Research needs

- Further evidence is needed on the impact (prevalence and incidence of malaria infection at the community level) and potential harms/unintended consequences of TDA for malaria in very low to low transmission or post-elimination settings.
- Evidence is needed on the acceptability, feasibility, impact (prevalence and incidence of malaria infection at the community level) and potential harms/unintended consequences (death, hospital admission, severe anaemia or any severe adverse events) of safe provision (including testing for G6PD deficiency and, additionally, an effective pharmacovigilance system and emergency access to blood transfusion services) of an 8-aminoquinoline as part of TDA for radical cure of *P. vivax* infections.
- Investigate approaches to characterizing higher-risk situations with respect to their contribution to the overall human infectious reservoir.
- Evidence is needed to optimize the delivery of TDA with respect to the synchronicity of treatments, time intervals between rounds of treatment, number of rounds needed per year and number of years needed to sustainably reduce malaria transmission.
- Evidence is needed on whether TDA stigmatizes groups that might already be socially isolated, such as migrants or refugee populations.

6.2.2 Targeted testing and treatment (TTaT)

Targeted testing and treatment (TTaT) is the parasitological testing of individuals at increased risk of malaria infection and treatment of all positive cases with an appropriate antimalarial medicine. TTaT is an active case detection strategy that is implemented among people considered to have a higher risk of malaria infection than the general public and whose infections likely constitute a large proportion of the infectious reservoir in an area. TTaT is generally conducted using point of contact malaria rapid diagnostic tests but also has been conducted using microscopy and nucleic acid-based tests.

TTaT, as opposed to MTaT, is provided to specific individuals or to a subset of the population rather than to everyone present in a delimited geographical area. As with TDA, the premise of the TTaT strategy is that diagnosing and treating infections in individuals whose occupations or behaviours put them at increased risk of malaria infection may reduce transmission in the community if their infections constitute a large proportion of the infectious reservoir. Unlike TDA, however, medicine is only provided to the positive cases in TTaT, reducing the number of people who benefit from protection during the drug's prophylactic period. However, providing antimalarial medicine only to those who have confirmed infections may improve adherence to treatment, population acceptance of the intervention and equity while decreasing the risk of unintended consequences.

Conditional recommendation against , Very low certainty evidence

Targeted testing and treatment to reduce transmission of malaria (2022)

Testing and treatment of people with an increased risk of infection relative to the general population to reduce the transmission of malaria is not recommended.

The GDG noted that there may be limited circumstances under which targeted testing and treatment (TTaT) could be beneficial. For example, TTaT could be used when people at a higher risk of infection can be easily identified and chemoprevention is not acceptable to the population. Additionally, TTaT could be used if safe and effective implementation of radical cure to prevent P. vivax relapses is only feasible for those with confirmed infections.

Evidence to decision

Benefits and harms

The systematic review identified three studies for inclusion: two cRCTs in Ghana and Kenya and one NRS in Malawi (Allen *et al* unpublished evidence). Only one study reported measures of malaria transmission outcomes at the community level. No studies were conducted in very low to low transmission or post-elimination settings.

The GDG determined that the TTaT strategy would be most relevant in very low to low transmission or post-elimination settings and, therefore, decided that the PICO question should

	be modified accordingly (i.e. limited to such settings). As a result, the GDG did not consider evidence on benefits from the studies included in the review. The potential harms (i.e. adverse events) from the intervention were considered likely to be trivial, as people who received treatment would be infected with malaria and, therefore, would receive treatment according to national guidelines. The judgements of the GDG related to the balance of effects was based on its expert opinions and indirect information from related interventions, such as MTaT and TDA. The GDG judged that the balance of effects probably favoured not implementing TTaT.
Certainty of the evidence	Very low The overall certainty of the evidence was judged to be very low.
Values and preferences	No studies were identified regarding preferences and values. The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.
Resources	No studies on the cost or cost-effectiveness of TTaT in very low to low transmission or post-elimination settings were found. The GDG judged that the costs required to implement TTaT were moderate, and that the cost-effectiveness probably favoured not implementing TTaT.
Equity	No studies were identified that addressed the issue of whether TTaT increased or decreased health equity. The GDG judged that a targeted strategy that intervenes in a small group of people more affected by malaria than the population surrounding them would improve health equity.
Acceptability	No studies were identified that addressed the issue of acceptability of TTaT in areas of very low to low transmission or post-elimination of malaria. The GDG judged that TTaT was probably acceptable to stakeholders, as it is a type of active case detection.
Feasibility	No studies were identified that addressed the issue of feasibility of TTaT in areas of very low to low transmission or post-elimination of malaria. The GDG noted that the type of parasitological test used (rapid diagnostic test, microscopy or nucleic acid-based test) would affect the feasibility of implementing the strategy as tests that are not point-of-contact would be more difficult to implement, require more technical staff and delay identification and treatment of positive cases. The feasibility of implementing TTaT would also depend on whether radical cure of *P. vivax* using an 8-aminoquinoline medicine was part of the TTaT strategy, which would necessitate testing for G6PD deficiency, an effective pharmacovigilance system and emergency access to blood transfusion services. The GDG judged that implementation of TTaT was probably feasible.

Justification

The GDG judged that the likely impact of TTaT on malaria transmission in very low to low or post-elimination settings would be trivial, based on experiences with MTaT, challenges with detecting very low parasite densities and a lack of diagnostics for hypnozoites. The GDG felt that there may be specific situations where TTaT could be beneficial, for example, when the parasite reservoir is very clearly limited to a small group of people and infections are detectable. Additionally, TTaT could be used if chemoprevention is either not acceptable to the population or safe and effective implementation of radical cure to prevent *P. vivax* is only feasible for those with confirmed infections, but in most settings, TTaT is not likely to reduce malaria transmission.

Research needs

While further evidence of the impact (prevalence and incidence of malaria infection at the community level) of TTaT could change the direction or strength of the recommendation given the lack of published studies on the impact of TTaT, the GDG did not judge that this research gap was a priority.

6.2.3 Testing and treatment at points of entry to reduce importation of malaria

Testing and treatment at points of entry (i.e. border screening) is the parasitological testing of individuals crossing a border whether by land, sea or air and treatment of all positive cases with an appropriate antimalarial medicine. Border screening has been used to try to reduce the number of imported cases of malaria into an area in order to eliminate or prevent re-establishment of malaria transmission. Border screening has generally been applied more often at land crossings than air or seaports.

Routine malaria testing and treatment at land crossings is often implemented at the borders between countries approaching elimination and their neighbours with higher levels of malaria transmission. However, many borders are highly porous with uncounted unofficial crossing points, making it difficult to achieve a high coverage of testing and treatment. Rather than attempting to test and treat individuals at a land crossing, several malaria elimination programmes target organized groups, such as the military or pilgrims, or set up testing and treatment at the points where migrant workers will be employed, such as plantations. This latter approach may improve the acceptability and feasibility of the strategy but depends on good multisectoral collaboration and knowledge of travel patterns.

Under the International Health Regulations (IHR) and for public health purposes, national authorities in the country of arrival may require travellers to undertake a non-invasive medical examination that would achieve the public health objective of preventing the international spread of disease, while respecting travellers' dignity, human rights and fundamental freedoms *[303]*. The IHR recommend that countries that share a land border consider entering into agreements concerning the prevention or control of international transmission of disease at ground crossings; public health measures to prevent international transmission of malaria may apply.

Conditional recommendation against , Very low certainty evidence

Routine malaria testing and treatment at points of entry (2022)

Routine malaria testing and treatment of people arriving at points of entry (land, sea or air) to reduce importation is not recommended.

No studies of the impact of testing and treatment at points of entry on the rate of malaria importation were found by the systematic review. Routine testing and treatment for malaria at points of entry is unlikely to be acceptable or feasible to implement.

Evidence to decision

Certainty of the evidence	Very low

Conditional recommendation for , Very low certainty evidence

Malaria testing and treatment of organized or identifiable groups arriving or returning from malaria-endemic areas (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, organized or identifiable groups arriving or returning from malaria-endemic areas can be tested and treated soon after entry to reduce importation of malaria.

Relatively easy access to these groups within a short time after entry is required for this strategy to be feasible and acceptable. This strategy may be particularly critical to areas in post-elimination that are working to prevent re-establishment of transmission.

Evidence to decision

Benefits and harms

The systematic review identified seven NRSs in six countries (Cambodia, China, Equatorial Guinea, Greece, Myanmar and the United Arab Emirates that reported on testing and treatment at points of entry (Coma-Cros *et al* *unpublished evidence*). None of the studies provided information on the outcome considered critical by the GDG, i.e. the number of positive cases identified by the strategy as a proportion of all imported cases found in the country during the same period.

The GDG noted that border screening may take two forms: the traditional approach of testing and treatment of individuals at the time of entry through land crossings, seaports or airports; and the testing and treatment of organized or identifiable groups (e.g. military, migrant workers or religious pilgrims) recently arriving or returning from malaria-endemic areas. Because there are clear differences in the feasibility and acceptability of these two approaches, the GDG developed two separate recommendations.

The benefits of testing and treatment at points of entry could not be assessed as no studies reporting on critical outcomes were identified by the review.

The potential harms (i.e. adverse events) from the intervention were considered likely to be trivial, as people who received treatment would be infected with malaria and, therefore, treated according to national guidelines.

The GDG judged that the balance of effects probably varied depending on the source population, strictness of entry into the area, coverage of the intervention, species of parasite, type of parasitological test and the area's epidemiological profile with respect to malaria.

Certainty of the evidence

Very low

The certainty of evidence was judged to be very low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.

Resources

The systematic review identified one study with data on the cost of testing and treatment at points of entry (Coma-Cros *et al* *unpublished evidence*). One NRS study of testing and treatment of recently arrived migrant workers estimated that the programme cost US$ 226 080 annually between 2013 and 2017. No studies of the cost-effectiveness of testing and treatment at points of entry were identified.

The GDG judged the costs required to implement testing and treatment at points of entry to be moderate, and the cost-effectiveness probably varied depending on whether the intervention was applied to individuals at the point of entry or to organized or identifiable groups immediately after arrival. In the latter case, the GDG judged that the intervention was probably cost-effective compared to not testing and treating organized or identifiable groups.

Equity

No studies were identified that addressed the issue of whether testing and treatment at points of entry increased or decreased health equity.

The GDG judged that the testing and treatment of organized or identifiable groups was likely to be more equitable than the routine testing and treatment of individuals at the point of entry.

Acceptability

The systematic review identified two studies of acceptability (Coma-Cros *et al* *unpublished evidence*). One study assessed the number of refusals for testing at border crossing points between Cambodia and Thailand, Viet Nam and Lao People's Democratic Republic. Out of 4110 people approached, 904 (22%) refused to be tested for malaria. The main reasons for refusal included: not having enough time (51.6%); not perceiving themselves to be at risk of malaria and thus not requiring testing (40.6%); being scared to give blood (34.2%); and having an apparent language or cultural barrier (23.9%) (multiple answers possible). A qualitative study conducted in 2010 in the Solomon Islands on the feasibility and acceptability of testing all travellers using rapid diagnostic tests and offering treatment to those found positive suggested that there was acceptance and support for such an approach.

The GDG judged that acceptance of testing and treatment at points of entry was likely to vary by stakeholder (less acceptable to travellers at the time of entry but potentially more acceptable to organized groups immediately after entry). Among travellers, acceptability is likely to vary considerably depending on factors such as the location of the screening, the time required and the travellers' level of concern regarding possible malaria infection.

Feasibility

No studies on the feasibility of implementing testing and treatment at points of entry were identified.

The GDG noted that the type of parasitological test used (rapid diagnostic test, microscopy or nucleic acid-based test) would affect the feasibility of implementing the strategy as tests that are not administered at point-of-contact would be more difficult to implement, require more technical staff and delay identification and treatment of positive cases.

The GDG judged that the feasibility of implementing routine testing and treatment at points of entry would likely vary. Implementing such an intervention at airports or seaports was considered unlikely to be feasible due to the high volume of travellers and the time required to test and treat. The feasibility of implementing testing and treatment at land crossings was considered to be more feasible but would depend on the volume of travellers. Additionally, the feasibility of covering a high proportion of people crossing into the country through land crossings would depend on the strictness with which entry into the country was controlled and the porosity of the border. In most areas with porous borders, the GDG judged that the feasibility of implementing a testing and treatment with sufficient coverage at land crossings would be low.

However, the feasibility of implementing testing and treatment among organized or identifiable groups arriving or recently returned from malaria-endemic areas was considered to be high. The GDG knew of many reports of military groups, labour migrants and religious groups in countries eliminating malaria or preventing re-establishment who were tested and treated for malaria after returning from periods in malaria-endemic areas.

Justification

With respect to routine testing and treatment at points of entry (land, sea or air), the GDG, in the absence of direct evidence, judged that the impact on importation of malaria was likely to be small except in areas nearing elimination or post-elimination.

