC: 0.004175 (*P falciparum* outcomes at baseline before MDA), 0 (*P falciparum* outcomes at post-MDA 1-3, 4-6, and 7-12 months); 0.02167 (*P vivax* outcomes at baseline before MDA), 0.01637 (*P vivax* outcomes at post-MDA 1-3 months), 0.02229 (*P vivax* outcomes at post-MDA 4-6 months), 0.002531 (*P vivax* outcomes at post-MDA 7-12 months)

Tripura 2018 KHM *(Continued)*

	Number of clusters randomized: 4 Number of clusters analysed: 4 Number of people: 2,770 Average cluster size: 693 Features: Two village pairs (4 villages) were established by geographical proximity, population size, and parasite prevalence. Within each pair, one village was randomly selected to receive early MDA, while the other village received deferred MDA
Participants	Age groups included: All ages ≥ 6 months. All pregnant women were excluded from MDA. Population targeted Intervention: 858 Comparison: 1912
Interventions	Intervention: Drug/dose: Dihydroartemisinin (7 mg/kg) plus piperaquine tetraphosphate (55 mg/kg) administered once a day for 3 days. Visitors or returning residents were offered a single course of piperaquine tetraphosphate. Number of rounds (timing/dates): 3 (July, August, September 2015) Interval: Every 1 month Duration implemented: 3 months Coverage (%): 74% in round 1, 60% in round 2, and 71% in round 3 Co-interventions: LLITNs, uninterrupted access to diagnosis and treatment in study villages Comparison: Type: Deferred MDA administered in control villages in July, August, and September 2016 Co-interventions: LLITNs, uninterrupted access to diagnosis and treatment in study villages
Outcomes	Parasitaemia prevalence (*P falciparum* and *P vivax*) Measurement: Cross-sectional surveys in all ages every 3 months by uPCR; all individuals present at the time of the survey in the study villages were sampled. Time points: Pre-MDA (July 2015) and at 1 (Oct 2015), 4 (Jan 2016), 7 (April 2016), and 10* (July 2016) months post-MDA Sample size (range): 470 to 543 (intervention) and 583 to 1090 (control) Confirmed malaria illness incidence (*P falciparum* and *P vivax*) Measurement: Passive case detection at malaria posts for measured or self-reported fever (≥ 37.5 °C) and confirmed *P falciparum* or *P vivax* infection by RDT or microscopy. Time points: Pre-MDA (July 2014 - June 2015) and at 9 (July 2015 to June 2016) months' post-MDA Adverse effects (AEs) AEs were assessed through active surveillance on days 1, 2, 3, and 7 following MDA rounds. AEs were reported by 46% (n=909) participants and a majority (96%) were mild; 4% (n=40) required medical attention and there were 3 non-study-related deaths. No serious AEs were reported. The most common AEs reported were dizziness (22%), headache (18%), fever (10%), and nausea (8%).

Tripura 2018 KHM *(Continued)*

Notes	One of four sites from a multi-country trial in Southeast Asia (ClinicalTrials.gov: NCT01872702) Abbreviations: ACT = artemisinin-based combination therapy, ICC = intracluster correlation coefficient, LLITN = long-lasting insecticide-treated bed net, MDA = mass drug administration, uPCR = ultrasensitive polymerase chain reaction * Data from this survey was analysed as post-MDA 7-12 month time point

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation was based on computer-generated random numbers provided by the trial statistician"
Allocation concealment (selection bias)	Low risk	Allocation was conducted by an institution.
Baseline imbalance (selection bias)	High risk	Baseline prevalence of *P falciparum* substantially higher in control compared to intervention villages baseline. Small number of clusters (4 villages) randomized.
Contamination protection	High risk	Intervention and control clusters were pair-matched by geographical proximity, which likely led to a high risk of contamination due to population movement.
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Unclear risk	Participants were not blinded to allocation.
Blinding of participants and personnel (performance bias) Confirmed malaria illness incidence	Unclear risk	Participants were not blinded to allocation, which may have impacted care-seeking.
Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Low risk	Laboratory staff performing PCR were unaware of the study arm allocation of samples.
Blinding of outcome assessment (detection bias) Confirmed malaria illness incidence	Unclear risk	Unclear if the health facility staff performing malaria testing were aware of which study arm participants were assigned to.
Incomplete outcome data (attrition bias) Parasitaemia prevalence	Low risk	Parasitaemia surveys were performed in all individuals aged six months or older residing in the study villages.
Incomplete outcome data (attrition bias) Confirmed malaria illness incidence	Low risk	Data collected at malaria health posts with dedicated study staff.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.

Tripura 2018 KHM *(Continued)*

Other bias	Low risk	No other bias detected.
Recruitment bias (cluster RCT)	Low risk	No recruitment following randomization.
Loss of clusters (cluster RCT)	Low risk	No clusters were lost.
Incorrect analysis (cluster RCT)	Low risk	Although no adjustment for clustering was performed by investigators, in this review, we performed cluster adjustment of the raw data using a study-provided ICC to calculate effective sample sizes
Comparability with individually randomized trials (cluster RCT)	Low risk	MDA, by definition, is applied at the population level, so this criteria is irrelevant for the intervention evaluated in this review.

von Seidlein 2003 GMB

Study characteristics

Methods	Dates of study: 1999 Location of study: The Gambia Malaria endemicity: 42.9% in children ≤ 5 years in control at baseline [High] Transmission season: June to December Malaria species: *Plasmodium falciparum* Vector species: Not described Antimalarial drug resistance context: Not described Study design: Cluster-randomized trial Statistical power: 90% power (alpha = 0.05) to detect a 40% reduction in malaria incidence among children < 11 years assuming coefficient of variation between pair-matched villages of 0.25, 20% loss to follow-up, and mean incidence of malaria of 1 attack per child per week during the 20 week transmission season. For cluster-RCTs Unit of randomization: Villages Adjusted analyses for clustering: Yes; however, in this review, we performed cluster adjustment of the raw data using an estimated ICC to calculate effective sample sizes Adjustment method: Poisson regression model adjusting for population size ICC: Not described Number of clusters randomized: 18 Number of clusters analysed: 18 Number of people: 3655 Average cluster size: 203

von Seidlein 2003 GMB *(Continued)*

	Feature: Matched villages by population size, spleen rate in children < 5 years, and distance from the river
Participants	Age groups included: All persons ≥ 6 months old; pregnant women excluded. Population targeted Intervention: 12,331 Control: 1686
Interventions	Intervention: Drug/dose: • Adults: Sulfadoxine-pyrimethamine (1500 mg/75 mg as 3 tablets) plus artesunate (200 mg as 4 tablets) given in a single day • Children (< 10 kg): Sulfadoxine-pyrimethamine (250 mg/37.5 mg as ½ tablet) plus artesunate (4 mg/kg) given in a single day. Additional quarter tablet of sulfadoxine-pyrimethamine given for every 5 kg increment in weight Number of rounds (timing/dates): 1 (June 1999) Interval: Not applicable Duration implemented: 1 month Coverage (%): 89% in total population, 90.8% in evaluated group Co-interventions: None Comparison: Type: Placebo Co-interventions: None *If placebo:* Number of rounds (timing/dates): 1 (June 1999) Interval: Not applicable Duration implemented: 1 month Coverage (%): 89% in total population, 90.8% in evaluated group
Outcomes	Parasitaemia prevalence Measurement: Cross-sectional surveys of *P falciparum* prevalence by microscopy in children and weekly surveillance in all ages Time points: Pre-MDA (children ≤ 5 years, May 1999) and at 6 months post-MDA (children < 11 years, November 1999) Sample size (range): 808 to 985 (intervention); 605 or 606 (comparison) Parasitaemia incidence Measurement: Weekly surveillance in children aged < 11 years for cases with temperature ≥ 37.5 °C and *P falciparum* parasitaemia > 5000 parasites per µL by microscopy Time points: at 5 months post-MDA (20 July 1999 to 2 December 1999) Sample size: 769 (intervention); 607 (comparison) Gametocytaemia prevalence

von Seidlein 2003 GMB *(Continued)*

	Measurement: Cross-sectional surveys of gametocytaemia prevalence by microscopy in children Time points: Pre-MDA (children ≤ 5 years) and at 6 months post-MDA (children < 11 years) Sample size (range): 808 to 985 (intervention); 605 or 606 (comparison) Malaria-specific mortality Measurement: Verbal autopsy confirmed by 3 physicians in children < 11 years Adverse effects (AEs) Monitored through passive and active surveillance. Active surveillance consisted of asking 90 randomly selected individuals across all 42 study area villages about AEs one month following MDA. AEs reported (passive surveillance system): 1 episode of pruritus in intervention group. AEs reported (active surveillance system): 25 of 75 individuals in intervention group remembered one or more complaints within 2 days of taking the drug including dizziness (13), fever (6), diarrhoea (5), vomiting (5) and itching (4). In the comparison group, 2 of 15 individuals (13%) who had received placebo remembered complaints
Notes	Abbreviations: ICC = intracluster correlation coefficient, MDA = mass drug administration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomization not described, but previous author correspondence revealed that randomization was computer generated.
Allocation concealment (selection bias)	Low risk	One study nurse administered all study drugs to the 18 villages and left the study area following administration. Study personnel and participants were blinded to the intervention status. Placebo-controlled trial, therefore allocation was concealed.
Baseline imbalance (selection bias)	Low risk	Intervention and control villages were similar across baseline characteristics reported.
Contamination protection	Low risk	All individuals in neighbouring non-randomized villages in the study area received MDA in order to minimize the risk of contamination.
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Low risk	Cluster-randomized, double-blind, placebo-controlled trial in which neither study personnel nor participants were aware of the intervention status of villages. Placebo tablets identical to intervention drug.
Blinding of participants and personnel (performance bias) Parasitaemia incidence	Low risk	Cluster-randomized, double-blind, placebo-controlled trial in which neither study personnel nor participants were aware of the intervention status of villages. Placebo tablets identical to intervention drug.
Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Low risk	Outcome assessment by microscopy was blinded to intervention status.
Blinding of outcome assessment (detection bias) Parasitaemia incidence	Low risk	Outcome assessment by microscopy was blinded to intervention status. Cases diagnosed at health centre by RDT, but neither study personnel nor participants were aware of the intervention status of villages.

von Seidlein 2003 GMB *(Continued)*

Incomplete outcome data (attrition bias) Parasitaemia prevalence	Low risk	All children < 11 years in the surveillance villages were surveyed.
Incomplete outcome data (attrition bias) Parasitaemia incidence	High risk	78-92% of children were examined weekly by field workers and 87% of planned visits took place. However, malaria cases were defined as a temperature ≥ 37.5 °C and parasitaemia > 5000/µL, which may have precluded asymptomatic or lower density infections and resulted in an underestimate of parasitaemia incidence.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	No other bias detected.
Recruitment bias (cluster RCT)	Low risk	No recruitment following randomization.
Loss of clusters (cluster RCT)	Low risk	One cluster pair (Daro Rahman and Misira villages) was not analysed due to political and logistical problems, but sensitivity analysis indicated similar results. "Analyses which omitted these 2 villages yielded similar results as the analyses including the 2 villages."
Incorrect analysis (cluster RCT)	Low risk	Analysis adjusted for clustering using Poisson regression model adjusting for population size; however, in this review, we performed cluster adjustment of the raw data using an estimated ICC to calculate effective sample sizes.
Comparability with individually randomized trials (cluster RCT)	Low risk	MDA, by definition, is applied at the population level, so this criteria is irrelevant for the intervention evaluated in this review.