The GDG felt that the acceptability and feasibility of testing and treating for malaria at points of entry would be low given the likely disruption to travel.

When considering organized or identifiable groups of people (e.g. military, migrant laborers or religious pilgrims) arriving or returning from malaria -endemic areas, the GDG judged that testing these groups for malaria and treating those who are positive could help countries nearing elimination or preventing re-establishment by reducing importation. The acceptability and feasibility of this strategy was considered higher than routine testing and treatment at points of entry but would depend upon the local circumstances.

Research needs

- Evidence is needed on the efficiency (number of imported cases identified as a proportion of all imported cases identified during the same period) of testing and treating organized or identifiable groups of people arriving or returning from malaria-endemic areas in terms of the importation of malaria.
- Investigate novel approaches to improving the efficiency of identifying and implementing testing and treatment among organized or identifiable groups, such as the plantation ambassador programme in Malaysia.

6.3 Interventions in response to detection of confirmed malaria cases

As transmission declines and approaches zero, there is evidence that malaria cases tend to cluster more than at higher levels of transmission *[300]*. This clustering could occur geographically, in small areas such as households and neighbourhoods, or socially, among people exposed at the same time and place, such as through a common occupation or shared travel to endemic areas *[301]*. If clusters can be identified and targeted with effective interventions, malaria transmission at the community level may be reduced.

Follow-up of confirmed cases of malaria at very low levels of transmission is one approach to identifying and targeting potential clusters of cases. A confirmed case of malaria, usually identified through passive case detection, is investigated to determine the likely location of infection. Interventions are subsequently implemented in and around the likely location of infection as well as among any people co-exposed with the index case. These strategies are called ‘reactive’ interventions because they are triggered ‘in reaction’ to the identification of a confirmed case of malaria.

The radius of implementation of interventions around the index case will need to be determined according to the strategy implemented, the likelihood that malaria cases could be afebrile and the degree of clustering of cases. For reactive drug administration (RDA) and reactive case detection and treatment (RACDT), programmes could begin with a larger radius of implementation and then evaluate their data to determine whether scaling back the size of the area or limiting activity to just the household of the index case is likely to be the most efficient. For reactive IRS, information on the behaviors and likely flight range of local vector mosquitoes will be needed to determine a reasonable radius of implementation.

Because cases of malaria, whether imported or local, may be identified in post-elimination settings, reactive strategies are also relevant to areas working to prevent re-establishment of malaria. Although data on the effectiveness of strategies in these settings will be extremely rare, evidence from areas with ongoing transmission can serve as indirect evidence for the likely impact in post-elimination settings.

Recommendations related to three reactive strategies, i.e. RDA, RACDT and reactive IRS, are reported below.

6.3.1 Reactive drug administration (RDA)

RDA is the provision of antimalarial medicine as chemoprevention to every person living with or near a person with a confirmed malaria infection, or to every person who was likely exposed to infection at the same time and place as the index case. The antimalarial medicines given during RDA aim to treat all existing infections and prevent new infections over the duration of the drug’s post-treatment prophylaxis period. At minimum, an RDA strategy deploys an antimalarial medicine that targets the asexual, blood-stage malaria parasites (e.g. ACTs or chloroquine). RDA interventions may include additional medicines that target hypnozoites in the liver (e.g. primaquine for radical cure of *P. vivax*) or gametocytes in the blood (e.g. single, low-dose primaquine for *P. falciparum*).

Reactive interventions should target the likely location of infection of the index case. The likely location of infection is determined through a case investigation, using the date of symptom onset and knowledge of the incubation period of the specific parasite species to determine the location of the person during the likely period of infection. If the likely location of infection is a residence, RDA can be administered to at least the household of the confirmed case, but could also be extended to neighbours. If the infection was imported from elsewhere, RDA can be administered to individuals who may have had the same exposure as the index case, such as co-travellers and co-workers.

Conditional recommendation for , Low certainty evidence

Reactive drug administration for reducing malaria transmission (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, antimalarial medicine can be given as chemoprevention to all people residing with or near a confirmed malaria case and all people who share the same risk of infection (e.g. co-travellers and co-workers) to prevent or reduce malaria transmission.

- *Programmes implementing reactive drug administration (RDA) should have the capacity to conduct case investigations at the residence to determine the likely location of infection and to identify those individuals co-exposed with the index case.*
- *Programmes implementing RDA should have the capacity to enumerate and provide antimalarials to the people residing with or near a confirmed malaria case and others that share the same risk of infection.*
- *The people given antimalarial medicine in an RDA intervention should share the same risk of having acquired infection as the index case or be at risk of acquiring infection from the index case. This includes residents in the same household or neighborhood, co-travellers and co-workers. However, if the infection was imported and the residence is not located in a receptive area, there may be no benefit from RDA.*
- *Programmes contemplating implementation of RDA for P. vivax should carefully consider how to safely and feasibly administer treatment to prevent relapses.*

Practical info

When used, RDA should be one of several components of a programme to eliminate or prevent re-establishment of malaria, including intensive follow-up of every case as described in the *Framework for malaria elimination [9]*.

RDA depends on a strong passive surveillance system that detects suspected cases, tests all suspected cases for malaria with a quality-assured parasitological test and investigates all cases at their residence. If these elements are not in place, it is unlikely that an RDA intervention will have any effect on transmission.

It is essential to determine the likely location of infection through a case investigation that identifies the location of the person during the likely period of infection in order to understand where or in what group of people the RDA intervention should take place. RDA should be administered to other residents of the same house if the person is determined to have been infected locally. Programmes may consider extending the radius of RDA to neighbours depending on the local epidemiology and ecology of malaria. If the index infection is not likely to have been acquired at the residence, programmes should administer RDA to all people identified as having the same exposure to infection as the index case. People with the same risk of infection are likely to be those who travelled, worked or engaged in leisure activities with the index case. If the infection was classified as imported from elsewhere and the household is not located in a receptive area, there may be no benefit to RDA.

Countries that are at very low or low transmission but not yet close to achieving zero indigenous cases should prioritize implementation of RDA and reactive IRS over RACDT. However, RACDT should be added on top of RDA when countries are closer to elimination to strengthen the sensitivity of the surveillance system to monitor progress towards elimination and, post-elimination, to provide additional evidence of a malaria-free status.

RDA should be implemented according to standardized operating procedures (SOPs). A household listing of all people residing within the limits of RDA as specified by the SOPs should be developed and verified, along with a list of all people who may have been co-exposed. The RDA programme should seek to provide antimalarial medicine to everyone listed, using different approaches as needed to reach everyone at risk.

Achieving high coverage of the targeted population and good adherence to the antimalarial medicine are critical aspects of RDA programmes. RDA programmes ask many asymptomatic, healthy people to take a medicine when they do not feel ill, with the potential for adverse reactions to occur. Improving coverage and adherence requires development of understanding and trust in the institutions implementing the programme. Community engagement is thus a key factor in determining the success of RDA, to improve participation rates and adherence to the full treatment course of the medicine.

A complete therapeutic course of antimalarial medicine, at doses recommended by the manufacturer, should be given to all eligible adults and children. Drug dosage should be determined by weight wherever possible, with dosing according to age only in situations where the person's weight is unknown. The antimalarial medicines chosen for use in RDA should: a) be WHO recommended and prequalified; b) be efficacious against local parasites; c) be different from the medicine used as first-line treatment, where possible c) have a superior safety and tolerability profile; d) provide a longer duration of post-treatment prophylaxis with component medicines that have closely matched pharmacology to reduce the risk of new infections encountering only a single drug; e) have a positive public reputation and acceptability and f) be available and low-cost.

Programmes in areas with *P. falciparum* may consider including a single, low-dose of primaquine in an RDA programmes in order to increase the gametocytocidal effect, although there is no evidence of additional benefit from provision of of single low-dose primaquine in an RDA programme. A drug regimen that can be administered as a directly-observed single dose is preferred to multi-day regimens.

Depending on the medicine chosen, certain population groups may need to be excluded from RDA, such as: pregnant women in their first trimester; infants < 6 months of age or weighing < 5kgs; people recently treated with the same medicine; people with a known allergy to the medicine; anyone with severe acute illness or unable to take oral medication; people taking medication known to interact with the medicine used for RDA; and people with specific contraindications to the medicine used *[166]*. Although rarely implemented in the same area, RDA should not be given to individuals receiving other forms of malaria chemoprevention (e.g. seasonal malaria chemoprevention, perennial malaria chemoprevention, or intermittent preventive treatment during pregnancy).

Programmes contemplating providing medicine for radical cure of *P. vivax* hypnozoites as part of RDA should carefully consider whether it is feasible to administer this treatment regimen safely, i.e. with testing for G6PD deficiency prior to treatment, an effective pharmacovigilance system and emergency access to blood transfusion services. Programmes should consider whether sufficient coverage and adherence to the full course of radical cure can be achieved.

Evidence to decision

Benefits and harms

The systematic review identified six cRCTs in four countries of sub-Saharan Africa (Eswatini, Gambia, Namibia and Zambia) and one NRS from Peru assessing the impact of RDA (Steinhardt *et al unpublished evidence (c)*). Almost all infections from the cRCTs in Africa were due to *P. falciparum* while the NRS in Peru included mainly *P. vivax* infections. The NRS from Peru provided chloroquine plus seven days of primaquine at a dosage of 0.5mg/kg. All studies except for the study from Zambia were from low-transmission settings. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available in the Research evidence.

Beneficial outcomes

- RDA may reduce malaria prevalence (RD: -5 per 1000 persons; 95% CI: -9 to 2 per 1000 persons; four cRCTs; low-certainty evidence).
- RDA probably reduces the incidence of parasitaemia (RD: -7 per 1000 p-y; 95% CI: -17 to 13 per 1000 p-y; two cRCTs; moderate-certainty evidence).
- RDA probably results in little to no difference in the incidence of clinical malaria (RD: -2 per 1000 p-y; -4 to 1 per 1000 p-y; six cRCTs; moderate-certainty evidence).
- The evidence is very uncertain about the effect of RDA on the incidence of clinical malaria. (RD: -2 per 1000 p-y; -3 to -1 per 1000 p-y; one NRS; very low-certainty evidence).

Adverse events

Four cRCTs reported on adverse events; however, only two studies reported adverse events from the RDA arm and the comparator arm. In RDA arms with DP:

- 123 (6.9%) mild adverse events were reported from 1775 participants receiving DP; all were resolved.
- 75 (7.6%) adverse events were reported from 979 participants receiving DP; 69 were rated as mild and six as moderate.
- 68 (3.8%) adverse events reported from 1776 participants receiving DP; 54 were rated as mild and 14 as moderate.

In RDA arms using AL:

- 17 (0.4%) adverse events were reported from 4247 participants.

The NRS in Peru that used chloroquine plus seven days of primaquine for radical cure of *P. vivax* hypnozoites reported no adverse events but there was no active pharmacovigilance system.

Judgement of the panel
The GDG judged both the benefits and undesirable effects of RDA to be small and the overall certainty of evidence to be low. The GDG noted that the comparator in several studies was RACDT rather than no RDA. As a result, the GDG judged that the systematic review likely underestimated the impact of RDA. Overall, the balance of effects was determined to favour neither the intervention nor the comparison.

Certainty of the evidence

Low

The overall certainty of the evidence was judged to be low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.

Resources

The systematic review identified one study from Zambia with data on the financial and economic costs of RDA (Steinhardt *et al* *unpublished evidence* *(c)*). The study identified index cases through active rather than passive surveillance. The total cost of two rounds of RDA (with DP) conducted between 2014 and 2015, covering a total population of 132 393 was US$ 912 767 (all figures in 2015 US$). The mean cost per person reached was US$ 85.69 (interquartile range [IQR] US$39.92).

The overall incremental costs per infection and case averted (vs. standard of care) for RDA were US$ 810 and US$ 6 353, respectively. In high transmission settings, the incremental costs per infection and case averted were US$ 429 and US$ 5951, respectively; in low transmission settings, they were US$ 1119 and US$ 6755, respectively. Incremental cost per DALY averted for infections and cases were US$ 4889 and US$ 38 344, respectively.

The GDG judged the resources required for RDA to be large but dependent on the number of index cases.

Equity

No studies were identified that addressed the issue of whether RDA increased or decreased health equity.

The GDG was unable to determine a judgement on equity.

Acceptability

The systematic review identified six studies in four countries (Eswatini, Gambia, Namibia and Zambia) with information on acceptability (Steinhardt *et al* *unpublished evidence* *(c)*). Community acceptance of RDA was high (refusal rate of 2% or lower) in Namibia and Zambia. However, in Eswatini, the overall refusal rate was about 4%, with refusal rates of 1.4% (11/776) and 5.3% (65/1232) in seasons 1 and 2, respectively. In Namibia, participants expressed concern over having “to take medicine without feeling sick”. Similarly, participants in Gambia “generally considered it unnecessary to take medicine without having any symptoms”. Continued community sensitization has been recommended to mitigate these stigmas. In the systematic review, no studies reporting on the acceptability of RDA to health care workers or policymakers were found.

The GDG judged that RDA was probably acceptable to key stakeholders given the high rate of participation in RDA programmes.

Feasibility

Data on the feasibility of implementing RDA were summarized from five studies in four countries (Eswatini, Gambia, Namibia and Zambia) (Steinhardt *et al* *unpublished evidence* *(c)*). All

countries used a three-day regimen of an ACT. RDA coverage, defined as the proportion of index cases followed up, varied between countries with a low of 62.4% in Eswatini to about 97% in Gambia.

RDA adherence data were abstracted from three studies in three countries (Eswatini, Gambia and Zambia). Full adherence, defined as taking all three doses of an ACT and verifying that no tablets remained in the blister pack, was above 90% in all the countries.

The feasibility of implementing RDA would also depend on whether radical cure of *P. vivax* using an 8-aminoquinoline medicine was part of the RDA strategy, which would necessitate testing for G6PD deficiency, an effective pharmacovigilance system and emergency access to blood transfusion services.

The GDG judged that RDA was likely feasible to implement.

Justification

While the GDG concluded that the balance of effects favoured neither RDA nor the comparison, the panel judged that the intervention would likely have been more effective if studies had compared RDA to no RDA rather than to RACDT. The GDG judged that RDA was probably an acceptable, feasible and potentially cost-effective strategy when numbers of cases are low enough to permit programmes to conduct case investigations, including in post-elimination settings working to prevent re-establishment of infection. The GDG concluded that a conditional recommendation for RDA as a component of an elimination programme should be issued.

Research needs

- Further evidence is needed on the impact (prevalence and incidence of malaria infection at the community level) and potential harms/unintended consequences of RDA.
- Evidence is needed on the acceptability, feasibility, impact (prevalence and incidence of malaria infection at the community level) and potential harms/unintended consequences (death, hospital admission, severe anaemia or any severe adverse event) of safe provision (including testing for G6PD deficiency and, additionally, an effective pharmacovigilance system and emergency access to blood transfusion services) of an 8-aminoquinoline as part of RDA for radical cure of *P. vivax* infections.
- Investigate the optimal approach to delimiting the target area for implementation of RDA around an index case in order to maximize reductions in transmission of malaria.
- Determine the optimal time interval between index case detection and RDA to maximize reductions in transmission of malaria.
- Determine whether additional rounds of RDA should be repeated in the same residences or neighborhood to prevent subsequent generations of transmission.

6.3.2 Reactive case detection and treatment (RACDT)

RACDT is the parasitological testing of every person living with or near a person who has a confirmed malaria case, or every person who was likely exposed to infection at the same time and place as the index case, and treatment of those who are positive for malaria. RACDT is an active case detection strategy that may improve the timeliness and coverage of treatment. RACDT is generally conducted using point-of-contact malaria rapid diagnostic tests but has also been conducted using microscopy and nucleic acid-based tests. Only people found to be positive receive a full therapeutic course of an effective antimalarial medicine. As a result, the intervention does not provide a population-level prophylactic period as RDA does.

In an RACDT strategy, individuals are provided with antimalarials only if they are round to be infected. As a result, the proportion of the population that is protected from new infections over the duration of the post-treatment prophylaxis period is substantially lower than the population that would be protected in an RDA intervention. However, providing antimalarial medicine only to those who are known to be infected may improve adherence to treatment, population acceptance of the intervention and equity while decreasing the risk of unintended consequences and depleting stocks of medicines.

Reactive interventions that are applied geographically should target the likely location of infection of the index case. The likely location of infection is determined through a case investigation, using the date of symptom onset and knowledge of the incubation period for the specific parasite species to determine the location of the person during the likely period of infection. If the likely location of infection is a residence, RACDT can be conducted at least in the household of the person with the confirmed case, but could also be extended to neighbours. The radius of the intervention should be determined based on an understanding of the epidemiology of malaria in the area. If the

index infection was imported from elsewhere, RACDT should be conducted among individuals who may have the same exposure as the index case, such as co-travellers and co-workers.

As an active case detection strategy, RACDT is an essential component of the final phase of elimination as it improves the sensitivity of the surveillance system while maintaining specificity; RACDT accomplishes this by increasing testing in areas more likely to experience transmission of malaria. RACDT provides important information to countries close to elimination by identifying any additional cases around the index case that could suggest gaps in the surveillance system. Once countries have reached zero indigenous cases, RACDT provides additional evidence to the Malaria Elimination Certification Panel that the country has interrupted indigenous transmission.

Conditional recommendation for , Very low certainty evidence

Reactive case detection and treatment to reduce transmission of malaria (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, all people residing with or near a confirmed malaria case and all people who share the same risk of infection (e.g. co-travellers and co-workers) can be tested for malaria and treated if positive.

Until an area is nearing elimination or is post-elimination, it is unlikely that reactive case detection and treatment (RACDT) will have any effect on malaria transmission. However, RACDT becomes an essential component of surveillance when countries are nearing interruption of transmission to monitor progress towards elimination. When countries are post-elimination and working towards certification, RACDT can strengthen a country's claim that it has reached and maintained zero indigenous cases. RACDT is an essential part of surveillance and response to prevent re-establishment of malaria.

Practical info

RACDT should be implemented when areas are nearing interruption of transmission and malaria cases are rare. When used, RACDT should be one of several components of a programme to eliminate or prevent re-establishment of malaria, including intensive surveillance as described in the *Framework for malaria elimination [9]*.

RACDT depends on a strong passive surveillance system that detects suspected cases, tests all suspected cases for malaria with a parasitological test and investigates all cases at their place of residence. RACDT complements this surveillance system through active case finding around index cases.

It is essential to determine the likely location of infection through a case investigation that identifies the location of the person during the likely period of infection in order to understand where or in what group of people an RACDT intervention should take place. RACDT should be administered to other residents of the same house if the person is determined to have been infected locally. Programmes may consider extending the radius of RACDT to neighbours depending on the local epidemiology and ecology of malaria. If a person was not likely to have been infected at the residence, programmes should administer RACDT to all people identified as having the same risk of acquiring infection as the index case. People with the same risk of infection are likely to be those who travelled, worked or engaged in leisure activities with the index case.

Countries that are at very low or low transmission but not yet close to achieving zero indigenous cases should prioritize implementation of RDA and reactive IRS over RACDT. However, RACDT may be added on top of RDA when countries are closer to elimination to strengthen the sensitivity of the surveillance system to monitor progress towards elimination and, post-elimination, to provide additional evidence of a malaria-free status. When RACDT and RDA are jointly implemented, chemoprevention is provided to everyone, irrespective of the results of the parasitological test. However, testing results are used to monitor progress towards elimination or demonstrate that the country has reached zero indigenous cases.

RACDT should be implemented according to SOPs. A household listing of all people residing within the limits of RDA as specified by the SOPs should be developed and verified, along with a list of all individuals who may have been co-exposed. The RACDT programme should seek to test everyone listed, using different approaches as needed to reach everyone at risk.

Malaria cases detected during RACDT should be treated with antimalarial medicine according to the national treatment protocol if not already provided chemoprevention through RDA.

Evidence to decision

Benefits and harms

The systematic review identified three cRCTs in three countries of sub-Saharan Africa (Eswatini, Namibia and Zambia) (Steinhardt *et al unpublished evidence (d)*). However, all three studies were intended to evaluate the impact of RDA, and RACDT was used as the comparator. The two NRSs identified from Brazil and Zambia reported on outcomes among those receiving the intervention, but did not evaluate impact at the community level. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available in the Research evidence.

Beneficial outcomes

- The evidence is very uncertain about the effect of RACDT on the prevalence of malaria (RD: 25 per 1000 persons; 95% CI [95% CI] -1 to 72 per 1000 persons; one cRCT; very low-certainty evidence).
- The evidence is very uncertain about the effect of RACDT on the incidence of clinical malaria (RD: 3 per 1000 p-y; 95% CI: -1 to 7 per 1000 p-y; three cRCTs; very low-certainty evidence).
- The evidence is very uncertain about the effect of RACDT on parasite prevalence among people who participate in RACDT (two NRSs; very low-certainty evidence).

Adverse events

Three cRCTs reported on adverse events. All trials used AL in the RACDT arms while DP was provided for the RDA arms.

- In Zambia, no events were reported from the RACDT arm compared to 123 (6.9%) adverse events reported from 1 775 persons administered DP in the RDA arm;
- In Namibia, 1 (1.0%) participant out of 96 reported an adverse event compared to 17 (0.4%) out of 4 247 in the RDA arm using DP;
- In Eswatini, no adverse events were reported from the RACDT arm while 68 (3.8%) of 1 776 participants reported adverse events in the RDA arm provided with DP.

Judgement of the panel

The GDG judged that the undesirable effects of RACDT were likely trivial. However, the GDG was unable to judge the benefit of RACDT as the cRCTs compared results with RDA rather than no intervention. The NRS studies provided results only for those who received the intervention, and as a result, could not provide evidence for the impact of RACDT on transmission. As a result, the GDG concluded that they could not judge whether the balance of effects favoured RACDT or not.

Certainty of the evidence

Very low

The overall certainty of the evidence was judged to be very low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies

Resources

The systematic review identified four studies with information on the costs of RACDT (Steinhardt *et al unpublished evidence (d)*). The average cost of RACDT varied across different regions – from US$ 5.21 in Thailand to US$ 27.60 in Indonesia. In Senegal, the cost per person screened by RACDT was US$ 14.00. Costing models developed based on the experience of implementing partners, operational documents and costing studies from Ethiopia, Senegal and Zambia found

that the average annual financial cost per capita (total population of 360 000 based on one region, three districts, 20 health facility catchment areas [HFCAs] each, and 6000 population per HFCA) were US$ 1.07 for the first year of RACDT, and US$ 0.65 per year for the subsequent five years (2014 US$) and the per capita economic cost was US$ 1.27 in first year of RACDT, and US$ 0.75 per year for the subsequent five years (2014 US$).

Total costs for RACDT varied between study areas ranging from US$ 3469 in Indonesia to US$ 10 486 in Thailand for total personnel and US$ 257 (Indonesia) to US$13 969 (Thailand) for commodities, services and other costs. The variations in personnel, commodity, service and other costs specific to case investigation and RACDT activities are likely due to differences in programme structure and the level of integration of malaria-related activities into the broader healthcare system.

In Zambia, the mean annual cost of RACDT per HFCA was US$ 1177 (median = US$ 923, IQR US$ 651–1417). The variation in costs was driven by the number of community health workers and index cases detected. Costs related to community health workers and data review meetings accounted for the largest share of total costs. Rapid diagnostic tests and medicines accounted for less than 10% of total costs.

Cost models based on studies from Ethiopia, Senegal, and Zambia showed that targeted search radius and per diems paid to community health workers dominated intervention parameters. In Indonesia, at 0.4% prevalence of infection, the cost per infection detected was US$ 7070, which declined to US$ 1767 when the prevalence was 1.6%. Cost declines began to plateau thereafter.

The GDG judged the resources required for RACDT to be moderate, depending on the number of index cases.

Equity

No studies were identified that addressed the issue of whether RACDT increased or decreased health equity.

The GDG was unable to determine a judgement on equity.

Acceptability

The systematic review identified community acceptability data from three studies conducted in Namibia, Senegal and Zambia (Steinhardt *et al* *unpublished evidence (d)*). Community acceptance of RACDT was high (refusal rate 2% or lower). In Namibia, some “hesitation/ resistance” during pre-trial was reported but community engagement and sensitization appear to have helped participation. Similarly, in Senegal, the high RACDT participation has been attributed to advanced cascade sensitization, making follow-up appointments to follow up absent members, and conducting return visits to the compound on the same or next day. Lack of community confidence in community health workers’ ability to address diseases other than malaria and community unwillingness to visit community health workers for malaria testing were reported in Zambia.

There were no studies reporting data directly on health care workers’ acceptance of RACDT. Related information was abstracted from two studies. In Zambia, community health workers reported lack of motivation to conduct RACDT, which was in part linked to community health workers feeling their community service went unrecognized. The lack of stipend or financial support was the biggest problem noted by community health workers, who were volunteers.

The GDG judged that RACDT was probably acceptable to key stakeholders.

Feasibility

The systematic review identified feasibility and health systems considerations data from 17 studies, of which seven were from sub-Saharan Africa and eight from the Asia-Pacific region (Steinhardt *et al* *unpublished evidence (d)*). The proportion of households reached by RACDT varied across different geographical locations – from 49% of index case households investigated in Zanzibar to 100% in Jiangsu, China. Similarly, the proportion of households reached in a

timely manner also varied across different locations – from about 20% in Zanzibar to 100% in China. Barriers and challenges to RACDT implementation were identified along all three steps of RACDT.