von Seidlein 2019 VNM

Study characteristics	
Methods	Dates of study: 2013-2015 Location of study: Binh Phuoc and Ninh Thuan provinces, Vietnam Malaria endemicity (prevalence): *Plasmodium falciparum* prevalence 3.9% in MDA villages and 4.1% in control villages at baseline by ultrasensitive polymerase chain reaction (uPCR); *P vivax* prevalence 6.3% in MDA villages and 7.3% in control villages at baseline by uPCR [Very low - estimated *P falciparum* slide prevalence 0.9%] Transmission season: May to November Malaria species: *P falciparum* and *P vivax* Vector species: Not described Antimalarial drug resistance context: At the start of the study, no evidence of resistance to piperaquine and cure rates following dihydroartemisinin piperaquine (DHAp) were satisfactory. In 2016, multidrug resistance was first detected and treatment failures with DHAp have increased since then. Statistical power: For the multi-country trial (Landier 2017 MMRa; Tripura 2018 KHM; Pongvongsa 2018 LAO; von Seidlein 2019 VNM), 80% power (alpha = 0.05) to detect a 95% reduction in parasite prevalence from a baseline prevalence of 10%

von Seidlein 2019 VNM *(Continued)*

	For cluster-RCTs Unit of randomization: Village Adjusted analyses for clustering: Yes; however, in this review, we performed cluster adjustment of the raw data using ICC values estimated from the study data to calculate effective sample sizes Adjustment method: Generalized estimating equations ICC: 0.002464 (*P falciparum* outcomes at baseline before MDA), 0 (*P falciparum* outcomes at post-MDA 1-3 months), 0.003616 (*P falciparum* outcomes at post-MDA 4-6 months), 0.006523 (*P falciparum* outcomes at post-MDA 7-12 months); 0.001502 (*P vivax* outcomes at baseline before MDA), 0.002539 (*P vivax* outcomes at post-MDA 1-3 months), 0 (*P vivax* outcomes at post-MDA 4-6 and 7-12 months) Number of clusters randomized: 4 Number of clusters analysed: 4 Number of people: 2846 Average cluster size: 712 Features: Two village pairs (4 villages) were established by geographical proximity, population size and parasite prevalence. Within each pair, one village was randomly selected to receive early MDA, while the other village received deferred MDA
Participants	Age groups included: All ages ≥ 6 months. All pregnant women in their first trimester were excluded from MDA and pregnant women in any trimester were excluded from primaquine. Population targeted Intervention: 1439 Comparison: 1407
Interventions	Intervention: Drug/dose: Dihydroartemisinin (7 mg/kg) plus piperaquine (55 mg/kg) administered once a day for 3 days with a single dose of primaquine (0.25 mg/kg). Number of rounds (timing/dates): 3 (November 2013, January and February 2014) Interval: Every 1 month Duration implemented: 3 months Coverage (%): 83% in round 1, 98% in round 2, and 99% in round 3 Co-interventions: LLITNs, uninterrupted access to diagnosis and treatment in study villages Comparison: Type: Deferred MDA administered in control villages in December 2014, January 2015, and February 2015 Co-interventions: LLITNs, uninterrupted access to diagnosis and treatment in study villages
Outcomes	Parasitaemia prevalence (*P falciparum* and *P vivax*) Measurement: Cross-sectional surveys in all ages every 3 months by uPCR; all individuals present at the time of the survey in the study villages were sampled. Time points: Pre-MDA (November 2013, just prior to first MDA round) and at 1 (March 2014), 4 (June 2014), 7 (September 2014), and 10* (December 2014) months post-MDA

von Seidlein 2019 VNM *(Continued)*

	Sample size (range): 745 to 859 (intervention) and 618 to 802 (control) Adverse effects (AEs) 22 AEs were reported which included vomiting, nausea, diarrhoea, labyrinth disorder, leg fracture and urticaria. Seven serious AEs were reported within the first year of the study including death from suicide, sudden death, drowning, decline due to aging, and gastric cancer.
Notes	One of four sites from a multi-country trial in Southeast Asia (ClinicalTrials.gov: NCT01872702) Abbreviations: ICC = intracluster correlation coefficient, LLITN = long-lasting insecticide-treated bed net, MDA = mass drug administration, uPCR = ultrasensitive polymerase chain reaction * Data from this survey was analysed as post-MDA 7-12 month time point

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation was based on computer-generated random numbers provided by the trial statistician"
Allocation concealment (selection bias)	Low risk	Allocation was conducted by an institution.
Baseline imbalance (selection bias)	Low risk	Small number of clusters (4 villages) randomized, but baseline malaria prevalence is balanced across arms.
Contamination protection	High risk	Intervention and control clusters were pair-matched by geographical proximity, which likely led to a high risk of contamination due to population movement.
Blinding of participants and personnel (performance bias) Parasitaemia prevalence	Unclear risk	Participants were not blinded to allocation.
Blinding of outcome assessment (detection bias) Parasitaemia prevalence	Low risk	Laboratory staff performing PCR were unaware of the study arm allocation of samples.
Incomplete outcome data (attrition bias) Parasitaemia prevalence	Low risk	Parasitaemia surveys were performed in all individuals aged six months or older residing in the study villages.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Low risk	No other bias detected.
Recruitment bias (cluster RCT)	Low risk	No recruitment following randomization.
Loss of clusters (cluster RCT)	Low risk	No clusters were lost.

von Seidlein 2019 VNM *(Continued)*

Incorrect analysis (cluster RCT)	Low risk	Although no adjustment for clustering was performed by investigators, in this review, we performed cluster adjustment of the raw data using a study-provided ICC to calculate effective sample sizes
Comparability with individually randomized trials (cluster RCT)	Low risk	MDA, by definition, is applied at the population level, so this criteria is irrelevant for the intervention evaluated in this review.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Affane 2012 COM	Considered for ITS analysis, but since LLINs were distributed at the time of the first round of MDA, it is not possible to evaluate the effect of MDA alone
Aregawi 2016 SLE	Insufficient pre- and/or post-MDA coverage of data points for ITS analysis
Deng 2018 COM	Insufficient pre- and/or post-MDA coverage of data points for ITS analysis
Escudie 1961 BFA	No control group
Fraser 2020 ZMB	Insufficient pre- and/or post-MDA coverage of data points for ITS analysis due to timing of IRS implementation in relation to MDA rounds
Galatas 2020 MOZ	Insufficient pre- and/or post-MDA coverage of data points for ITS analysis due to timing of IRS implementation in relation to MDA rounds
Jones 1958 KEN	Fewer than 2 sites or clusters per arm
Kagaya 2019 KEN	Fewer than 2 sites or clusters per arm
Kaneko 2000 VUT	Unbalanced co-interventions across arms (Intervention: MDA+ITNs+larvivorous fish, Control: no MDA and delayed distribution of ITNs)
Landier 2017 MMRb	Intervention targeted to hotspots of malaria infection (targeted MDA)
Mwesigwa 2018 GMB	Insufficient pre- and post-MDA coverage of data points for ITS analysis
Najera 1973 NGA	Unbalanced co-interventions across arms (Intervention: MDA+IRS, Control: no MDA and no IRS)
Singh 1953 IND	Inadequate treatment dose

LLIN = long-lasting insecticide-treated bed net, IRS = indoor residual spraying, ITS = interrupted time series, MDA = mass drug administration.

Characteristics of studies awaiting classification *[ordered by study ID]*

El-Sayed SDN

Methods	Dates of study: 2006 Location of study: Sudan Malaria endemicity: 15% [Moderate]

El-Sayed SDN *(Continued)*	
	Transmission season: October to November Malaria species: *Plasmodium falciparum* Vector species: Not described Antimalarial drug resistance context: Not described Study design: Cluster-randomized trial Statistical power: 90% power (alpha = 0.05) to detect a reduction in malaria prevalence from 15% to 5% among all ages, assuming a baseline malaria prevalence of 15% For cluster-RCTs Unit of randomization: Village Adjusted analyses for clustering: No Adjustment method: Not applicable ICC: Not described Number of clusters randomized: 8 Number of clusters analysed: 8 Number of people: Not described Average cluster size: Not described
Participants	Age groups included: All persons ≥ 1 year old; pregnant women and persons with a history of allergy to sulfa drugs excluded. Population targeted Not described
Interventions	Intervention: Drug/dose: Sulfadoxine-pyrimethamine (dose not described) plus artesunate (dose not described) given over three days Number of rounds (timing/dates): 1 (July 2006) Interval: Not applicable Duration implemented: Not described Coverage (%): Not described Co-interventions: Not described Comparison: Type: Placebo Co-interventions: None *If placebo:* Number of rounds (timing/dates): 1 (July 2006) Interval: Not applicable Duration implemented: Not described

El-Sayed SDN *(Continued)*

	Coverage (%): Not described Co-interventions: Not described
Outcomes	Parasitaemia prevalence Measurement: Cross-sectional survey of *P falciparum* prevalence by microscopy in all ages Time points: at 4 months' post-MDA (November 2006) Sample size: 200 participants per village; approximately 800 participants per study arm Adverse events
Notes	Placebo tablet similar to active drug in shape and size. Unclear if a pre-MDA parasitaemia survey was conducted. According to author communication: data collection complete and results from trial will be published. Characteristics of study completed using information from clinicaltrials.gov (NCT00646126) and communications with author

Song TGO

Methods	Dates of study: Not described Location of study: Est-Mono in the Plateaux region, Togo Malaria endemicity (prevalence): Not described Transmission season: Not described Malaria species: Not described Vector species: Not described Antimalarial drug resistance context: Not described Study design: Interrupted time series or controlled before-and-after study Statistical power: Not described
Participants	Age groups included: All persons ≥ 6 months old; pregnant women in their first trimester and persons with serious illness or allergies to drug excluded. Population targeted: 125,611
Interventions	Artemisinin-piperaquine Drug/dose: Artemisinin-piperaquine as a single tablet (62.5 mg artemisinin and 375 mg piperaquine) given for two days Number of rounds (timing/dates): 3 Interval: 1 month Duration implemented: 3 months Coverage (%): Not described

Song TGO *(Continued)*	
	Co-interventions: Not described
Outcomes	Parasitaemia prevalence Parasitaemia incidence among children < 5 years Confirmed malaria illness incidence
Notes	ChiCTR-POC-16009019 After multiple attempts to contact investigators, the status of this trial is unknown.