First, index case detection and notification from private health facilities was low and these cases were largely reported to be missed by RACDT in Cambodia and Zanzibar. Collaborating and engaging the private sector in malaria surveillance systems has been identified as critical, particularly in areas where many patients resort to private providers, facilities including drug shops, and pharmacies. Within the public health sector, delayed presentation of malaria patients to health facilities, poor preparation of village clinics to participate in surveillance programmes, and the lack of adequate human resources and malaria rapid diagnostic tests haves been reported as barriers and challenges to effective implementation of RACDT. Second, the complexity of case investigation procedures and lack of standard operating procedures have been identified as barriers to effective case investigation. Difficulty with case classification (imported vs. local) due to incomplete travel histories has also been reported. During peak malaria transmission seasons, the proportions of case investigations conducted were lower than in other times mainly because community health workers were overwhelmed by patient volumes and there were insufficient numbers of malaria rapid diagnostic tests. To overcome these barriers, authors from a study in Zambia suggested that the programme would benefit from additional community health workers or the suspension of RACDT during the high-transmission season. Third, difficulty accessing mountainous terrains, flooded areas, and border areas with highly mobile populations were reported as barriers to timely follow up during the RACDT intervention. To overcome the barriers posed by flooding during the rainy season, study authors from Zambia recommended that community health workers, particularly those serving flood-prone areas, be provided with rain gear and access to boats.

Another barrier to effective implementation of RACDT was identified as the large numbers of households to screen, particularly in high-density areas of the Asia-Pacific region. Incomplete case investigation forms also limited follow-up and the lack of household-level listings of all individuals in the RACDT area meant that those conducting RACDT did not always know which households to include in the RACDT. Imported cases posed a major challenge for RACDT interventions. District-level responses alone were unlikely to be effective in interrupting transmission when most malaria cases were imported from outside the district. Communication and surveillance linkages with other operational districts and their malaria response teams were considered necessary. In the case of Bhutan, RACDT buffer zones sometimes extended beyond international borders, limiting implementation of adequate RACDT activities. Strengthened cross-border collaborations are needed to ensure adequate coverage of households across borders, as well as migrant and mobile populations. Other barriers to conducting effective RACDT were stockouts of malaria rapid diagnostic tests, which prevented testing around index cases, the limit of detection of most rapid diagnostic tests, and the inability of *P. falciparum*-only rapid diagnostic tests to detect other species and low-density infections. In Botswana, malaria microscopy was used as the gold standard for malaria diagnosis, so all RDT-positive malaria cases were re-examined by microscopy; however, it was challenging to ensure a high quality of malaria microscopy slides prepared by health centre staff in these settings. A lack of health care workers to conduct malaria activities and lack of surveillance officers at the district level were reported to result in inadequate supervision, case investigation and follow-up. Lack of motivation among health care workers to pursue case investigation and contact testing, particularly on weekends and public holidays, was also reported. Maintaining workforce motivation and providing consistent support, supervision and incentives were recommended to overcome these challenges.

The feasibility of implementing RACDT would also depend on whether radical cure of *P. vivax* using an 8-aminoquinoline medicine was part of the RACDT strategy, which would necessitate testing for G6PD deficiency, an effective pharmacovigilance system and emergency access to blood transfusion services.

The GDG judged that RACDT was likely feasible to implement.

Justification

Although the GDG was not presented with any relevant evidence for the benefit of RACDT in reducing transmission of malaria, RACDT is considered an essential surveillance strategy for countries nearing elimination in order to ensure that there are no cases remaining around or associated with a confirmed case. The GDG concluded that a conditional recommendation for RACDT as a component of the end-stage of an elimination programme should be issued.

Research needs

No research needs were identified by the GDG.

6.3.3 Reactive indoor residual spraying

Indoor residual spraying (IRS) is the application of a residual insecticide to the interior surfaces of dwellings (i.e. walls, ceilings, windows and doors) to kill resting mosquitoes and reduce malaria transmission. IRS is generally conducted campaign-style across a large geographical area or a higher-risk area prior to the start of a malaria transmission season (i.e. proactive spraying). By contrast, reactive IRS is the use of IRS in the houses of a confirmed case and neighbours at approximately the same time.

Reactive IRS should be implemented in the likely location of infection of the index case. The likely location of infection is determined through a case investigation by using the date of symptom onset and knowledge of the incubation period for the specific parasite species in order to determine the location of the person during the likely period of infection. If the likely location of infection was a residence, reactive IRS should be deployed to the dwelling of the confirmed case and extended to neighbouring houses. If the index infection was imported, reactive IRS at the residence of the index case may still have some effect on reducing onward transmission. The size of the radius of implementation of reactive IRS should be determined by the behaviours and likely flight range of local vector mosquitoes.

Conditional recommendation for , Moderate certainty evidence

Reactive indoor residual spraying (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, indoor residual spraying of insecticide can be conducted in in the houses of confirmed cases and neighbours to prevent or reduce transmission of malaria.

- *In areas approaching elimination or post-elimination settings where proactive indoor residual spraying (IRS) is occurring, programmes can consider switching to reactive IRS only, depending on the receptivity of the area.*
- *Programmes considering adding reactive IRS on top of proactive IRS should balance the potential added benefit with increasing cost and the risk of insecticide resistance.*
- *In areas approaching elimination or post-elimination settings where no IRS is occurring, initiating reactive IRS may be beneficial, depending on whether IRS is a suitable vector control strategy. IRS is most effective where the vector population is susceptible to the insecticide(s) being applied, the majority of mosquitoes feed and rest indoors and where most structures are suitable for spraying.*
- *If the index infection was imported and the residence is not located in a receptive area, there may be no benefit from reactive IRS.*

Practical info

Please refer to the Practical Info section for IRS (4.1.1) for more information on operational issues related to IRS.

When used, reactive IRS should be one among several components of a programme to eliminate or prevent re-establishment of malaria, including intensive surveillance as described in the *Framework for malaria elimination [9]*.

Reactive IRS depends on a strong passive surveillance system that detects suspected cases, tests all suspected cases for malaria with a parasitological test and investigates all cases at their place of residence. If these elements are not in place, it is unlikely that an reactive IRS intervention can be effectively implemented.

It is essential to determine the likely location of infection through a case investigation that identifies the location of the person during the likely period of infection in order to understand where the reactive IRS intervention should take place. Reactive IRS should be applied to the residence if the person is determined to have been infected locally. Programmes should extend RIRS

to neighbours, with the radius of implementation depending on the local epidemiology and ecology of malaria. If the index infection is not likely to have been acquired at the residence, reactive IRS might still reduce the chances of onward transmission. However, if the infection was classified as imported and the household is not located in a receptive area, there may be no benefit to reactive IRS.

In very low to low transmission settings where standard IRS is occurring (proactive spraying), there may be advantages to programmes from switching to reactive IRS. Decisions to switch from standard IRS to reactive IRS should be based on assessments that include:

- the potential risk of increasing malaria transmission by scaling back proactive IRS;
- the potential cost savings;
- the potential for increased acceptance and equity; and
- the potential for reducing insecticide resistance.

In settings where no standard IRS is occurring, reactive IRS may be beneficial, depending on the factors listed below.

- The programme has the capacity to conduct case investigations at the residences of cases to determine whether the case is imported or local.
- The capacity of the vector control programme to respond quickly to conduct reactive IRS after identification of a confirmed case.
- The population living in the houses where RIRS is applied are at risk of infection.
- The majority of the vector population feeds and rests indoors.
- The vectors are susceptible to the insecticide that is being deployed.
- People mainly sleep indoors at night.
- The majority of structures are suitable for spraying.

Programmes considering adding reactive IRS on top of proactive IRS should balance the potential added benefit with the risk of insecticide resistance and increased cost, and develop protocols that take into account the time since the dwelling was last sprayed. Reactive IRS depends upon a strong passive surveillance system that detects suspected cases, tests all suspected cases for malaria with a parasitological test and investigates all cases at the residence. If these elements are not in place, it is unlikely that an reactive IRS intervention will have an impact on malaria transmission.

Evidence to decision

Benefits and harms

The systematic review identified two cRCTs in Namibia and South Africa (Gimnig *et al* *unpublished evidence*). The study from Namibia (superiority trial design) was conducted as a 2x2 factorial design with RACDT alone, RDA alone, RACDT plus reactive IRS, and RDA plus reactive IRS. The study from South Africa was designed as a non-inferiority trial comparing reactive IRS to proactive IRS (used in defined priority areas) that reached one third of houses. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available in the Research evidence.

Beneficial outcomes

- Reactive IRS reduces the prevalence of malaria (RD: -27 per 1000 persons; 95% CI: -35 to -8 per 1000 persons; one cRCT [superiority design]; high-certainty evidence).
- Reactive IRS may have little to no effect on the incidence of clinical malaria. (RD: -14 per 1000 p-y; 95% CI: -32 to 4 per 1000 p-y; one cRCT [superiority design]; moderate-certainty evidence).
- Reactive IRS probably results in little to no difference in incidence of clinical malaria compared with proactive IRS (mean difference: 0.1 per 1000 p-y; 95% CI: -0.38 to 0.59 per 1000 p-y; one cRCT [non-inferiority design]; moderate-certainty evidence).

Adverse events

- Reactive IRS results in little to no difference in reported adverse events (RD: 2 per 1000 persons; 95% CI: -2 to 1 per 1000 persons; one cRCT [superiority design]; high-certainty

evidence).
- Reactive IRS results in little to no difference in serious adverse events (deaths) compared with proactive IRS (one cRCT [non-inferiority design]; high-certainty evidence).

Judgement of the panel
The GDG judged the benefits of reactive IRS to be moderate, undesirable effects to be trivial and the overall certainty of evidence to be moderate. The GDG noted that studies were only available from southern Africa. The variability of mosquito and human ecology may influence the effectiveness of the strategy where vectors differ from those in the trial areas. Additionally, the different designs (superiority vs. non-inferiority) and different comparators (no reactive IRS or proactive IRS) complicated the GDG's judgement. However, the GDG judged that the balance of effects probably favoured reactive IRS.

Certainty of the evidence

Moderate

The overall certainty of the evidence was judged to be moderate.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.

Resources

The systematic review identified one study from South Africa with data on cost and cost-effectiveness of reactive IRS compared to proactive IRS (non-inferiority trial) (Gimnig *et al* *unpublished evidence*). Over the two-year study, the average annual economic cost was US$ 184 319 per 100 000 population in the proactive IRS arm compared to US$ 88 258 per 100 000 population in the reactive IRS arm, a 52% cost savings. Using the cost per DALY, the incremental cost-effectiveness ratios were estimated overall and for each year of the study. It was estimated that per additional DALY averted, reactive IRS saved US$ 7845 (95% CI: US$ 2902–64 907) over proactive IRS. During year 1, when the incidence of malaria was low, the savings per additional DALY averted in the RIRS arm was estimated at US$ 35 149. The lower bound of the 95% CI was US$ 6481, while at the higher bound, RIRS was both less expensive and more effective. In year 2, when incidence was higher, the savings per additional DALY averted in the reactive IRS arm was US$ 3869 (95% CI: US$ 1371–50 689). The cost-effectiveness thresholds were set at US$ 2637 (43% of GDP per capita) and US$ 3557 (58% of GDP per capita). At the incidence observed during the trial, reactive IRS would have a 94–98% probability of being the cost-effective choice at either threshold. It was estimated that reactive IRS would remain the preferred strategy up to an incidence of 2.0–2.7 cases per 1000 person-years using the higher and lower cost-effectiveness thresholds.

The GDG judged that the resources required for reactive IRS are likely to vary depending on whether the programme is moving from proactive IRS to reactive IRS or starting an RIRS programme from scratch. The resource requirements are also likely to vary depending on the number of index cases. However, the GDG judged that cost-effectiveness probably favours reactive IRS.

Equity

No studies were identified that addressed the issue of whether reactive IRS increased or decreased health equity.

Because reactive IRS focuses resources where they are needed, the GDG judged that reactive IRS probably increased health equity.

Acceptability

The systematic review identified one study from Namibia with information on the acceptability of reactive IRS (Gimnig *et al unpublished evidence*). Refusals of households to participate in reactive IRS were due to lack of notification before arrival and reluctance to move furniture at short notice. In year two of the study, advance notification was provided to households and < 1% refused reactive IRS. Community participants generally considered reactive IRS to be a useful tool for malaria prevention, and participants in the study arms that did and did not receive reactive IRS indicated a desire to have their houses sprayed. Participants specifically referenced IRS's effectiveness, noting reductions in both flies and mosquitoes. In the endline survey, 616 of 624 respondent (98.7%) from the reactive IRS arm indicated that they would participate in the same intervention again.

The GDG noted that reactive IRS would likely be more accepted by households than proactive IRS because residents would know that a malaria case had been detected in or near their home. The GDG judged that reactive IRS was probably acceptable to key stakeholders.

Feasibility

The systematic review identified two case studies from China that reported on their implementation of reactive IRS (Gimnig *et al unpublished evidence*).

The GDG judged that reactive IRS was likely feasible to implement.

Justification

Proactive IRS applied campaign-style across a geographical area has long been a staple of malaria vector control and is currently recommended by WHO for large-scale deployment in areas of ongoing transmission. Reactive IRS uses the same intervention (application of a residual insecticide to the interior surfaces of a dwelling) as does proactive IRS; however, reactive IRS is triggered by a single case of malaria and applied in a limited geographical area around the likely location of infection of the index case. When transmission is low and cases are clustered, the GDG noted that RIRS might be more cost-effective than proactive IRS as the area at risk of transmission is more limited. However, the benefits gained by introducing RIRS are likely to depend on whether the programme already has a proactive IRS programme or not; whether the programme intends to scale back proactive IRS to reactive IRS or add reactive IRS on top of proactive IRS; and the characteristics of the vector and human populations. As a result, the GDG provided a conditional recommendation for reactive IRS.

Research needs

- Further evidence is needed on the impact (prevalence and incidence of malaria infection at the community level) and potential harms/unintended consequences of reactive IRS.
- Determine the impact (prevalence and incidence of malaria infection at the community level) of reactive IRS in areas with different mosquito behaviours.
- Determine the impact (prevalence and incidence of malaria infection at the community level) of reactive IRS in areas where *P. vivax* is transmitted.
- Investigate the optimal approach to delimiting the target area for implementation of reactive IRS around an index case.
- Determine the optimal time interval between case detection and reactive IRS.
- Determine whether additional rounds of reactive IRS should be repeated in the same households to prevent subsequent generations of transmission.
- Determine the benefit and acceptability of switching from IRS to reactive IRS or adding reactive IRS on top of proactive IRS.

7. Surveillance

Surveillance is "the continuous and systematic collection, analysis and interpretation of disease-specific data, and the use of that data in the planning, implementation and evaluation of public health practice" *[304]*.

Pillar 3 of the *Global technical strategy for malaria 2016–2030 [4]* is to transform malaria surveillance into a key intervention in all malaria-endemic countries and in those countries that have eliminated malaria but remain susceptible to re-establishment of transmission.

Although surveillance guidance is not evaluated using the GRADE framework, surveillance forms is the basis of operational activities in settings at any level of transmission and is therefore included in these Guidelines for reference. The objective of surveillance is to support reduction of the burden of malaria, eliminate the disease and prevent its re-establishment. In settings where transmission

remains relatively high and the aim of national programmes is to reduce the burden of morbidity and mortality, malaria surveillance is often integrated into broader routine health information systems to provide data for overall analysis of trends, stratification and planning of resource allocation. In settings where malaria is being eliminated, the objectives of surveillance are to identify, investigate and eliminate foci of continuing transmission, prevent and cure infections, and confirm elimination. After elimination has been achieved, the role of surveillance becomes that of preventing re-establishment of malaria.

A malaria surveillance system comprises the people, procedures, tools and structures necessary to generate information on malaria cases and deaths. The information is used for planning, implementing, monitoring and evaluating malaria programmes. An effective malaria surveillance system enables programme managers to:

- identify and target areas and population groups most severely affected by malaria, to deliver the necessary interventions effectively and to advocate for resources;
- regularly assess the impact of intervention measures and progress in reducing the disease burden and help countries to decide whether adjustments or combinations of interventions are required to further reduce transmission;
  - detect and respond to epidemics in a timely way;
  - provide relevant information for certification of elimination; and
  - monitor whether the re-establishment of transmission has occurred and, if so, guide the response.

Please refer to the WHO *Malaria surveillance, monitoring & evaluation: a reference manual [30]*.

Subnational stratification

WHO has made guidance available on the strategic use of data to inform subnational stratification (see chapter 2 of *WHO technical brief for countries preparing malaria funding requests for the Global Fund (2020-2022)*) *[305]*. This guidance was developed in recognition of the increasing heterogeneity of malaria risk within countries as malaria control improves and the need to use problem-solving approaches to identify appropriate, context-specific packages of interventions to target different sub- populations. For example, case management should be accessible wherever there is a possibility of malaria cases seeking treatment. How case management is delivered will vary according to factors such as health-seeking behaviour, the accessibility and functioning of the public health infrastructure, availability of the private retail sector and the potential for community services. Local data are essential to complete the malaria stratification and select the optimal mixes of interventions. The guidance explains how to undertake a comprehensive multi-indicator stratification process to define sub-national intervention mixes that are optimized to achieve strategic goals. As countries will rarely have all the resources they need to fully implement their ideal plan, a careful resource prioritization process is then required to maximize the impact of available resources. Prioritization should be based on the expected impact of interventions and consider value for money across the whole country, driven by local evidence.

8. Methods

The consolidated *WHO Guidelines for malaria* were prepared in accordance with WHO standards and methods for guideline development and originally published as the *Guidelines for the treatment of malaria* (3rd edition, 2015) and the *Guidelines for malaria vector control* (1st edition, 2019). Details of the approach can be found in the WHO *Handbook for guideline development [1]*. Here we provide an overview of the standards, methods, processes and platforms applied by the Global Malaria Programme across the topics covered in this guideline *[127][306][307]* and a description of the joint process (with WHO Immunization, Vaccination and Biologicals department) used to develop the malaria vaccine recommendation.

Organization and process

The WHO guideline development process involved planning; conducting a “scoping” and needs assessment; establishing an internal WHO Guidelines Steering Groups and external Guidelines Development Groups (GDGs); formulating key recommendation questions using the PICO (Population, Intervention, Comparison, Outcome) format; commissioning evidence reviews or where a recent review was already available, commissioning an independent assessment of the review using the AMSTAR checklist *[139]*; applying GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to assess the certainty of evidence; and using evidence-to-decision (EtD) frameworks to take the GRADE results and contextual factors into account in developing recommendations. This methodology ensures that the link between the evidence base and the recommendations is transparent. The Guidelines have been consolidated and will be continuously updated in the online MAGICapp publication platform (www.magicapp.org) as new evidence becomes available and published in user-friendly formats available on all electronic devices.

Technical leads in the Global Malaria Programme established Guidelines Steering Groups for each technical area to support drafting the scope of the Guidelines and preparing the planning proposal, including formulating key questions, as well as suggesting potential members for the GDGs. Technical leads then obtained declarations of interest from GDG members, assessed these and oversaw the management of any potential conflicts of interest, as well as the finalization and submission of a planning proposal to the Guidelines Review Committee (GRC) for review and approval.

The GDGs - external bodies of experts and stakeholders - were responsible for the development of the evidence-based recommendations contained in the Guidelines. As well as providing expert opinion, the specific tasks of the GDGs included:

- providing inputs on the scope of the Guidelines;
- building on the work of the Guidelines Steering Groups to

finalize the key recommendation questions in PICO format;
- choosing and ranking priority outcomes to guide the evidence reviews and focus the recommendations;
- reviewing eligibility criteria for the inclusion of studies in the evidence reviews;
- providing input on appropriate measures of outcomes of interest to be included in the evidence reviews;
- validating the list of included and excluded studies;
- reviewing the meta-analyses, GRADE evidence profiles or other assessments of the certainty of evidence used to inform the recommendations;
- interpreting the evidence, considering different factors included in the EtD framework and judging how these factors may impact the direction and strength of a recommendation, particularly in terms of the overall balance of benefits and harms;
- formulating recommendations, taking into account benefits, harms, values and preferences, feasibility, equity, acceptability, resource requirements, cost and cost-effectiveness and other factors, as appropriate;
- identifying methodological shortcomings and evidence gaps in the available body of evidence, and providing guidance on how to address these as part of future research;
- reviewing and approving the final recommendations prior to submission to the GRC; and
- contributing to the dissemination of the final recommendations.

Different GDGs were used to develop the *WHO Guidelines for malaria* (see Section 10: Contributors and interests), each with experts in that particular field. The composition of each GDG was balanced according to geographical representation and gender. Potential interests we identified and managed appropriately within the Global Malaria Programme (see section below). Membership included the following categories of stakeholders:

- relevant technical experts (e.g. clinicians with relevant expertise; epidemiologists; entomologists)
- intended end-users (programme managers and health professionals responsible for adopting, adapting and implementing the Guidelines)
- patients and/or other representatives from malaria-endemic countries.

In selecting the chair of each GDG, each Steering Group ensured that the individual had content expertise, had no conflicts of interest and was able to approach the recommendations with an open mind, i.e. having no preconceptions about the final recommendations. Chairs of the GDGs and/or members were sensitized to ensure that equity, human rights, gender and social determinants were taken into consideration in efforts to improve public health outcomes.

External Review Groups (ERGs) (see Section 10: Contributors and interests) were identified by the respective Steering Group for each technical area for malaria. Each ERG was composed of people interested in the subject of the Guidelines and included members of the Malaria Policy Advisory Group (MPAG; formerly the Malaria Policy Advisory Committee [MPAC]) and individuals affected by or interested in the recommendations, such as technical experts, end-users, programme managers, implementing partners, advocacy groups and funders. The ERGs reviewed the draft Guidelines prior to their submission to the GRC for approval. The role of each group was to identify any errors or missing evidence and to provide comment on clarity, context-specific issues, and implications for implementation. The groups were not expected to change the recommendations formulated by the GDGs. In cases where external reviewers raised major concerns related to the recommendations, these were taken back to the GDG for discussion. Comments from external reviewers were incorporated into the revised Guidelines as appropriate. The final drafts were circulated to the GDGs.

Guideline methodologists

Experts in guideline development processes complemented the technical expertise of the GDG members. Different methodologists supported the development of recommendations and guidance for each technical area. Methodologists were identified by the Steering Groups based on their experience, ensuring they had expertise in the prioritization of questions and outcomes, evidence synthesis, GRADEing of evidence, translation of evidence into recommendations, and guideline development processes. The methodologists supported the planning, scoping and development of key questions and assisted the GDG in formulating evidence-informed recommendations in a transparent and explicit manner. The methodologists served as the methodological co-chairs of some GDG meetings.

Evidence synthesis methods

Following the initial GDG meeting, existing systematic reviews already published were identified or new systematic reviews were commissioned to systematically assess the certainty of the evidence for each priority question across the guideline topics. Where there was an existing published review, the review was assessed independently using the AMSTAR-2 checklist *[139]*.

The reviews involved extensive searches for published and unpublished trials using highly sensitive searches of established registers such as the Cochrane Infectious Diseases Group trials register, the Cochrane Central Register of Controlled Trials, MEDLINE®, Embase and LILACS. Types of outcome measures for consideration in the evidence reviews included: rate of all-cause child mortality; rate of severe malaria episodes; rate of clinical malaria; rate of uncomplicated episodes of *P. falciparum* illness; parasite prevalence (also specifically *P. falciparum* and *P. vivax* prevalence); anaemia prevalence; and, in the case of vector control interventions, entomological inoculation rate (EIR); mosquito mortality and blood-feeding success; density of immature vector stages; and number of larval sites positive for immature vector stages. Harms and undesirable outcomes such as adverse events, development of antimalarial drug resistance, reduced use of other malaria interventions or changes in mosquito behaviour were also assessed, where appropriate, to permit determination of the balance of benefits and harms. Epidemiological outcomes, namely, demonstration that an intervention has proven protective efficacy to reduce, prevent or eliminate infection and/or disease in humans, were prioritized over entomological outcomes, given that the correlation between the effect of interventions on entomological outcomes and the effect of interventions on public health outcomes has not been well established. Depending on the question posed, outcomes were measured at the individual and/or community level. The specific search methods, inclusion criteria, data collection and

analysis plans for each evidence review were detailed in the published review protocols. Systematic review teams were encouraged to publish their protocols in an online register of systematic reviews and to write their final reports using the 2020 PRISMA reporting guidelines.

When limited evidence was available from randomized trials, some systematic reviews included non-randomized studies such as quasi-experimental designs, including controlled before-and-after studies, interrupted time series (controlled and uncontrolled), and stepped wedge designs. As per WHO guidelines, the GDGs also considered systematically collected evidence on contextual factors to develop the EtD frameworks. The GDGs used GRADEPro software and/or the MAGICapp platform, and the interactive EtD framework to assist in the process of evidence review and recommendation-setting.

The EtD framework considered several criteria to arrive at a recommendation for or against an intervention; these were *[127]*:

1. How substantial are the desirable anticipated effects?
2. How substantial are the undesirable anticipated effects?
3. What is the overall certainty of the evidence of effects?
4. Is there important uncertainty about or variability in how much people value the main outcomes?
5. How large are the resource requirements (costs)?
6. Does the cost-effectiveness of the intervention favour the intervention or the comparison?
7. What would be the impact on health equity?
8. Is the intervention acceptable to key stakeholders?
9. Is the intervention feasible to implement?