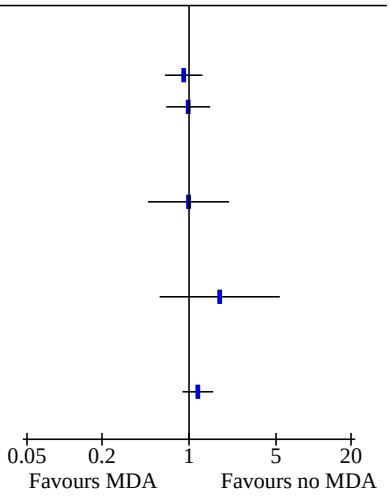
DATA AND ANALYSES

Comparison 1. MDA versus no MDA in moderate to high endemicity (cRCTs) on *P falciparum* outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Parasitaemia prevalence (*P falciparum*)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1.1 Baseline before MDA	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1.2 During MDA	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1.3 Post-MDA 1-3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1.4 Post-MDA 4-6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2 Parasitaemia incidence (*P falciparum*)	2		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
1.2.1 Post-MDA 1-3 months	1		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
1.2.2 Post-MDA 4-6 months	1		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
1.3 Confirmed malaria illness incidence (*P falciparum*)	1		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
1.3.1 Baseline before MDA	1		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
1.3.2 Post-MDA 1-3 months	1		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
1.4 Gametocytaemia prevalence (*P falciparum*)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4.1 Baseline before MDA	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4.2 Post-MDA 4-6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.5 Malaria-specific mortality	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
1.5.1 Post-MDA 4-6 months	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: MDA versus no MDA in moderate to high endemicity (cRCTs) on *P falciparum* outcomes, Outcome 1: Parasitaemia prevalence (*P falciparum*)

Study or Subgroup	MDA Events	MDA Total	No MDA Events	No MDA Total	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Baseline before MDA					
Eisele 2020 ZMBb (1)	28	55	32	57	0.91 [0.64 , 1.28]
von Seidlein 2003 GMB (2)	35	84	22	52	0.98 [0.66 , 1.48]
1.1.2 During MDA					
Eisele 2020 ZMBb (3)	12	76	11	69	0.99 [0.47 , 2.10]
1.1.3 Post-MDA 1-3 months					
Eisele 2020 ZMBb (4)	7	85	5	107	1.76 [0.58 , 5.36]
1.1.4 Post-MDA 4-6 months					
von Seidlein 2003 GMB (5)	50	77	32	58	1.18 [0.89 , 1.56]

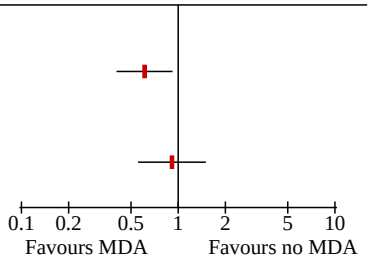


Footnotes

(1) Children ≤ 5 years; RDT; raw data: 248 (MDA events), 490 (MDA total), 283 (Control events), 505 (Control total)
(2) Children ≤ 5 years; microscopy; raw data: 410 (MDA events), 985 (MDA total), 260 (Control events), 605 (Control total)
(3) Children ≤ 5 years; RDT; raw data: 56 (MDA events), 366 (MDA total), 55 (Control events), 332 (Control total)
(4) Children ≤ 5 years; RDT; raw data: 28 (MDA events), 348 (MDA total), 22 (Control events), 438 (Control total)
(5) Children < 11 years; microscopy; raw data: 530 (MDA events), 808 (MDA total), 333 (Control events), 606 (Control total)

Analysis 1.2. Comparison 1: MDA versus no MDA in moderate to high endemicity (cRCTs) on *P falciparum* outcomes, Outcome 2: Parasitaemia incidence (*P falciparum*)

Study or Subgroup	log[Rate Ratio]	SE	MDA Total	No MDA Total	Rate Ratio IV, Fixed, 95% CI
1.2.1 Post-MDA 1-3 months					
Eisele 2020 ZMBb (1)	-0.494	0.21	339	337	0.61 [0.40 , 0.92]
1.2.2 Post-MDA 4-6 months					
von Seidlein 2003 GMB (2)	-0.0916	0.254	769	607	0.91 [0.55 , 1.50]

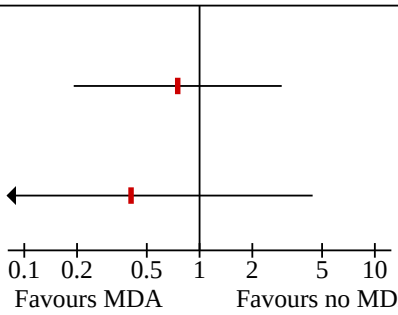


Footnotes

(1) Persons ≥ 3 months; RDT
(2) Malaria events defined as a temperature ≥ 37.5 °C and parasitaemia > 5000/uL in children < 11 years followed weekly

Analysis 1.3. Comparison 1: MDA versus no MDA in moderate to high endemicity (cRCTs) on *P falciparum* outcomes, Outcome 3: Confirmed malaria illness incidence (*P falciparum*)

Study or Subgroup	log[Rate Ratio]	SE	Rate Ratio IV, Fixed, 95% CI
1.3.1 Baseline before MDA			
Eisele 2020 ZMBb (1)	-0.287	0.697	0.75 [0.19 , 2.94]
1.3.2 Post-MDA 1-3 months			
Eisele 2020 ZMBb (2)	-0.9	1.217	0.41 [0.04 , 4.42]



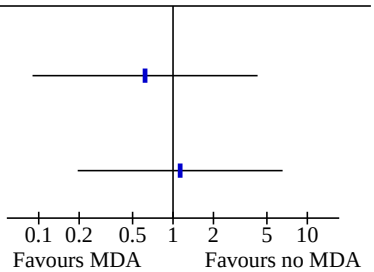
Footnotes

(1) All ages; January-May 2013 and 2014; denominator assumed to be average of 2013 and 2014 mid-year HFCA populatic

(2) All ages; January-May 2015 and 2016; denominator assumed to be average of 2015 and 2016 mid-year HFCA populatic

Analysis 1.4. Comparison 1: MDA versus no MDA in moderate to high endemicity (cRCTs) on *P falciparum* outcomes, Outcome 4: Gametocytaemia prevalence (*P falciparum*)

Study or Subgroup	MDA Events	MDA Total	No MDA Events	No MDA Total	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Baseline before MDA					
von Seidlein 2003 GMB (1)	2	84	2	52	0.62 [0.09 , 4.26]
1.4.2 Post-MDA 4-6 months					
von Seidlein 2003 GMB (2)	3	77	2	58	1.13 [0.20 , 6.54]



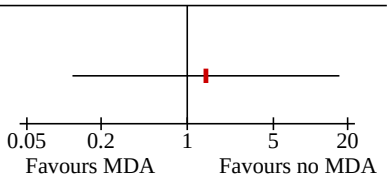
Footnotes

(1) Children ≤ 5 years; microscopy; raw data: 19 (MDA events), 985 (MDA total), 22 (Control events), 605 (Control total)

(2) Children < 11 years; microscopy; raw data: 30 (MDA events), 808 (MDA total), 21 (Control events), 606 (Control total)

Analysis 1.5. Comparison 1: MDA versus no MDA in moderate to high endemicity (cRCTs) on *P falciparum* outcomes, Outcome 5: Malaria-specific mortality

Study or Subgroup	log[RR]	SE	MDA Total	No MDA Total	Risk Ratio IV, Fixed, 95% CI
1.5.1 Post-MDA 4-6 months					
von Seidlein 2003 GMB (1)	0.349	1.272	1986	1689	1.42 [0.12 , 17.15]



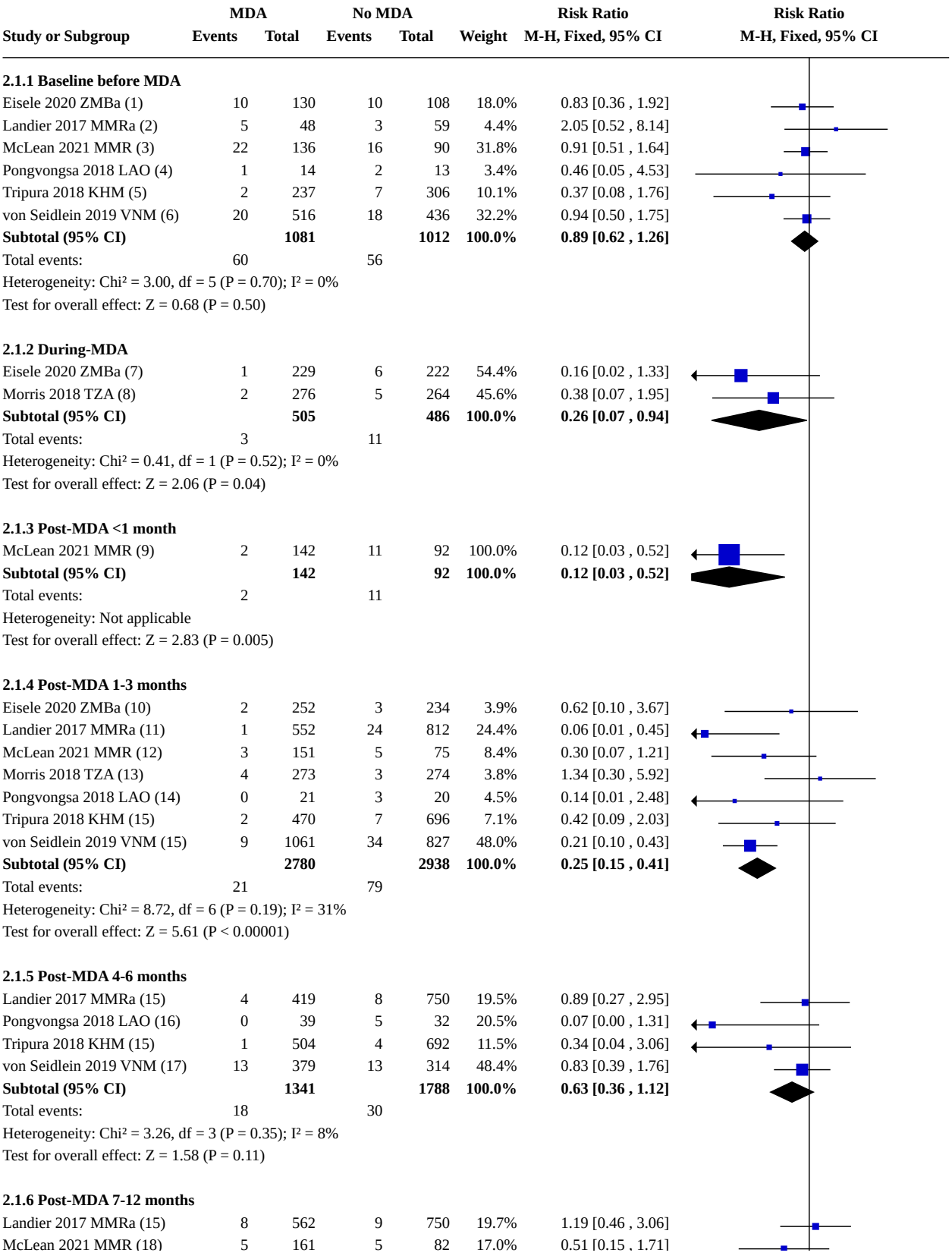
Footnotes

(1) Standard error adjusted using ICC of 0.01 due implausible error using ICC of 0.1225; raw data: 5 (MDA events), 3 (Control events)

Comparison 2. MDA versus no MDA in very low to low endemicity (cRCTs) on *P falciparum* outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Parasitaemia prevalence (*P falciparum*)	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1.1 Baseline before MDA	6	2093	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.62, 1.26]
2.1.2 During-MDA	2	991	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.07, 0.94]
2.1.3 Post-MDA <1 month	1	234	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.03, 0.52]
2.1.4 Post-MDA 1-3 months	7	5718	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.15, 0.41]
2.1.5 Post-MDA 4-6 months	4	3129	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.36, 1.12]
2.1.6 Post-MDA 7-12 months	5	3704	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.36]
2.1.7 Post-MDA 13-18 months	1	243	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.20, 3.34]
2.1.8 Post-MDA 19-24 months	1	239	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.06, 1.97]
2.1.9 Post-MDA 25-30 months	1	242	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.22, 3.62]
2.1.10 Post-MDA 31-36 months	1	246	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.25, 6.31]
2.2 Parasitaemia incidence (*P falciparum*)	1		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
2.2.1 Post-MDA 1-3 months	1		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
2.3 Confirmed malaria illness incidence (*P falciparum*)	4		Rate Ratio (IV, Fixed, 95% CI)	Subtotals only
2.3.1 Baseline before MDA	3		Rate Ratio (IV, Fixed, 95% CI)	0.87 [0.45, 1.69]
2.3.2 Post-MDA 1-3 months	2		Rate Ratio (IV, Fixed, 95% CI)	0.58 [0.12, 2.73]
2.3.3 Post-MDA 4-6 months	1		Rate Ratio (IV, Fixed, 95% CI)	0.93 [0.07, 12.43]
2.3.4 Post-MDA 7-12 months	3		Rate Ratio (IV, Fixed, 95% CI)	0.47 [0.21, 1.03]
2.3.5 Post-MDA 13-18 months	1		Rate Ratio (IV, Fixed, 95% CI)	0.77 [0.20, 3.03]