While criteria 1-3 relate to the health effects of recommendations, criteria 4-9 relate to contextual factors. In some cases, the GDG opted to omit factors or add factors as deemed relevant. Recommendations formulated before 2021 may not have included assessment of all factors. In MAGICapp, the EtD framework summaries for each of the recommendations contained in the *WHO Guidelines for malaria* are presented in a tab below the recommendation alongside the GRADE tables in the evidence profile tab.

Subgroup and sensitivity analysis

Where the data was available, several potential effect modifiers were assessed through subgroup analyses. These included:

- Insecticides used for both active ingredients and manufacturer
- Malaria vector species
- Setting (Urbanicity, classed as rural/ urban/ peri-urban)

Subgroups were assessed on their credibility of being a genuine effect modifier using the Instrument for assessing the Credibility of Effect Modification (ICEMAN)*[308]*. This is a tool that reviewers can use based on answering a series of questions that address specific criteria that can be used to evaluate whether an effect modification is likely. ICEMAN credibility assessment statements are expressed as very low (very likely no effect modification), low (likely no effect modification), moderate (likely effect modification), and high (very likely effect modification).

Certainty of evidence

The certainty of evidence in the systematic reviews was rated for each outcome using a four-level categorization (Table 1). The certainty of evidence considered the study design, factors that would lead to rating down the certainty (the risk of bias, inconsistency, indirectness, imprecision of the effect estimates, and publication bias) as well as factors that would lead to rating up the certainty (large effect size and dose-response effect). The terms used in the certainty assessments refer to the level of certainty in the estimate of effect relative to the recommendation question, and not necessarily to the scientific quality of the investigations reviewed. Informative statements of results for each outcome were aligned to the certainty of evidence based on standard GRADE methodology *[309]*.

Table 1. The four categories of certainty of evidence used in GRADE

Certainty of evidence	Interpretation
High	The Group is very confident in the estimate of effect and considers that further research is very unlikely to change this confidence.
Moderate	The Group has moderate confidence in the estimate of effect and considers that further research is likely to have an important impact on that confidence and may change the estimate.
Low	The Group has low confidence in the estimate of effect and considers that further research is very likely to have an important impact on that confidence and is likely to change the estimate.
Very Low	The Group is very uncertain about the estimate of effect.

Formulation of recommendations

The systematic reviews, GRADE tables and other relevant materials were provided to all members of the GDG prior to meeting to discuss particular key questions. Recommendations were formulated after considering the criteria included in the EtD framework listed above. Values and preferences, acceptability, feasibility and resource needs were important considerations. Given that these contextual factors are important in setting national policies and are broadly considered in the recommendation formulation process, efforts were made to collect information about these factors in preparation for the GDG meeting. This was achieved through systematic reviews of the literature, survey of stakeholders, or directly from the GDG. Expanded evidence-based recommendations on resource implications for malaria interventions, deployed alone or in combination, are a focus of ongoing work and guidance and will be developed where possible and incorporated into the Guidelines.

After reviewing and judging the different criteria, the GDG discussed and reached a consensus on the final recommendation at in-person or online meetings, or through e-mail correspondence. Typically, the GDG was presented with a ‘neutral’ recommendation and decided on its direction and strength. The

guideline development process aimed to generate group consensus through open and transparent discussion. In most cases, anonymous voting was used to judge the different criteria and develop the final recommendation in order to reduce peer pressure. Voting was used as a starting point to build consensus or to reach a final decision when no consensus was reached.

Types of guidance

Two types of guidance are presented in the Guidelines:.

- GRADEd recommendations: These recommendations were formulated by the GDG using the GRADE approach described above, supported by systematic reviews of the evidence, with formal assessment of the certainty of evidence.
- Good practice statements: These statements reflect a consensus within the GDG that the net benefits of adhering to the statement are large and unequivocal, and that the implications of the statement are common sense. These statements were not usually supported by a systematic review of evidence. In some cases, good practice statements were taken or adapted from existing recommendations or guidance initially developed through broad consultation, such as through the WHO Vector Control Technical Expert Group (VCTEG) or MPAG. These statements are made to reinforce the basic principles of good management practice for implementation.

Strength of recommendations

Each intervention recommendation was classified as strong or conditional, for or against an intervention, according to the GRADE system *[307]*. A strong recommendation is one for which the GDG was confident that the desirable effects of adhering to the recommendation outweighed the undesirable effects. A conditional recommendation is one for which the GDG concluded that the desirable effects of adhering to the recommendation probably outweighed the undesirable effects, but the GDG was not confident about these trade-offs. In addition to considering certainty of evidence regarding the benefits and harms and their relative effect, the strength of the recommendation was influenced by the contextual factors considered in the EtD framework. The reasons that favoured making a conditional recommendation included lower certainty evidence; smaller effect sizes and/or a tight balance between benefits and harms; variability or uncertainty in the values and preferences of individuals regarding the outcomes of interventions; high costs; equity-related concerns; feasibility issues; and acceptability issues. The implications of strong and conditional recommendations for various groups are given in Tables 2a and 2b.

Table 2a. Interpretations of recommendations

Strength of recommendation	Interpretation	
	For policy-makers and programme panagers	For end-users
Strong for	This recommendation can be adopted as policy in most situations.	Most people in this situation would want the recommended intervention, and only a small proportion would not.
Conditional for	The recommended intervention can be adopted as a policy after relevant stakeholders judge its positive consequences to outweigh its negative ones based on a careful assessment of the contextual factors.	The majority of people in this situation would want the recommended intervention, but many would not.

Table 2b. Interpretations of recommendations against an intervention

Strength of recommendation	Interpretation	
	For policy-makers and programme managers	For end-users
Strong against	This recommendation should not be adopted as policy in most situations.	Most people in this situation would not want the intervention, and only a small proportion would.
Conditional against	The recommended intervention should not be adopted as a policy unless relevant stakeholders judge its positive consequences to outweigh its negative ones based on a careful assessment of the contextual factors.	The majority of people in this situation would not want the intervention, but many would.

Presentation of evidence and recommendations

For clarity, the recommendations are presented in individual boxes on the MAGICapp platform, colour-coded and labelled by strength and certainty of evidence based on the evidence reviewed. Strong recommendations for are green, conditional recommendations for are yellow, conditional recommendations against are orange, strong recommendations against are red, and best practice statements are blue. More information on how to interpret the strength of a recommendation can be obtained by clicking on the label in the online platform. By expanding the tabs directly below the

recommendation, further detail can be obtained on the research evidence; the EtD framework; the justification including judgements by the GDG; practical information, including dosing and contextual factors; and related references. Details about the evidence can be found by clicking on the outcomes included in the evidence (e.g. the "Summary of findings" tables show the estimates of effects and relevant literature).

Management of conflicts of interest

All members of the GDGs were requested to make declarations of interest, which were managed in accordance with WHO procedures and summarized at the beginning of each meeting to all participants. Where necessary, GDG members were excluded from the discussion and/or decision-making on topics for which they had declared interests. The members of the GDGs and a summary of their declarations of interest are listed in Section 10: Contributors and Interests.

Link to WHO prequalification

When a recommendation is linked to the introduction of a new tool or product, there is a parallel process managed by the WHO Prequalification Team to ensure that diagnostics, medicines, vaccines and vector control products meet global standards of quality, safety and efficacy, in order to optimize use of health resources and improve health outcomes. The prequalification process consists of a transparent, scientifically sound assessment that, includes dossier review, consistency testing or performance evaluation, and site visits to manufacturers. This information, in conjunction with other procurement criteria, is used by United Nations and other procurement agencies to make purchasing decisions regarding these health products. This parallel process aims to ensure that recommendations are linked to prequalified products and that prequalified products are linked to a recommendation for their use.

Joint process for developing the malaria vaccine recommendation

In order to enable joint decision-making on a malaria vaccine, the different guideline development processes of the Global Malaria Programme and the WHO Department for Immunization, Vaccines and Biologicals (IVB) were harmonized following discussion with the WHO Department of Quality, Norms and Standards. The standard process for the development of WHO vaccine recommendations was used as the basis for developing the malaria vaccine recommendation. The process employed by the Strategic Group of Experts (SAGE) on Immunization, described here, complies with the principles and requirements of the standard GRC process which is described above and used for the development of the *WHO Guidelines for malaria.* MPAG members exceptionally participated in the guideline development process given their previous role in developing the malaria vaccine recommendation in 2015 and because both advisory groups had been kept up to date with the progress of the Malaria Vaccine Implementation Programme (MVIP).

A SAGE/MPAG Working Group was established with Terms of Reference and an open call for members. The SAGE/MPAG Working Group members (biographies are publicly accessible on the WHO Malaria Vaccine Implementation Programme website) were required to complete a Declaration of Interest (DOI) form prior to their appointment in advance of each meeting. Review of DOI forms revealed no relevant conflicts and all members participated in all discussions. Support for the closed sessions of the SAGE/MPAG Working Group's full evidence review was provided by a restricted WHO Secretariat - known as the SAGE/MPAG Working Group Secretariat - composed of the IVB and GMP Directors, and other staff who were not involved in the generation or synthesis of evidence being reviewed by the MVIP Programme Advisory Group (see Section 10.2 Contributors – malaria vaccine).

The SAGE/MPAG Working Group performed the following functions: developed relevant and answerable question(s) in PICO format, reviewed and interpreted the evidence, with explicit consideration of the overall balance of benefits and harms; examined and provided input to the GRADE evidence profiles developed by the Cochrane Response; and formulated the proposed recommendations for SAGE/MPAG in alignment with the 2019 RTS,S Framework for WHO recommendation (*unpublished evidence*), taking into account benefits, harms, values and preferences, feasibility, equity, acceptability, resource requirements and other factors, as appropriate.

SAGE and MPAG were jointly convened on 6 October 2021 to review the work of the SAGE/MPAG Working Group, to consider the malaria vaccine evidence and to reach consensus on their vaccine recommendations to the Director-General of WHO *[310][311]*.

Following the Director General's endorsement of the SAGE/MPAG recommendations, the evidence and deliberations that informed the WHO malaria vaccine position paper were put into the format required for the Weekly Epidemiological Record by the WHO Secretariat and reviewed by the a WHO Editorial Board as per the standard SAGE process. The draft was subject to broad peer review. Reviewers included members of SAGE, WHO Regional Offices, external subject matter experts, selected national immunization and malaria control programme managers, other interested parties (who had not been involved in the process to that point) and industry. Request for peer review from industry was coordinated through the International Federation of Pharmaceutical Manufacturers Association and the Developing Country Vaccine Manufacturer Network.

The final recommendation, GRADE and evidence-to-decision frameworks, and other relevant components were included in the *WHO Guidelines for malaria* and submitted for GRC review in parallel with the development of the WHO position paper in the Weekly Epidemiologic Record.

9. Glossary

The Glossary lists the terms contained in the *WHO malaria terminology 2021 update [312]* which is reviewed and agreed by the Drafting Committee on Malaria Terminology first convened in 2015. Please refer to that document for additional information on the

Drafting Committee and the process to review and update malaria terminology and for more detailed notes on the glossary contained here.

adherence	Compliance with a regimen (chemoprophylaxis or treatment) or with procedures and practices prescribed by a health care worker
adverse drug reaction	A response to a medicine that is harmful and unintended and which occurs at doses normally used in humans
adverse event	Any untoward medical occurrence in a person exposed to a biological or chemical product, which does not necessarily have a causal relationship with the product
adverse event, serious	Any untoward medical occurrence in a person exposed to a biological or chemical product, which is not necessarily causally related to the product, and results in death, requirement for or prolongation of inpatient hospitalization, significant disability or incapacity or is life-threatening
aestivation	A process by which mosquitoes at one or several stages (eggs, larvae, pupae, adults) survive by means of behavioural and physiological changes during periods of drought or high temperature
age group	Subgroup of a population classified by age. The following grouping is usually recommended: • 0–11 months • 12–23 months • 2–4 years • 5–9 years • 10–14 years • 15–19 years • ≥ 20 years
age, physiological	Adult female mosquito age in terms of the number of gonotrophic cycles completed: nulliparous, primiparous, 2-parous, 3-parous et seq.
age-grading, of female adult mosquitoes	Classification of female mosquitoes according to their physiological age (number of gonotrophic cycles) or simply as nulliparous or parous (parity rate)
age-grading, of mosquito larvae	Classification of mosquito larvae as instars (development stages) 1, 2, 3 and 4
annual blood examination rate	The number of people receiving a parasitological test for malaria per unit population per year
Anopheles, infected	Female *Anopheles* mosquitoes with detectable malaria parasites
Anopheles, infective	Female *Anopheles* mosquitoes with sporozoites in the salivary glands
anopheline density	Number of female anopheline mosquitoes in relation to the number of specified shelters or hosts (e.g. per room, per trap or per person) or to a given period (e.g. overnight or per hour), specifying the method of collection
anthropophilic	Description of mosquitoes that show a preference for feeding on humans, even when non-human hosts are available
antimalarial medicine	A pharmaceutical product used in humans for the prevention, treatment or reduction of transmission of malaria
artemisinin-based combination therapy	A combination of an artemisinin derivative with a longer-acting antimalarial drug that has a different mode of action
basic reproduction number	The number of secondary cases that a single infection (index case) would generate in a completely susceptible population (referred to as R0)
bioassay	In applied entomology, experimental testing of the biological effectiveness of a treatment (e.g. infection, insecticide, pathogen, predator, repellent) by deliberately exposing insects to it
biting rate	Average number of mosquito bites received by a host in a unit time, specified according to host and mosquito species (usually measured by human landing collection)
capture site	Site selected for periodic sampling of the mosquito population of a locality for various purposes
case, confirmed	Malaria case (or infection) in which the parasite has been detected in a diagnostic test, i.e. microscopy, a rapid diagnostic test or a molecular diagnostic test
case, fever	The occurrence of fever (current or recent) in a person
case, imported	Malaria case or infection in which the infection was acquired outside the area in which it is diagnosed
case, index	A case of which the epidemiological characteristics trigger additional active case or infection detection. The term “index case” is also used to designate the case identified as the origin of infection of one or a number of introduced cases
case, indigenous	A case contracted locally with no evidence of importation and no direct link to transmission from an imported case

case, induced	A case the origin of which can be traced to a blood transfusion or other form of parenteral inoculation of the parasite but not to transmission by a natural mosquito-borne inoculation
case, introduced	A case contracted locally, with strong epidemiological evidence linking it directly to a known imported case (first-generation local transmission)
case, locally acquired	A case acquired locally by mosquito-borne transmission
case, malaria	Occurrence of malaria infection in a person in whom the presence of malaria parasites in the blood has been confirmed by a diagnostic test
case, presumed	Case suspected of being malaria that is not confirmed by a diagnostic test
case, recrudescent	Malaria case attributed to the recurrence of asexual parasitaemia after antimalarial treatment, due to incomplete clearance of asexual parasitaemia of the same genotype(s) that caused the original illness. A recrudescent case must be distinguished from reinfection and relapse, in the case of *P. vivax* and *P. ovale*
case, relapsing	Malaria case attributed to activation of hypnozoites of *P. vivax* or *P. ovale* acquired previously
case, suspected malaria	Illness suspected by a health worker to be due to malaria, generally on the basis of the presence of fever with or without other symptoms
case detection	One of the activities of surveillance operations, involving a search for malaria cases in a community
case detection, active	Detection by health workers of malaria cases at community and household levels, sometimes in population groups that are considered at high risk. Active case detection can consist of screening for fever followed by parasitological examination of all febrile patients or as parasitological examination of the target population without prior screening for fever
case detection, passive	Detection of malaria cases among patients who, on their own initiative, visit health services for diagnosis and treatment, usually for a febrile illness
case follow-up	Periodic re-examination of patients with malaria (with or without treatment)
case investigation	Collection of information to allow classification of a malaria case by origin of infection, i.e. imported, indigenous, induced, introduced, relapsing or recrudescent
case management	Diagnosis, treatment, clinical care, counselling and follow-up of symptomatic malaria infections
case notification	Compulsory reporting of all malaria cases by medical units and medical practitioners to either the health department or the malaria control programme, as prescribed by national laws or regulations
catchment area	A geographical area defined and served by a health programme or institution, such as a hospital or community health centre, which is delineated on the basis of population distribution, natural boundaries and accessibility by transport
cerebral malaria	Severe *P. falciparum* malaria with impaired consciousness (Glasgow coma scale < 11, Blantyre coma scale < 3) persisting for > 1 hour after a seizure
certification of malaria-free status	Certification granted by WHO after it has been proved beyond reasonable doubt that local human malaria transmission by Anopheles mosquitoes has been interrupted in an entire country for at least three consecutive years and a national surveillance system and a programme for the prevention of reintroduction are in place
chemoprevention, seasonal malaria	Intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness. The objective is to maintain therapeutic concentrations of an antimalarial drug in the blood throughout the period of greatest risk for malaria.
chemoprophylaxis	Administration of a medicine, at predefined intervals, to prevent either the development of an infection or progression of an infection to manifest disease
cluster	Aggregation of relatively uncommon events or diseases in space and/or time in numbers that are considered greater than could be expected by chance
combination therapy	A combination of two or more classes of antimalarial medicine with unrelated mechanisms of action
coverage	A general term referring to the fraction of the population of a specific area that receives a particular intervention
coverage, optimal	Optimal coverage is the outcome of an explicit prioritization process guiding resource allocation decisions. The process

	combines the analysis of impact and value for money with extensive stakeholder engagement and discussion that explicitly outlines the trade-offs involved in the selection of interventions and combining them in an intervention package. The process should take into account a country's programmatic goals, context-specific factors, and should consider equity implications of the resource allocation decisions.
coverage, universal health	Ensuring all individuals and communities receive the health services they need without suffering financial hardship. It includes the full spectrum of essential quality health services from health promotion to prevention, treatment, rehabilitation, and palliative care.
cure	Elimination from an infected person of all malaria parasites that caused the infection
cure, radical	Elimination of both blood-stage and latent liver infection in cases of *P. vivax* and *P. ovale* infection, thereby preventing relapses
cure rate	Percentage of treated individuals whose infection is cured
cyto-adherence	Propensity of malaria-infected erythrocytes to adhere to the endothelium of the microvasculature of the internal organs of the host
diagnosis	The process of establishing the cause of an illness (for example, a febrile episode), including both clinical assessment and diagnostic testing
diagnosis, molecular	Use of nucleic acid amplification-based tests to detect the presence of malaria parasites
diagnosis, parasitological	Diagnosis of malaria by detection of malaria parasites or *Plasmodium*-specific antigens or genes in the blood of an infected individual
diapause	Condition of suspended animation or temporary arrest in the development of immature and adult mosquitoes
dosage regimen (or treatment regimen)	Prescribed formulation, route of administration, dose, dosing interval and duration of treatment with a medicine
dose	Quantity of a medicine to be taken at one time or within a given period
dose, loading	One or a series of doses that may be given at the start of therapy with the aim of achieving the target concentration rapidly
drug efficacy	Capacity of an antimalarial medicine to achieve the therapeutic objective when administered at a recommended dose, which
	is well tolerated and has minimal toxicity
drug resistance	The ability of a parasite strain to survive and/or multiply despite the absorption of a medicine given in doses equal to or higher than those usually recommended
drug safety	(see Medicine safety)
drug, gametocytocidal	A drug that kills male and/or female gametocytes, thus preventing them from infecting a mosquito
drug, schizontocidal	A drug that kills schizonts, either in the liver or the blood
endemic area	An area in which there is an ongoing, measurable incidence of malaria infection and mosquito-borne transmission over a succession of years
endemicity, level of	Degree of malaria transmission in an area
endophagy	Tendency of mosquitoes to blood-feed indoors
endophily	Tendency of mosquitoes to rest indoors
entomological inoculation rate (EIR)	Number of infective bites received per person in a given unit of time, in a human population
epidemic	Occurrence of a number of malaria cases highly in excess of that expected in a given place and time
epidemiological investigation	Study of the environmental, human and entomological factors that determine the incidence or prevalence of infection or disease
erythrocytic cycle	Portion of the life cycle of the malaria parasite from merozoite invasion of red blood cells to schizont rupture. The duration is approximately 24 h in *P. knowlesi*, 48 h in *P. falciparum*, *P. ovale* and *P. vivax,* and 72 h in *P. malariae*.
exophagy	Tendency of mosquitoes to feed outdoors
exophily	Tendency of mosquitoes to rest outdoors
experimental huts	For vector investigations, simulated house with entry and exit traps for sampling mosquitoes entering and exiting, blood-feeding indoors (when a host is present), and surviving or dying in each sub-sample, per day or night
fixed-dose combination	A combination in which two antimalarial medicines are formulated together in the same tablet, capsule, powder, suspension or granule

focus, malaria	A defined circumscribed area situated in a currently or formerly malarious area that contains the epidemiological and ecological factors necessary for malaria transmission
gametocyte	Sexual stage of malaria parasites that can potentially infect anopheline mosquitoes when ingested during a blood meal
gametocyte rate	Percentage of individuals in a defined population in whom sexual forms of malaria parasites have been detected
geographical reconnaissance	Censuses and mapping to determine the distribution of the human population and other features relevant for malaria transmission in order to guide interventions
gonotrophic cycle, mosquito	The period of reproductive development in the female mosquito, including host-seeking, blood feeding, digestion of a blood meal, ovarian development, search for a breeding site and oviposition.
gonotrophic discordance (dissociation)	Female mosquitoes that take more than one blood meal per gonotrophic cycle
hibernation	Process in which mosquitoes at one or several stages (eggs, larvae, pupae, adults) survive by means of behavioural or physiological changes during cold periods
house	Any structure other than a tent or mobile shelter in which humans sleep
household	The ecosystem, including people and animals occupying the same house and the accompanying vectors
house-spraying	Application of liquid insecticide formulation to specified (mostly interior) surfaces of buildings
human landing catch	A method for collecting vectors as they land on individuals
hyperparasitaemia	A high density of parasites in the blood, which increases the risk that a patient's condition will deteriorate and become severe malaria
hypnozoite	Persistent liver stage of *P. vivax* and *P. ovale* malaria that remains dormant in host hepatocytes for variable periods, from three weeks to one year (exceptionally even longer), before activation and development into a pre-erythrocytic schizont, which then causes a blood-stage infection (relapse)
importation rate	Rate of influx of parasites via infected individuals or infected *Anopheles* spp. mosquitoes
importation risk	Probability of influx of infected individuals and/or infective anopheline mosquitoes
incidence, malaria	Number of newly diagnosed malaria cases during a defined period in a specified population
incubation period	Period between inoculation of malaria parasites and onset of clinical symptoms
index, host preference	Proportion of blood-fed female *Anopheles* mosquitoes that feed on the host species and/or individual of interest
index, human blood	Proportion of mosquito blood meals from humans
index, parasite-density	Mean parasite density on slides examined and found positive for a sample of the population; calculated as the geometric mean of individual parasite density counts
indoor residual spraying	Operational procedure and strategy for malaria vector control involving spraying interior surfaces of dwellings with a residual insecticide to kill or repel endophilic mosquitoes
indoors	Inside any shelter likely to be used by humans or animals, where mosquitoes may feed or rest
infection, chronic	Long-term presence of parasitaemia that is not causing acute or obvious illness but could potentially be transmitted
infection, mixed	Malaria infection with more than one species of *Plasmodium*
infection, reservoir of	Any person or animal in which *Plasmodium* species live and multiply, such that they can be transmitted to a susceptible host
infection, submicroscopic	Low-density blood-stage malaria infections that are not detected by conventional microscopy
infectious	Capable of transmitting infection, a term commonly applied to human hosts
infective	Capable of producing infection, a term commonly applied to parasites (e.g., gametocytes, sporozoites) or to the vector (mosquito)
infectivity	Ability of sporozoites of a specific strain of *Plasmodium* to be injected by *Anopheles* mosquitoes into susceptible humans and develop through the liver stage to infect red blood cells ("infectivity to humans") and the ability of competent *Anopheles* mosquitoes to ingest human *Plasmodium* gametocytes which undergo development until the mosquito has infective sporozoites in its