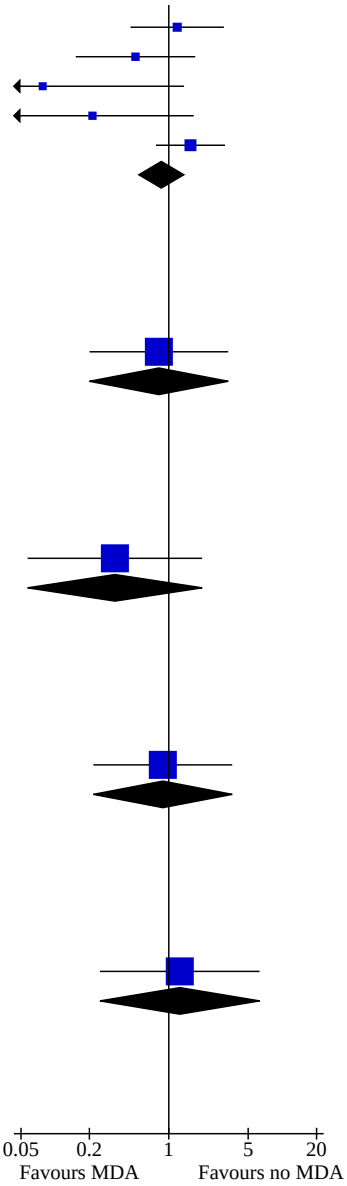
Analysis 2.1. Comparison 2: MDA versus no MDA in very low to low endemicity (cRCTs) on *P falciparum* outcomes, Outcome 1: Parasitaemia prevalence (*P falciparum*)



Study or Subgroup	MDA Events	MDA Total	No MDA Events	No MDA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Baseline before MDA						
Eisele 2020 ZMBa (1)	10	130	10	108	18.0%	0.83 [0.36 , 1.92]
Landier 2017 MMRa (2)	5	48	3	59	4.4%	2.05 [0.52 , 8.14]
McLean 2021 MMR (3)	22	136	16	90	31.8%	0.91 [0.51 , 1.64]
Pongvongsa 2018 LAO (4)	1	14	2	13	3.4%	0.46 [0.05 , 4.53]
Tripura 2018 KHM (5)	2	237	7	306	10.1%	0.37 [0.08 , 1.76]
von Seidlein 2019 VNM (6)	20	516	18	436	32.2%	0.94 [0.50 , 1.75]
Subtotal (95% CI)		**1081**		**1012**	**100.0%**	**0.89 [0.62 , 1.26]**
Total events:	60		56			
Heterogeneity: Chi² = 3.00, df = 5 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
2.1.2 During-MDA						
Eisele 2020 ZMBa (7)	1	229	6	222	54.4%	0.16 [0.02 , 1.33]
Morris 2018 TZA (8)	2	276	5	264	45.6%	0.38 [0.07 , 1.95]
Subtotal (95% CI)		**505**		**486**	**100.0%**	**0.26 [0.07 , 0.94]**
Total events:	3		11			
Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						
2.1.3 Post-MDA <1 month						
McLean 2021 MMR (9)	2	142	11	92	100.0%	0.12 [0.03 , 0.52]
Subtotal (95% CI)		**142**		**92**	**100.0%**	**0.12 [0.03 , 0.52]**
Total events:	2		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.83 (P = 0.005)						
2.1.4 Post-MDA 1-3 months						
Eisele 2020 ZMBa (10)	2	252	3	234	3.9%	0.62 [0.10 , 3.67]
Landier 2017 MMRa (11)	1	552	24	812	24.4%	0.06 [0.01 , 0.45]
McLean 2021 MMR (12)	3	151	5	75	8.4%	0.30 [0.07 , 1.21]
Morris 2018 TZA (13)	4	273	3	274	3.8%	1.34 [0.30 , 5.92]
Pongvongsa 2018 LAO (14)	0	21	3	20	4.5%	0.14 [0.01 , 2.48]
Tripura 2018 KHM (15)	2	470	7	696	7.1%	0.42 [0.09 , 2.03]
von Seidlein 2019 VNM (15)	9	1061	34	827	48.0%	0.21 [0.10 , 0.43]
Subtotal (95% CI)		**2780**		**2938**	**100.0%**	**0.25 [0.15 , 0.41]**
Total events:	21		79			
Heterogeneity: Chi² = 8.72, df = 6 (P = 0.19); I² = 31%						
Test for overall effect: Z = 5.61 (P < 0.00001)						
2.1.5 Post-MDA 4-6 months						
Landier 2017 MMRa (15)	4	419	8	750	19.5%	0.89 [0.27 , 2.95]
Pongvongsa 2018 LAO (16)	0	39	5	32	20.5%	0.07 [0.00 , 1.31]
Tripura 2018 KHM (15)	1	504	4	692	11.5%	0.34 [0.04 , 3.06]
von Seidlein 2019 VNM (17)	13	379	13	314	48.4%	0.83 [0.39 , 1.76]
Subtotal (95% CI)		**1341**		**1788**	**100.0%**	**0.63 [0.36 , 1.12]**
Total events:	18		30			
Heterogeneity: Chi² = 3.26, df = 3 (P = 0.35); I² = 8%						
Test for overall effect: Z = 1.58 (P = 0.11)						
2.1.6 Post-MDA 7-12 months						
Landier 2017 MMRa (15)	8	562	9	750	19.7%	1.19 [0.46 , 3.06]
McLean 2021 MMR (18)	5	161	5	82	17.0%	0.51 [0.15 , 1.71]

Analysis 2.1. (Continued)

Landier 2017 MMRa (15)	8	562	9	750	19.7%	1.19 [0.46 , 3.06]
McLean 2021 MMR (18)	5	161	5	82	17.0%	0.51 [0.15 , 1.71]
Pongvongsa 2018 LAO (19)	0	47	5	40	15.2%	0.08 [0.00 , 1.36]
Tripura 2018 KHM (15)	1	512	10	1090	16.4%	0.21 [0.03 , 1.66]
von Seidlein 2019 VNM (20)	22	259	11	201	31.7%	1.55 [0.77 , 3.13]
Subtotal (95% CI)		**1541**		**2163**	**100.0%**	**0.86 [0.55 , 1.36]**
Total events:	36		40			
Heterogeneity: Chi² = 8.38, df = 4 (P = 0.08); I² = 52%						
Test for overall effect: Z = 0.65 (P = 0.52)						
2.1.7 Post-MDA 13-18 months						
McLean 2021 MMR (21)	5	163	3	80	100.0%	0.82 [0.20 , 3.34]
Subtotal (95% CI)		**163**		**80**	**100.0%**	**0.82 [0.20 , 3.34]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
2.1.8 Post-MDA 19-24 months						
McLean 2021 MMR (22)	2	159	3	80	100.0%	0.34 [0.06 , 1.97]
Subtotal (95% CI)		**159**		**80**	**100.0%**	**0.34 [0.06 , 1.97]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
2.1.9 Post-MDA 25-30 months						
McLean 2021 MMR (23)	5	158	3	84	100.0%	0.89 [0.22 , 3.62]
Subtotal (95% CI)		**158**		**84**	**100.0%**	**0.89 [0.22 , 3.62]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.87)						
2.1.10 Post-MDA 31-36 months						
McLean 2021 MMR (24)	5	164	2	82	100.0%	1.25 [0.25 , 6.31]
Subtotal (95% CI)		**164**		**82**	**100.0%**	**1.25 [0.25 , 6.31]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						



Footnotes

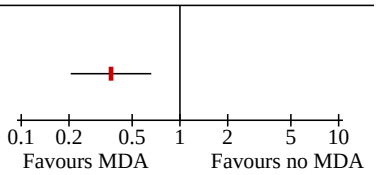
(1) Children ≤ 5 years; RDT; raw data: 42 (MDA events), 545 (MDA total), 42 (Control events), 453 (Control total)
(2) All ages ≥ 6 months; uPCR; raw data: 76 (MDA events), 689 (MDA total), 46 (Control events), 848 (Control total)
(3) Ages 18-55 years; uPCR; raw data: 101 (MDA events), 621 (MDA total), 74 (Control events), 412 (Control total)
(4) All ages ≥ 6 months; uPCR; raw data: 41 (MDA events), 859 (MDA total), 140 (Control events), 802 (Control total)
(5) All ages ≥ 6 months; uPCR; raw data: 5 (MDA events), 543 (MDA total), 17 (Control events), 701 (Control total)
(6) All ages ≥ 6 months; uPCR; raw data: 48 (MDA events), 1247 (MDA total), 43 (Control events), 1054 (Control total)
(7) Children ≤ 5 years; RDT; raw data: 2 (MDA events), 372 (MDA total), 9 (Control events), 361 (Control total)
(8) All ages; qPCR; raw data: 24 (MDA events), 4042 (MDA total), 76 (Control events), 3875 (Control total)
(9) Ages 18-55 years; uPCR; raw data: 12 (MDA events), 747 (MDA total), 56 (Control events), 485 (Control total)
(10) Children ≤ 5 years; RDT; raw data: 3 (MDA events), 392 (MDA total), 5 (Control events), 365 (Control total)
(11) All ages ≥ 6 months; uPCR; raw data: 1 (MDA events), 552 (MDA total), 24 (Control events), 812 (Control total)
(12) Ages 18-55 years; uPCR; raw data: 14 (MDA events), 675 (MDA total), 21 (Control events), 336 (Control total)
(13) All ages; qPCR; raw data: 67 (MDA events), 4896 (MDA total), 53 (Control events), 4905 (Control total)
(14) All ages ≥ 6 months; uPCR; raw data: 0 (MDA events), 745 (MDA total), 90 (Control events), 722 (Control total)
(15) All ages ≥ 6 months; uPCR; ICC = 0
(16) All ages ≥ 6 months; uPCR; raw data: 9 (MDA events), 801 (MDA total), 98 (Control events), 655 (Control total)

Analysis 2.1. (Continued)

(15) All ages ≥ 6 months; uPCR; ICC = 0
(16) All ages ≥ 6 months; uPCR; raw data: 9 (MDA events), 801 (MDA total), 98 (Control events), 655 (Control total)
(17) All ages ≥ 6 months; uPCR; raw data: 36 (MDA events), 1012 (MDA total), 35 (Control events), 837 (Control total)
(18) Ages 18-55 years; uPCR; raw data: 34 (MDA events), 1013 (MDA total), 33 (Control events), 515 (Control total)
(19) All ages ≥ 6 months; uPCR; raw data: 6 (MDA events), 808 (MDA total), 80 (Control events), 689 (Control total)
(20) All ages ≥ 6 months; uPCR; raw data: 86 (MDA events), 1026 (MDA total), 45 (Control events), 795 (Control total)
(21) Ages 18-55 years; uPCR; raw data: 34 (MDA events), 1029 (MDA total), 22 (Control events), 508 (Control total)
(22) Ages 18-55 years; uPCR; raw data: 14 (MDA events), 927 (MDA total), 15 (Control events), 466 (Control total)
(23) Ages 18-55 years; uPCR; raw data: 30 (MDA events), 993 (MDA total), 18 (Control events), 528 (Control total)
(24) Ages 18-55 years; uPCR; raw data: 34 (MDA events), 1117 (MDA total), 17 (Control events), 562 (Control total)

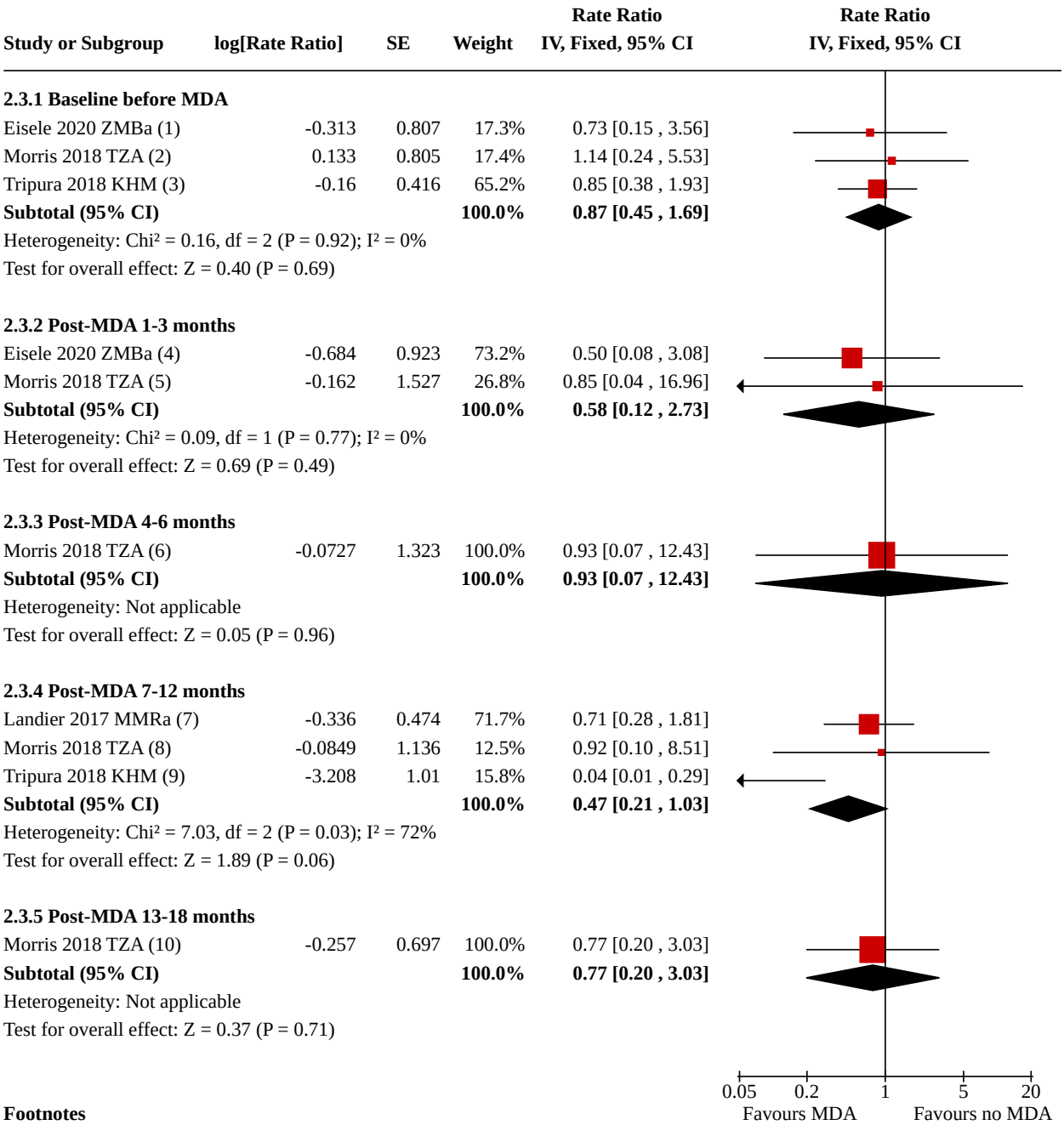
Analysis 2.2. Comparison 2: MDA versus no MDA in very low to low endemicity (cRCTs) on *P falciparum* outcomes, Outcome 2: Parasitaemia incidence (*P falciparum*)

Study or Subgroup	log[Rate Ratio]	SE	MDA Total	No MDA Total	Rate Ratio IV, Fixed, 95% CI
2.2.1 Post-MDA 1-3 months					
Eisele 2020 ZMBa (1)	-1	0.298	260	271	0.37 [0.21 , 0.66]



Footnotes
(1) Persons ≥ 3 months; RDT

Analysis 2.3. Comparison 2: MDA versus no MDA in very low to low endemicity (cRCTs) on *P falciparum* outcomes, Outcome 3: Confirmed malaria illness incidence (*P falciparum*)



Footnotes

(1) All ages; January-May 2013 and 2014; denominator assumed to be average of 2013 and 2014 mid-year HFCA population
(2) All ages; May-Nov 2015
(3) All ages; July 2014 - June 2015; *Plasmodium falciparum* or mixed infections
(4) All ages; January-May 2015 and 2016; denominator assumed to be average of 2015 and 2016 mid-year HFCA population
(5) All ages; May-August 2016
(6) All ages; May-November 2016
(7) All ages; May 2013 to January 2014; *Plasmodium falciparum* or mixed infections
(8) All ages; May 2016 - April 2017
(9) All ages; July 2015 - June 2016; *Plasmodium falciparum* or mixed infections
(10) All ages; May 2016 - August 2017

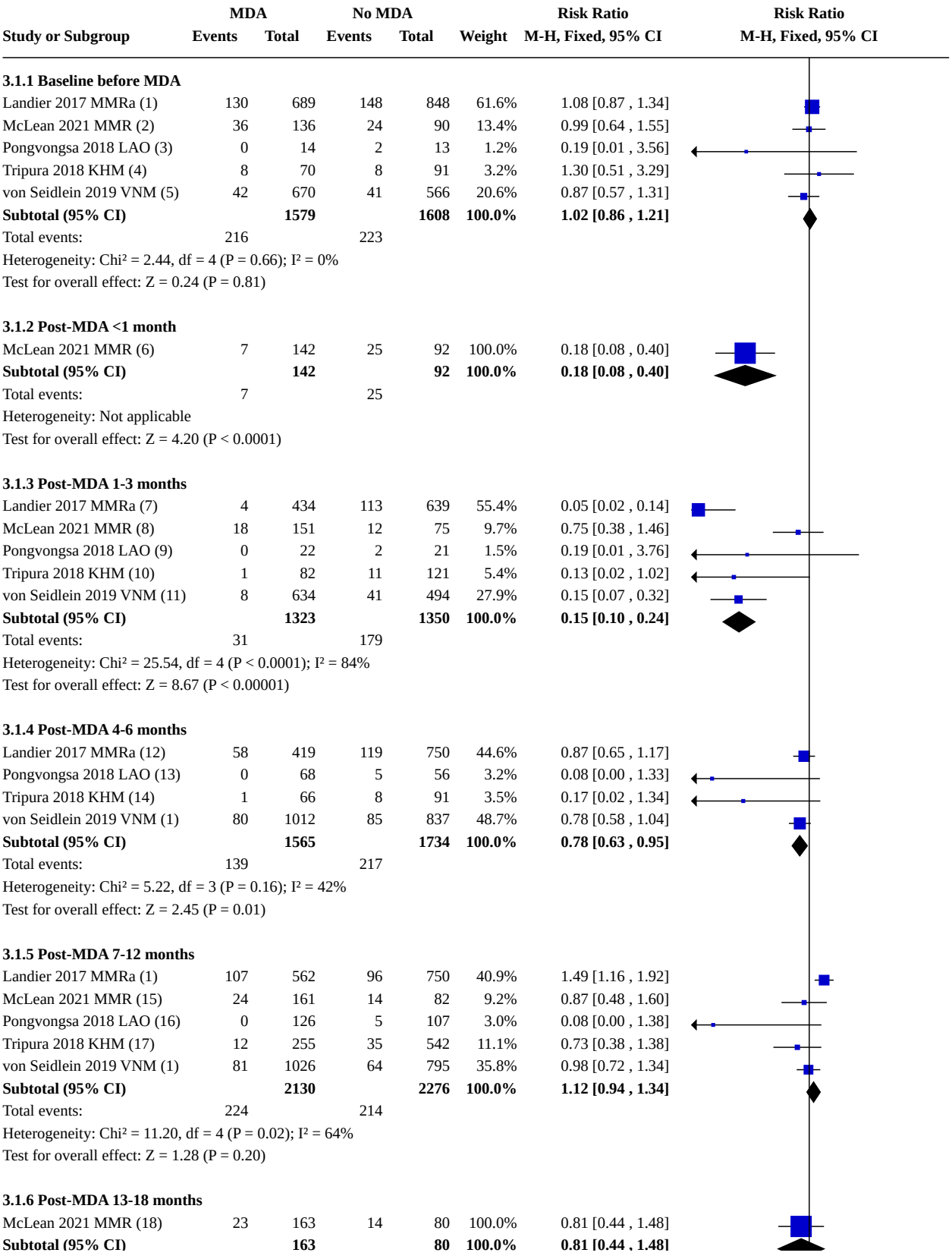
Analysis 2.3. (Continued)

(9) All ages; July 2015 - June 2016; *Plasmodium falciparum* or mixed infections
(10) All ages; May 2016 - August 2017

Comparison 3. MDA versus no MDA in very low to low endemicity (cRCTs) on *P vivax* outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Parasitaemia prevalence (*P vivax*)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1.1 Baseline before MDA	5	3187	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.86, 1.21]
3.1.2 Post-MDA <1 month	1	234	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.08, 0.40]
3.1.3 Post-MDA 1-3 months	5	2673	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.10, 0.24]
3.1.4 Post-MDA 4-6 months	4	3299	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.63, 0.95]
3.1.5 Post-MDA 7-12 months	5	4406	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.94, 1.34]
3.1.6 Post-MDA 13-18 months	1	243	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.44, 1.48]
3.1.7 Post-MDA 19-24 months	1	239	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.38, 1.83]
3.1.8 Post-MDA 25-30 months	1	242	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.41, 1.94]
3.1.9 Post-MDA 31-36 months	1	246	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.44, 3.29]
3.2 Confirmed malaria illness incidence (*P vivax*)	2		Rate Ratio (IV, Fixed, 95% CI)	Subtotals only
3.2.1 Baseline before MDA	1		Rate Ratio (IV, Fixed, 95% CI)	1.74 [0.67, 4.53]
3.2.2 Post-MDA 7-12 months	2		Rate Ratio (IV, Fixed, 95% CI)	1.38 [0.97, 1.95]

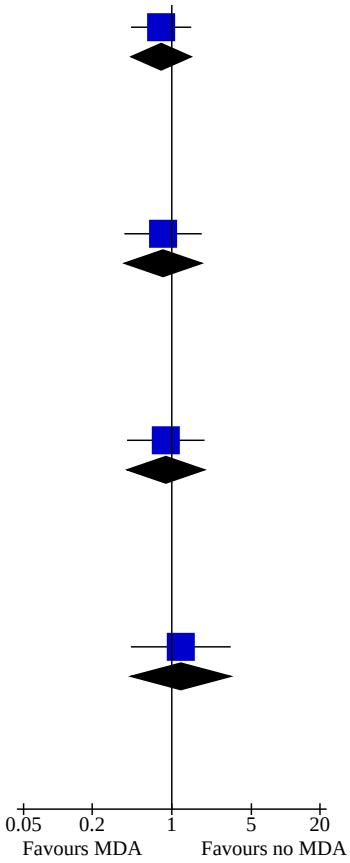
Analysis 3.1. Comparison 3: MDA versus no MDA in very low to low endemicity (cRCTs) on *P vivax* outcomes, Outcome 1: Parasitaemia prevalence (*P vivax*)



Study or Subgroup	MDA Events	MDA Total	No MDA Events	No MDA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Baseline before MDA						
Landier 2017 MMRa (1)	130	689	148	848	61.6%	1.08 [0.87 , 1.34]
McLean 2021 MMR (2)	36	136	24	90	13.4%	0.99 [0.64 , 1.55]
Pongvongsa 2018 LAO (3)	0	14	2	13	1.2%	0.19 [0.01 , 3.56]
Tripura 2018 KHM (4)	8	70	8	91	3.2%	1.30 [0.51 , 3.29]
von Seidlein 2019 VNM (5)	42	670	41	566	20.6%	0.87 [0.57 , 1.31]
Subtotal (95% CI)		**1579**		**1608**	**100.0%**	**1.02 [0.86 , 1.21]**
Total events:	216		223			
Heterogeneity: Chi² = 2.44, df = 4 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
3.1.2 Post-MDA <1 month						
McLean 2021 MMR (6)	7	142	25	92	100.0%	0.18 [0.08 , 0.40]
Subtotal (95% CI)		**142**		**92**	**100.0%**	**0.18 [0.08 , 0.40]**
Total events:	7		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.20 (P < 0.0001)						
3.1.3 Post-MDA 1-3 months						
Landier 2017 MMRa (7)	4	434	113	639	55.4%	0.05 [0.02 , 0.14]
McLean 2021 MMR (8)	18	151	12	75	9.7%	0.75 [0.38 , 1.46]
Pongvongsa 2018 LAO (9)	0	22	2	21	1.5%	0.19 [0.01 , 3.76]
Tripura 2018 KHM (10)	1	82	11	121	5.4%	0.13 [0.02 , 1.02]
von Seidlein 2019 VNM (11)	8	634	41	494	27.9%	0.15 [0.07 , 0.32]
Subtotal (95% CI)		**1323**		**1350**	**100.0%**	**0.15 [0.10 , 0.24]**
Total events:	31		179			
Heterogeneity: Chi² = 25.54, df = 4 (P < 0.0001); I² = 84%						
Test for overall effect: Z = 8.67 (P < 0.00001)						
3.1.4 Post-MDA 4-6 months						
Landier 2017 MMRa (12)	58	419	119	750	44.6%	0.87 [0.65 , 1.17]
Pongvongsa 2018 LAO (13)	0	68	5	56	3.2%	0.08 [0.00 , 1.33]
Tripura 2018 KHM (14)	1	66	8	91	3.5%	0.17 [0.02 , 1.34]
von Seidlein 2019 VNM (1)	80	1012	85	837	48.7%	0.78 [0.58 , 1.04]
Subtotal (95% CI)		**1565**		**1734**	**100.0%**	**0.78 [0.63 , 0.95]**
Total events:	139		217			
Heterogeneity: Chi² = 5.22, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 2.45 (P = 0.01)						
3.1.5 Post-MDA 7-12 months						
Landier 2017 MMRa (1)	107	562	96	750	40.9%	1.49 [1.16 , 1.92]
McLean 2021 MMR (15)	24	161	14	82	9.2%	0.87 [0.48 , 1.60]
Pongvongsa 2018 LAO (16)	0	126	5	107	3.0%	0.08 [0.00 , 1.38]
Tripura 2018 KHM (17)	12	255	35	542	11.1%	0.73 [0.38 , 1.38]
von Seidlein 2019 VNM (1)	81	1026	64	795	35.8%	0.98 [0.72 , 1.34]
Subtotal (95% CI)		**2130**		**2276**	**100.0%**	**1.12 [0.94 , 1.34]**
Total events:	224		214			
Heterogeneity: Chi² = 11.20, df = 4 (P = 0.02); I² = 64%						
Test for overall effect: Z = 1.28 (P = 0.20)						
3.1.6 Post-MDA 13-18 months						
McLean 2021 MMR (18)	23	163	14	80	100.0%	0.81 [0.44 , 1.48]
Subtotal (95% CI)		**163**		**80**	**100.0%**	**0.81 [0.44 , 1.48]**

Analysis 3.1. (Continued)

McLean 2021 MMR (18)	23	163	14	80	100.0%	0.81 [0.44 , 1.48]
Subtotal (95% CI)		**163**		**80**	**100.0%**	**0.81 [0.44 , 1.48]**
Total events:	23		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
3.1.7 Post-MDA 19-24 months						
McLean 2021 MMR (19)	15	159	9	80	100.0%	0.84 [0.38 , 1.83]
Subtotal (95% CI)		**159**		**80**	**100.0%**	**0.84 [0.38 , 1.83]**
Total events:	15		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
3.1.8 Post-MDA 25-30 months						
McLean 2021 MMR (20)	15	158	9	84	100.0%	0.89 [0.41 , 1.94]
Subtotal (95% CI)		**158**		**84**	**100.0%**	**0.89 [0.41 , 1.94]**
Total events:	15		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
3.1.9 Post-MDA 31-36 months						
McLean 2021 MMR (21)	12	164	5	82	100.0%	1.20 [0.44 , 3.29]
Subtotal (95% CI)		**164**		**82**	**100.0%**	**1.20 [0.44 , 3.29]**
Total events:	12		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.72)						
Test for subgroup differences: Chi^2 = 92.26, df = 8 (P < 0.00001), I^2 = 91.3%						

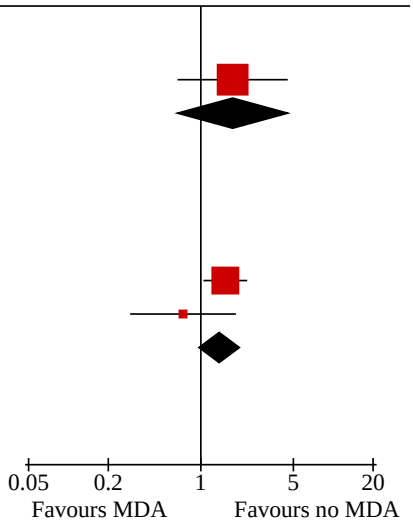


Footnotes

(1) All ages ≥ 6 months; uPCR; ICC = 0
(2) Ages 18-55 years; uPCR; raw data: 164 (MDA events), 621 (MDA total), 109 (Control events), 412 (Control total)
(3) All ages ≥ 6 months; uPCR; raw data: 20 (MDA events), 859 (MDA total), 118 (Control events), 802 (Control total)
(4) All ages ≥ 6 months; uPCR; raw data: 58 (MDA events), 543 (MDA total), 62 (Control events), 701 (Control total)
(5) All ages ≥ 6 months; uPCR; raw data: 79 (MDA events), 1247 (MDA total), 77 (Control events), 1054 (Control total)
(6) Ages 18-55 years; uPCR; raw data: 37 (MDA events), 747 (MDA total), 131 (Control events), 485 (Control total)
(7) All ages ≥ 6 months; uPCR; raw data: 5 (MDA events), 552 (MDA total), 144 (Control events), 812 (Control total)
(8) Ages 18-55 years; uPCR; raw data: 82 (MDA events), 675 (MDA total), 54 (Control events), 336 (Control total)
(9) All ages ≥ 6 months; uPCR; raw data: 0 (MDA events), 745 (MDA total), 84 (Control events), 722 (Control total)
(10) All ages ≥ 6 months; uPCR; raw data: 3 (MDA events), 470 (MDA total), 64 (Control events), 696 (Control total)
(11) All ages ≥ 6 months; uPCR; raw data: 14 (MDA events), 1061 (MDA total), 68 (Control events), 827 (Control total)
(12) All ages ≥ 6 months; uPCR; raw data: ICC = 0
(13) All ages ≥ 6 months; uPCR; raw data: 2 (MDA events), 801 (MDA total), 54 (Control events), 655 (Control total)
(14) All ages ≥ 6 months; uPCR; raw data: 11 (MDA events), 504 (MDA total), 63 (Control events), 692 (Control total)
(15) Ages 18-55 years; uPCR; raw data: 154 (MDA events), 1013 (MDA total), 88 (Control events), 515 (Control total)
(16) All ages ≥ 6 months; uPCR; raw data: 3 (MDA events), 808 (MDA total), 33 (Control events), 689 (Control total)
(17) All ages ≥ 6 months; uPCR; raw data: 24 (MDA events), 512 (MDA total), 71 (Control events), 1090 (Control total)
(18) Ages 18-55 years; uPCR; raw data: 148 (MDA events), 1029 (MDA total), 87 (Control events), 508 (Control total)
(19) Ages 18-55 years; uPCR; raw data: 86 (MDA events), 927 (MDA total), 51 (Control events), 466 (Control total)
(20) Ages 18-55 years; uPCR; raw data: 92 (MDA events), 993 (MDA total), 56 (Control events), 528 (Control total)
(21) Ages 18-55 years; uPCR; raw data: 85 (MDA events), 1117 (MDA total), 35 (Control events), 562 (Control total)

Analysis 3.2. Comparison 3: MDA versus no MDA in very low to low endemicity (cRCTs) on *P vivax* outcomes, Outcome 2: Confirmed malaria illness incidence (*P vivax*)

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI
3.2.1 Baseline before MDA				
Tripura 2018 KHM (1)	0.553	0.489	100.0%	1.74 [0.67 , 4.53]
Subtotal (95% CI)			**100.0%**	**1.74 [0.67 , 4.53]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.13 (P = 0.26)				
3.2.2 Post-MDA 7-12 months				
Landier 2017 MMRa (2)	0.426	0.194	85.4%	1.53 [1.05 , 2.24]
Tripura 2018 KHM (3)	-0.31	0.469	14.6%	0.73 [0.29 , 1.84]
Subtotal (95% CI)			**100.0%**	**1.38 [0.97 , 1.95]**
Heterogeneity: Chi² = 2.10, df = 1 (P = 0.15); I² = 52%				
Test for overall effect: Z = 1.78 (P = 0.08)				



Footnotes

(1) All ages; July 2014 - June 2015; *Plasmodium vivax*

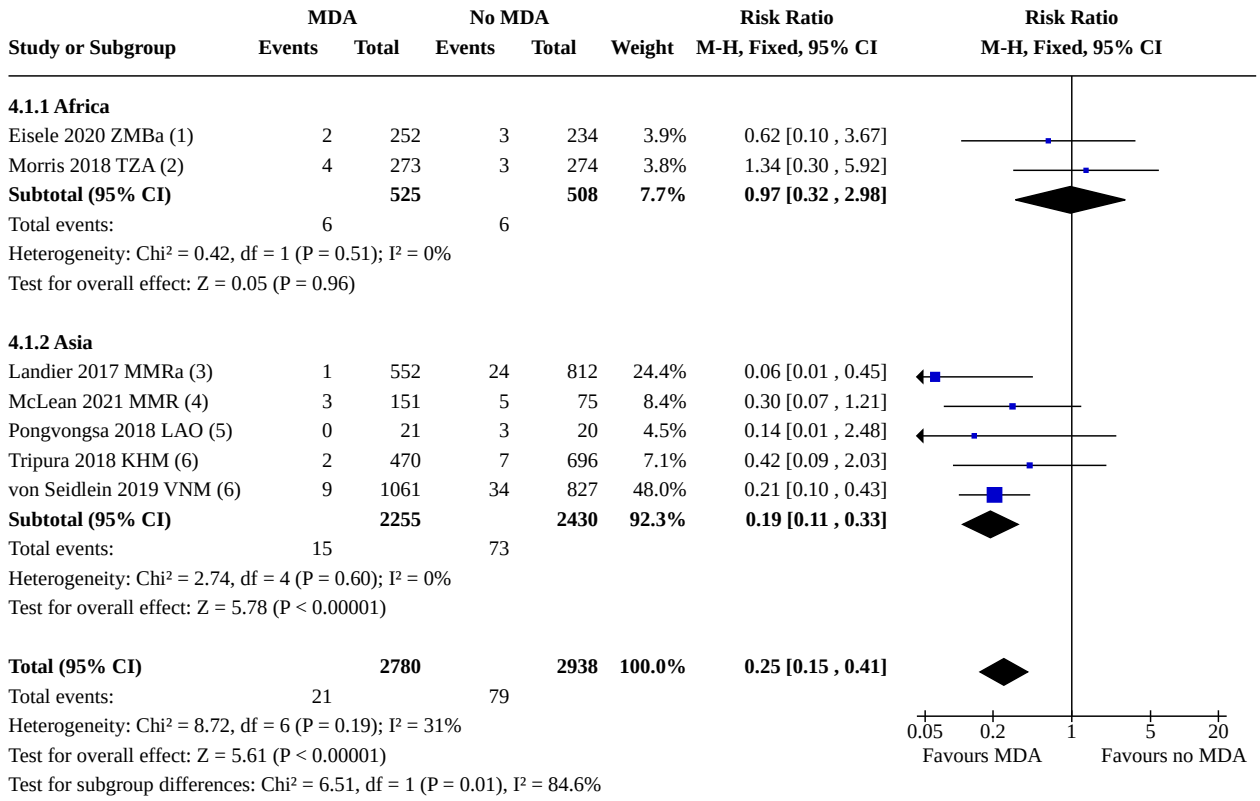
(2) All ages; May 2013 to January 2014; *Plasmodium vivax*

(3) All ages; July 2015 - June 2016; *Plasmodium vivax*

Comparison 4. Supplemental analysis: post-hoc subgroup analysis by continent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 *Plasmodium falciparum* parasitaemia prevalence post-MDA 1-3 months	7	5718	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.15, 0.41]
4.1.1 Africa	2	1033	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.32, 2.98]
4.1.2 Asia	5	4685	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.11, 0.33]

Analysis 4.1. Comparison 4: Supplemental analysis: post-hoc subgroup analysis by continent, Outcome 1: *Plasmodium falciparum* parasitaemia prevalence post-MDA 1-3 months



Footnotes

(1) Children ≤ 5 years; RDT; raw data: 3 (MDA events), 392 (MDA total), 5 (Control events), 365 (Control total)
(2) All ages; qPCR; raw data: 67 (MDA events), 4896 (MDA total), 53 (Control events), 4905 (Control total)
(3) All ages ≥ 6 months; uPCR; raw data: 1 (MDA events), 552 (MDA total), 24 (Control events), 812 (Control total)
(4) Ages 18-55 years; uPCR; raw data: 14 (MDA events), 675 (MDA total), 21 (Control events), 336 (Control total)
(5) All ages ≥ 6 months; uPCR; raw data: 0 (MDA events), 745 (MDA total), 90 (Control events), 722 (Control total)
(6) All ages ≥ 6 months; uPCR; ICC = 0

ADDITIONAL TABLES

Table 1. Description of studies

Study ID (Design)	Year(s) of study	Malaria endemicity[a]	*Plasmodium* species	Antimalarial drug resistance	MDA group			Control group	Co-intervention(s)[b]	Outcomes reported (months of follow-up post-MDA[c])
					Drug	Rounds, interval, and duration implemented	Population targeted (coverage)			
Eisele 2020 ZMBa (cRCT)	2014-2017	Low	*P falciparum*	Widespread resistance to CQ and SP, but no evidence of resistance to artemisinin	DHAp	4 rounds administered at start of rainy season, during rainy season, during dry season, and at start of rainy season over 15 months	37,694 (79% in round 1; 63% in round 2; 76% in round 3; 66% in round 4)	No drug and no placebo	IRS, ITNs, and enhanced standard of care	• Parasitaemia prevalence (2) • Parasitaemia incidence (2) • Confirmed malaria case incidence (2) • Adverse effects
Eisele 2020 ZMBb (cRCT)	2014-2017	High	*P falciparum*	Widespread resistance to CQ and SP, but no evidence of resistance to artemisinin	DHAp	4 rounds administered at start of rainy season, during rainy season, during dry season, and at start of rainy season over 15 months	45,442 (79% in round 1; 63% in round 2; 76% in round 3; 66% in round 4)	No drug and no placebo	IRS, ITNs, and enhanced standard of care	• Parasitaemia prevalence (2) • Parasitaemia incidence (2) • Confirmed malaria case incidence (2) • Adverse effects
Escudie 1962 BFA (CBA)	1960-1961	High	*P falciparum*, *P ovale*, *P malariae*	ND	AQ-PQ or CQ-PQ	(Low frequency MDA) 7 rounds administered 28 days apart over 7 months	1890 (75% to 91% per round)	No drug and no placebo	None (IRS arms excluded)	• Parasitaemia prevalence (3) • Gametocytaemia prevalence (3)
						(High frequency MDA) 15 rounds administered 14 days apart over 7 months	2560 (84% to 97% per round)			• Parasitaemia prevalence (3) • Gametocytaemia prevalence (3)

Table 1. Description of studies *(Continued)*

Landier 2017 MMRa (cRCT)	2013-2015	Low	*P falciparum*, *P vivax*	Artemisinin resistance firmly established	DHAp with PQ	3 rounds administered 1 month apart over 3 months	1434 (66% in round 1, 56% in round 2, and 65% in round 3)	Delayed MDA	ITNs, uninterrupted access to case management	• Parasitaemia prevalence (7) • Confirmed malaria illness incidence (7) • Adverse effects
McLean 2021 MMR (cRCT)	2014-2017	Very low	*P falciparum*, *P vivax*	Artemisinin resistance: Kelch 13 mutation in 57% of samples at baseline	DHAp with PQ	3 rounds administered 1 month apart over 3 months	4622 (86% in round 1, 86% in round 2, 88% in round 3)	No drug and no placebo	ITNs, routine malaria control by village health workers	• Parasitaemia prevalence (31) • Adverse effects
Molineaux 1980 NGA (CBA)	1970-1975	High	*P falciparum*, *P malariae*, *P ovale*	ND	SP	(Low frequency MDA) 9 rounds administered 10 weeks apart over 18 months	14,129 (73% to 92% per round)	No drug and no placebo	IRS	• Parasitaemia prevalence (0) • Gametocytaemia prevalence (0)
						(High frequency MDA) 23 rounds administered 2 weeks apart during the wet seasons and 10 weeks apart during the dry seasons over 18 months	1810 (72% to 91% per round)			
Morris 2018 TZA (cRCT)	2016-2017	Very low	*P falciparum*, *P malariae*, *P ovale*, and *P vivax*	No evidence of resistance to first line treatment AS-AQ	DHAp with PQ	2 rounds administered 4 weeks apart over 6 weeks	10,944 (91% in round 1, 88% in round 2)	No drug and no placebo	IRS and ITNs	• Parasitaemia prevalence (0) • Confirmed malaria illness incidence (14) • Adverse effects

Table 1. Description of studies *(Continued)*

Pongvongsa 2018 LAO (cRCT)	2016-2017	Low	*P falciparum*, *P vivax*	ND	DHAp with PQ	3 rounds administered 1 month apart over 3 months	1006 (81% in round 1, 80% in round 2, and 82% in round 3)	Delayed MDA	ITNs, uninterrupted access to case management	• Parasitaemia prevalence (10) • Adverse effects
Roberts 1964 KEN (CBA)	1953-1954	Moderate	*P falciparum*	ND	Pyrimethamine	2 rounds administered 1 year apart over 13 months	101,000 (95% in round 1, 93% in round 2)	No drug and no placebo	None	• Parasitaemia prevalence (7)
Shekalaghe 2011 TZA (cRCT)	2008	Very low	*P falciparum*	ND	SP+AS with PQ	1 round over 16 days	1110 (95%)	Placebo	ITNs, single treatment campaign for trachoma with azithromycin	• Parasitaemia prevalence (4) • Confirmed malaria illness incidence (4) • Gametocytaemia prevalence (4) • Adverse effects
Tripura 2018 KHM (cRCT)	2014-2016	Very low	*P falciparum*, *P vivax*	Reduced susceptibility to artemisinins and ACT partner drug resistance	DHAp	3 rounds administered 1 month apart over 3 months	858 (74% in round 1, 60% in round 2, and 71% in round 3)	Delayed MDA	ITNs, uninterrupted access to case management	• Parasitaemia prevalence (10) • Confirmed malaria case incidence (9) • Adverse effects
von Seidlein 2003 GMB (cRCT)	1999	High	*P falciparum*	ND	SP+AS	1 round over 1 month	12,331 (89%)	Placebo	None	• Parasitaemia prevalence (5) • Parasitaemia incidence (5) • Gametocytaemia prevalence (5) • Malaria-specific mortality • Adverse effects

Table 1. Description of studies *(Continued)*

von Seidlein 2019 VNM (cRCT)	2013-2015	Very low	*P falciparum*, *P vivax*	No evidence of resistance to DHAp at the start of study, but treatment failure to DHAp has increased following study	DHAp with PQ	3 rounds administered 1 month apart over 3 months	1439 (83% in round 1, 98% in round 2, and 99% in round 3)	Delayed MDA	ITNs, uninterrupted access to case management	• Parasitaemia prevalence (10) • Adverse effects

ACT = artemisinin-based combination therapy, AQ = amodiaquine, AS = artesunate, CBA = controlled before-and-after study, CQ = chloroquine, cRCT = cluster-randomized controlled trial, DHAp = dihydroartemisinin piperaquine, ITNs = insecticide-treated bed nets, IRS = indoor residual spraying, MDA = mass drug administration, PQ = primaquine, SP = sulfadoxine- (or sulfalene-) pyrimethamine, NA = not applicable, ND = not described.

[a]Malaria endemicity classified as very low (> 0% to < 1%), low (1% to < 10%), moderate (10% to < 35%) or high (≥ 35%) (WHO 2017).

[b]Co-interventions were balanced across intervention and control groups, as per inclusion criteria.

[c]Post-MDA refers to the length of time, in months, after the last round of MDA that the outcome was evaluated.

Table 2. Description of outcomes

Study ID (design)	Parasitaemia prevalence	Parasitaemia incidence	Confirmed malaria illness incidence	All-cause or malaria-specific mortality	Gametocytaemia prevalence	Adverse effects
Eisele 2020 ZMBa (cRCT)	Yes	Yes	Yes	No	No	Yes
Eisele 2020 ZMBb (cRCT)	Yes	Yes	Yes	No	No	Yes
Escudie 1962 BFA (CBA)	Yes	No	No	No	Yes	No
Landier 2017 MMRa (cRCT)	Yes	No	Yes	No	No	Yes
McLean 2021 MMR (cRCT)	Yes	No	No	No	No	Yes
Molineaux 1980 NGA (CBA)	Yes	No	No	No	Yes	No
Morris 2018 TZA (cRCT)	Yes	No	Yes	No	No	Yes
Pongvongsa 2018 LAO (cRCT)	Yes	No	No	No	No	Yes
Roberts 1964 KEN (CBA)	Yes	No	No	No	No	No
Shekalaghe 2011 TZA (cRCT)	Yes	No	Yes	No	Yes	Yes
Tripura 2018 KHM (cRCT)	Yes	No	Yes	No	No	Yes
von Seidlein 2003 GMB (cRCT)	Yes	Yes	Yes	Yes	Yes	Yes
von Seidlein 2019 VNM (cRCT)	Yes	No	No	No	No	Yes

CBA = controlled before-and-after study, cRCT = cluster-randomized controlled trial

Table 3. Difference-in-differences analysis of *P falciparum* parasitaemia prevalence in non-randomized studies

Study	Intervention, % (n)					Control % (n)					Difference-in-differences, percentage points[a]			
	Pre-MDA	During MDA	Post-MDA			Pre-MDA	During MDA	Post-MDA			During MDA	Post-MDA		
			1 to 3 months	4 to 6 months	7 to 12 months			1 to 3 months	4 to 6 months	7 to 12 months		1 to 3 months	4 to 6 months	7 to 12 months
Escudie 1962 BFA [b]														
Low frequency MDA with AQ-PQ or CQ-PQ	67.6 (190)	21.6 (75)	38.3 (105)	ND	ND	59.4 (129)	74.8 (517)	386 (72.3)	ND	ND	-61.4	-42.1	ND	ND
High frequency MDA with AQ-PQ or CQ-PQ	33.6 (131)	12.6 (59)	61.4 (286)	ND	ND	59.4 (129)	74.8 (517)	386 (72.3)	ND	ND	-36.3	14.9	ND	ND
Molineaux 1980 NGA [c]														
Low frequency MDA with SP	41.8 (525)	1.9 (40)	ND	ND	ND	49.1 (493)	32.5 (380)	ND	ND	ND	-23.2	ND	ND	ND
High frequency MDA with SP	44.9 (754)	7.3 (109)	ND	ND	ND	49.1 (493)	32.5 (380)	ND	ND	ND	-20.9	ND	ND	ND
Roberts 1964 KEN														
MDA with pyrimethamine	8.3 (25)	9 (188)	2.9 (26)	(27) (4.5)	(15) (5)	18 (154)	34.4 (723)	40.7 (366)	37 (222)	26 (78)	-15.8	-28.1	-22.8	-11.3

AQ = amodiaquine, CQ = chloroquine, MDA = mass drug administration, ND = no data, PQ = primaquine, SP = sulfalene-pyrimethamine

[a]Calculated as difference in proportion at the time period of during MDA or post-MDA minus the proportion at pre-MDA in the intervention and control separately and the difference in these two proportion differences between the intervention and control groups.

[b]MDA with AQ-PQ or CQ-PQ either every 4 weeks ('low frequency MDA') or every 2 weeks ('high frequency MDA').

[c]MDA with sulfalene-pyrimethamine either every 10 weeks (low frequency MDA') or every 2 weeks during the wet season and every 10 weeks during the dry season ('high frequency MDA') to all ages except infants prior to their first malaria episode.

Table 4. Difference-in-differences analysis of *P falciparum* gametocytaemia prevalence in non-randomized studies

Study	Intervention, % (n)	Control, % (n)	Difference-in-differences percentage point[a]

Table 4. Difference-in-differences analysis of *P falciparum* gametocytaemia prevalence in non-randomized studies *(Continued)*

	Pre-MDA	During MDA	Post-MDA 1 to 3 months	Pre-MDA	During MDA	Post-MDA 1 to 3 months	During MDA	Post-MDA 1 to 3 months
Escudie 1962 BFA [b]								
Low frequency MDA with AQ-PQ or CQ-PQ	20.3 (57)	0.9 (3)	38.3 (35)	19.4 (42)	14 (97)	19.1 (102)	-14.1	18.3
High frequency MDA with AQ-PQ or CQ-PQ	8.2 (32)	1.9 (9)	61.4 (107)	19.4 (42)	14 (97)	19.1 (102)	-1.0	53.4
Molineaux 1980 NGA [c]								
Low frequency MDA with SP	10.1 (127)	0.6 (12)	ND	12.4 (124)	7.9 (92)	ND	-5.0	ND
High frequency MDA with SP	12.4 (208)	3.2 (48)	ND	12.4 (124)	7.9 (92)	ND	-4.7	ND

AQ = amodiaquine, CQ = chloroquine, MDA = mass drug administration, ND = no data, SP = sulfalene-pyrimethamine

[a]Calculated as difference in proportion at the time period of during MDA or post-MDA minus the proportion at pre-MDA in the intervention and control separately and the difference in these two proportion differences between the intervention and control groups.

[b]MDA with AQ-PQ or CQ-PQ either every 4 weeks ('low frequency MDA') or every 2 weeks ('high frequency MDA').

[c]MDA with sulfalene-pyrimethamine either every 10 weeks ('low frequency MDA') or every 2 weeks during the wet season and every 10 weeks during the dry season ('high frequency MDA') to all ages except infants prior to their first malaria episode.

APPENDICES

Appendix 1. Search strategies

The search strategies carried out for databases are provided below.

Search Name: Cochrane Central Register of Controlled Trials

ID	Search
#2	"antimalarial":ti,ab,kw (Word variations have been searched)
#3	malaria:ti,ab,kw (Word variations have been searched)
#4	MeSH descriptor: [Malaria] explode all trees
#5	MeSH descriptor: [Antimalarials] explode all trees
#6	#2 or #3 or #4 or #5
#7	"mass chemoprophylaxis" or "mass drug administration" or "mass administration"
#8	"mass screening and treatment"
#9	"mass treatment"
#10	MDA or MSAT or iMSaT
#11	MeSH descriptor: [Mass Drug Administration] explode all trees
#12	#7 or #8 or #9 or #10 or #11
#13	#6 and #12

Database: Embase 1947-Present, updated daily

1	malaria/ or malaria control/
2	antimalarial agent/ or antimalarial*.mp.
3	(malaria or antimalarial*).ab. or (malaria or antimalarial*).ti.
4	1 or 2 or 3
5	("mass chemoprophylaxis" or "mass drug administration" or "mass administration").mp.
6	mass drug administration.mp.
7	mass treatment.mp.
8	"mass screening and treatment".mp.

(Continued)

9	5 or 6 or 7 or 8
10	4 and 9
11	randomized controlled trial/
12	controlled clinical trial.mp. or Controlled Clinical Trial/
13	(randomized or placebo or double-blind* or single-blind*).mp.
14	crossover procedure/ or crossover study.mp.
15	time series.mp. or time series analysis/
16	(before and after).mp.
17	11 or 12 or 13 or 14 or 15 or 16
18	10 and 17

PubMed search history

Search	Query
#1	malaria Field: Title/Abstract
#2	antimalarial*or anti-malarial* Field:Title/Abstract
#3	(malaria[MeSH Terms]) OR antimalarials[MeSH Terms]
#4	#1 or #2 or #3
#5	((mass chemoprophylaxis) OR mass drug administration) OR mass administration Field:Title/Abstract
#6	"mass screening and treatment" Field: Title/Abstract
#7	(MDA[Title/Abstract] OR MSAT[Title/Abstract] OR iMSaT[Title/Abstract])
#8	mass drug administration[MeSH Terms]
#9	#5 or #6 or #7 or #8
#10	#4 and #9
#11	"Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]
#12	(randomized or placebo or double-blind* or single-blind*) [Title/Abstract]
#13	"Cross-Over Studies"[Mesh]

(Continued)

#14	"Interrupted Time Series Analysis"[Mesh]
#15	"Controlled Before-After Studies"[Mesh]
#16	#11 or #12 or #13 or #14 or #15
#17	#10 and #16

Database :	**LILACS**
Search on :	**malaria or antimalarial$ [Words] and mass administration [Words]**

Appendix 2. Prespecified changes for review update

Protocol section	Author responses
Background and research question	• We have updated the background section to highlight current gaps in knowledge surrounding MDA in all malaria transmission settings and in light of evidence and policy recommendations since the previous (2013) review was published. • Given the focus on synthesizing evidence for the sustained impact of MDA in both low and moderate- to high-transmission settings, the primary objectives have been modified to reflect evidence of interruption of transmission in low transmission settings and reduction in transmission in moderate- to high-transmission settings.
Inclusion criteria	• Inclusion criteria (including selection of more rigorous study designs and control groups) has been updated from the previous (2013) review. • We have clarified the inclusion of special groups (i.e. refugees, soldiers) if these studies meet eligibility criteria. • The description of the intervention (MDA) has also been updated to reflect the current definition.
Methods	• Primary and secondary outcomes have also been updated to align with the objectives and include method of measurement. • The search strategy has been refreshed since the previous review. • Data items for the summary of findings table have been added and modified, including definitions of malaria endemicities to match current criteria for very low, low, moderate, and high transmission settings (in the 'Data synthesis' section). In addition, we have specified that only molecular data were available for baseline prevalence. A tool developed by Okell 2012 was used to estimate equivalent microscopy prevalence from PCR data. • Additional details on ICC estimation have been provided for methodology related to analysis of cRCTs • Subgroup analyses have been revised and pre-specified. • The time points at which outcomes will be stratified have been specified in the 'Data synthesis' section.

Abbreviations: MDA: mass drug administration.

This table was approved by the CIDG editorial team on 4 April 2018.

WHAT'S NEW

Date	Event	Description
23 September 2021	New citation required and conclusions have changed	The last published version of this review included 32 studies: two cRCTs, eight non-randomized trials, and 22 uncontrolled before-and-after studies (Poirot 2013). Following the revised inclusion criteria, which restricted the review to more rigorous study designs with a control group and balanced co-interventions across study arms (described in detail in Differences between protocol and review), the updated literature search (to 11 February 2021) identified 13 studies that met the inclusion criteria.
23 September 2021	New search has been performed	The author team was amended for this review update version. Pre-specified revisions made to the background, inclusion criteria, and methods sections are detailed in Appendix 2. In addition, we analysed non-randomized studies using a difference-in-difference analysis, as detailed in the Methods section. We also conducted a post-hoc analysis to explore differences in malaria epidemiology by continent as a reason for heterogeneity in effect of MDA on *P falciparum* parasitaemia prevalence at one to three months after MDA in very low- to low-endemicity settings.

HISTORY

Protocol first published: Issue 11, 2010
Review first published: Issue 12, 2013

CONTRIBUTIONS OF AUTHORS

MD, JH, SPK, and KAL conceived of and designed the protocol. MPS and MD reviewed the literature and extracted the data. KAL and LC helped to resolve discrepancies. MPS, LC, and MD conducted the analyses. MPS, LC, and MD drafted the manuscript. All authors reviewed and provided final approval of the manuscript prior to publication.

DECLARATIONS OF INTEREST

MPS has no known conflicts of interest.

JH has no known conflicts of interest.

LC has no known conflicts of interest.

KAL has no known conflicts of interest.

SPK has no known conflicts of interest.

MD has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Centers for Disease Control and Prevention, USA
- US President's Malaria Initiative, USA

  JH received salary support
- Liverpool School of Tropical Medicine, UK

External sources

- Foreign, Commonwealth and Development Office (FCDO), UK

  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between review and review update

A new author team was formed for this 2021 review update, with several authors from the previous review version (JH, SPK). Dr Monica Shah is the contact author for this 2021 review update.

Pre-specified revisions made to the background, inclusion criteria, and methods sections are detailed in Appendix 2. In addition, we analysed non-randomized studies using a difference-in-difference analysis, as detailed in the methods section of this review update. We also conducted a post-hoc analysis to explore differences in malaria epidemiology by continent as a reason for heterogeneity in effect of MDA on *P falciparum* parasitaemia prevalence at one to three months after MDA in very low- to low-endemicity settings. The post-hoc analysis by subgroup (studies conducted in Africa and Asia) is presented in Analysis 4.1.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*administration & dosage] [adverse effects]; Disease Eradication [methods]; *Endemic Diseases; Malaria [*drug therapy]; Parasitemia [*drug therapy]; Program Evaluation

MeSH check words

Humans