	salivary glands ("infectivity to mosquitoes").
insecticide	Chemical product (natural or synthetic) that kills insects. Ovicides kill eggs; larvicides (larvacides) kill larvae; pupacides kill pupae; adulticides kill adult mosquitoes. Residual insecticides remain active for an extended period
insecticide, cross-resistance	Resistance to one insecticide by a mechanism that also confers resistance to another insecticide, even when the insect population has not been selected by exposure to the latter
insecticide discriminating dose, or diagnostic dose for resistance	Amount of an insecticide (usually expressed as the concentration per standard period of exposure), which, in a sample of mosquitoes containing resistant individuals, distinguishes between susceptible and resistant phenotypes and determines their respective proportions
insecticide, dose	Amount of active ingredient of insecticide applied per unit area of treatment (mg/m^2) for indoor residual spraying and treated mosquito nets, or per unit of space (mg/m^3) for space spraying and per unit area of application (g/ha or mg/m^2) or per volume of water (mg/L) for larvicides
insecticide, mixture	Insecticide product consisting of two or more active ingredients mixed as one formulation so that, when applied, the mosquito will contact both simultaneously
insecticide mosaic	Strategy for mitigating resistance, whereby insecticides with different modes of action are applied in different parts of an area under coverage (usually in a grid pattern), so that parts of the mosquito populations are exposed to one insecticide and others to another
insecticide resistance	Property of mosquitoes to survive exposure to a standard dose of insecticide; may be the result of physiological or behavioural adaptation
insecticide rotation	Strategy involving sequential applications of insecticides with different modes of action to delay or mitigate resistance
insecticide tolerance	Less-than-average susceptibility to insecticide but not inherited as resistance
insecticide, contact	Insecticide that exerts a toxic action on mosquitoes when they rest on a treated surface; the insecticide is absorbed via the tarsi (feet).
insecticide, fumigant	Insecticide that acts by releasing vapour from a volatile substance
insecticide, residual	Insecticide that, when suitably applied onto a surface, maintains its insecticidal activity for a considerable time by either contact or fumigant action
integrated vector management (IVM)	Rational decision-making for optimal use of resources for vector control
intermittent preventive treatment of malaria in school-aged children	Administration of a full treatment course of an antimalarial medicine at predefined intervals to school children, in order to prevent illness in areas with moderate to high malaria transmission
intermittent preventive treatment in infants (IPTi)	Please see ‘perennial malaria chemoprevention’
intermittent preventive treatment in pregnancy (IPTp)	A full therapeutic course of antimalarial medicine given to pregnant women at routine prenatal visits, regardless of whether the woman is infected with malaria
invasive species	A non-native species that establishes in a new ecosystem, and causes, or has the potential to cause, harm to the environment, economy, or human health
larval source management	Management of aquatic habitats (water bodies) that are potential habitats for mosquito larvae, in order to prevent completion of development of the immature stages
larvicide	Substance used to kill mosquito larvae
latent period	For *P. vivax* and *P. ovale* infections, the period between the primary infection and subsequent relapses. This stage is asymptomatic; parasites are absent from the bloodstream but present in hepatocytes.
long-lasting insecticidal net (LLIN)	A factory-treated mosquito net made of material into which insecticide is incorporated or bound around the fibres. The net must retain its effective biological activity for at least 20 WHO standard washes under laboratory conditions and three years of recommended use under field conditions.
malaria case	(See Case, malaria)
malaria, cerebral	(See Cerebral malaria)
malaria control	Reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts. Continued interventions are required to sustain control.

malaria elimination	Interruption of local transmission (reduction to zero incidence of indigenous cases) of a specified malaria parasite in a defined geographical area as a result of deliberate activities. Continued measures to prevent re-establishment of transmission are required.
malaria eradication	Permanent reduction to zero of the worldwide incidence of infection caused by human malaria parasites as a result of deliberate activities. Interventions are no longer required once eradication has been achieved.
malaria infection	Presence of *Plasmodium* parasites in blood or tissues, confirmed by diagnostic testing
malaria mortality rate	Number of deaths from malaria per unit of population during a defined period
malaria pigment (haemozoin)	A brown-to-black granular material formed by malaria parasites as a by-product of haemoglobin digestion. Pigment is evident in mature trophozoites and schizonts. It may also be phagocytosed by monocytes, macrophages and polymorphonuclear neutrophils.
malaria prevalence (parasite prevalence)	Proportion of a specified population with malaria infection at one time
malaria rebound	Increased malaria incidence following time-limited reduction of malaria transmission (through effective interventions such as chemoprevention, vaccination or vector control), when the population becomes exposed to more transmission
malaria receptivity	Degree to which an ecosystem in a given area at a given time allows for the transmission of *Plasmodium* spp. from a human through a vector mosquito to another human.
malaria reintroduction	The occurrence of introduced cases (cases of the first-generation local transmission that are epidemiologically linked to a confirmed imported case) in a country or area where the disease had previously been eliminated
malaria risk stratification	Classification of geographical areas or localities according to factors that determine receptivity and vulnerability to malaria transmission
malaria stratification	Classification of geographical areas or localities according to epidemiological, ecological, social and economic determinants for the purpose of guiding malaria interventions
malaria, cross-border	Malaria transmission associated with the movement of individuals or mosquitoes across borders
malaria-free	Describes an area in which there is no continuing local mosquito-borne malaria transmission and the risk for acquiring malaria is limited to infection from introduced cases
malariogenic potential	Potential level of transmission in a given area arising from the combination of malaria receptivity, importation rate of malaria parasites and infectivity
malariometric survey	Survey conducted in a representative sample of selected age groups to estimate the prevalence of malaria and coverage of interventions
malarious area	Area in which transmission of malaria is occurring or has occurred during the preceding three years
mass drug administration (MDA)	Administration of full treatment course of an antimalarial to all age groups of a population in a defined geographical area (except those for whom the medicine is contraindicated) at approximately the same time and often at repeated intervals
mass screening	Population-wide assessment of risk factors for malaria infection to identify subgroups for further intervention, such as diagnostic testing, treatment or preventive services
mass screening, testing and treatment	Screening of an entire population for risk factors, testing individuals at risk and treating those with a positive test result
mass testing and focal drug administration	Testing a population and treating groups of individuals or entire households in which one or more infections is detected
mass testing and treatment	Parasitological screening of the entire population of a delimited geographical area and treating those with a positive test result at approximately the same time
medicine safety	Characteristics of a medicine that reflects its potential to cause harm, including the important identified risks of a drug and important potential risks
merozoite	Extracellular stage of a parasite released into host plasma when a hepatic or erythrocytic schizont ruptures; the merozoites can then invade red blood cells.
moderate to high perennial transmission	Persistent *P. falciparum* transmission at rates which result in a parasite prevalence greater than 10%, or an annual parasite incidence greater than 250 per 1000.

monotherapy	Antimalarial treatment with a single active compound or a synergistic combination of two compounds with related mechanisms of action
national focus register	Centralized database of all foci of malaria infection in a country, which includes relevant data on physical geography, parasites, hosts and vectors for each focus
national malaria case register	Centralized database with individual records of all malaria cases registered in a country
net, insecticide-treated (ITN)	Mosquito net that repels, disables or kills mosquitoes that come into contact with the insecticide on the netting material. Insecticide treated nets (ITNs) include those that require treatment and retreatment (often referred to as conventional nets) and those that are “long-lasting” (see definition of long-lasting insecticidal net).
oocyst	The stage of malaria parasite that develops from the ookinete; the oocyst grows on the outer wall of the midgut of the female mosquito.
oocyst rate	Percentage of female *Anopheles* mosquitoes with oocysts on the midgut
ookinete	Motile stage of malaria parasite after fertilization of macrogamete and preceding oocyst formation
parasitaemia	Presence of parasites in the blood
parasitaemia, asymptomatic	The presence of asexual parasites in the blood without symptoms of illness
parasite clearance time	Time between first drug administration and the first examination in which no parasites are present in the blood by microscopy
parasite density	Number of asexual parasites per unit volume of blood or per number of red blood cells
parasite density, low	Presence of *Plasmodium* parasites in the blood at parasite density below 100 parasites/µl
patent period	Period during which malaria parasitaemia is detectable
perennial malaria chemoprevention	Administration of a full treatment course of an antimalarial medicine at predefined intervals to children at risk of severe malaria, in order to prevent illness in moderate to high perennial malaria transmission settings.
Plasmodium	Genus of protozoan blood parasites of vertebrates that includes the causal agents of malaria. *P. falciparum, P. malariae*, *P. ovale* and *P. vivax* cause malaria in humans. Human infection with the monkey malaria parasite *P. knowlesi* and very occasionally with other simian malaria species may occur in tropical forest areas.
population at risk	Population living in a geographical area where locally acquired malaria cases have occurred in the past three years
population, target	An implementation unit targeted for activities or services (e.g., prevention, treatment)
post-discharge malaria chemoprevention	Administration of a full treatment course of an antimalarial medicine to children hospitalized for severe anemia, starting at time of discharge from hospital and continuing at predefined intervals.
pre-erythrocytic development	Development of the malaria parasite from the time it first enters the host and invades liver cells until the hepatic schizont ruptures
pre-patent period	Period between inoculation of parasites and the first appearance of parasitaemia
prequalification	Process to ensure that health products are safe, appropriate and meet stringent quality standards for international procurement
preventive chemotherapy	Use of medicines either alone or in combination to prevent malaria infections and their consequences
prophylaxis	Any method of protection from or prevention of disease; when applied to chemotherapy, it is commonly termed “chemoprophylaxis”.
prophylaxis, causal	Complete prevention of erythrocytic infection by destroying the pre-erythrocytic forms of the parasite
rapid diagnostic test (RDT)	Immunochromatographic lateral flow device for rapid detection of malaria parasite antigens
rapid diagnostic test, combination	Malaria rapid diagnostic test that can detect a number of different malaria species
rapid diagnostic test positivity rate	Proportion of positive results among all rapid diagnostic tests performed
reactive case detection and treatment	Parasitological screening of every person living with or near a person who has a confirmed malaria case, and/or every person who was likely exposed to infection at the same time and place as the index case, and treating those with a malaria positive test result
reactive drug administration	Administration of a full treatment course of an antimalarial medicine as chemoprevention to every person living with or near a person with a confirmed malaria infection, and/or to every person who was likely exposed to infection at the same time

	and place as the index case
reactive indoor residual spraying	Application of residual insecticide to the interior surfaces of dwellings in the location of the index case and neighboring houses at approximately the same time
receptivity	Receptivity of an ecosystem to transmission of malaria
recrudescence	Recurrence of asexual parasitaemia of the same genotype(s) that caused the original illness, due to incomplete clearance of asexual parasites after antimalarial treatment
recurrence	Reappearance of asexual parasitaemia after treatment, due to recrudescence, relapse (in *P. vivax* and *P. ovale* infections only) or a new infection
reinfection	A new infection that follows a primary infection; can be distinguished from recrudescence by the parasite genotype, which is often (but not always) different from that which caused the initial infection
reintroduction risk	The risk that endemic malaria will be re-established in a specific area after its elimination
relapse	Recurrence of asexual parasitaemia in *P. vivax* or *P. ovale* infections arising from hypnozoites
repellent	Any substance that causes avoidance in mosquitoes, especially substances that deter them from settling on the skin of the host (topical repellent) or entering an area or room (area repellent, spatial repellent, excito-repellent)
resistance	(See Drug resistance, Insecticide resistance)
ring form (ring stage, ring-stage trophozoite)	Young, usually ring-shaped malaria trophozoites, before pigment is evident by microscopy
schizont	Stage of the malaria parasite in host liver cells (hepatic schizont) or red blood cells (erythrocytic schizont) that is undergoing nuclear division by schizogony and, consequently, has more than one nucleus
screening	Identification of groups at risk that may require further intervention, such as diagnostic testing, treatment or preventive services
seasonal malaria chemoprevention	Intermittent administration of full treatment courses of an antimalarial medicine to children at risk of severe malaria, to prevent malarial illness in areas with seasonal malaria. The objective is to maintain therapeutic concentrations of an antimalarial drug in the blood throughout the period of greatest risk for malaria.
selection pressure	The force of an external agent that confers preferential survival; examples are the pressure of antimalarial medicines on malaria parasites and of insecticides on anopheline mosquitoes
sensitivity (of a test)	Measured as the proportion of people with malaria infection (true positives) who have a positive result
serological assay	Procedure used to measure antimalarial antibodies in serum
severe anaemia	Haemoglobin concentration of < 5 g/100 mL (haematocrit < 15%)
severe falciparum malaria	Acute falciparum malaria with signs of severe illness and/or evidence of vital organ dysfunction
single-dose regimen	Administration of a medicine as a single dose to achieve a therapeutic objective
slide positivity rate	Proportion of blood smears found to be positive for *Plasmodium* among all blood smears examined
specificity (of a test)	Measured as the proportion of people without malaria infection (true negatives) who have a negative result
sporozoite	Motile stage of the malaria parasite that is inoculated by a feeding female anopheline mosquito and may cause infection
sporozoite rate	Percentage of female *Anopheles* mosquitoes with sporozoites in the salivary glands
spray round	Spraying of all sprayable structures in an area designated for coverage in an indoor residual spraying programme during a discrete period
sprayable	In the context of a malaria vector control programme, a unit (dwelling, house, room, shelter, structure, surface) suitable for spraying or required to be sprayed
spraying cycle	Repetition of spraying operations at regular intervals, often designated in terms of the interval between repetitions, e.g., a 6-month spraying cycle when spraying is repeated after a 6-month interval
spraying frequency	Number of regular applications of insecticide per house per year, usually by indoor residual spraying
spraying interval	Time between successive applications of insecticide
spraying, focal	Spray coverage by indoor residual spraying

	and/or space spraying of houses or habitats in a limited geographical area
spraying, residual (IRS)	Spraying the interior walls and ceilings of dwellings with a residual insecticide to kill or repel endophilic mosquito vectors of malaria
surveillance	Continuous, systematic collection, analysis and interpretation of disease-specific data and use in planning, implementing and evaluating public health practice
surveillance, entomological	The regular, systematic collection, analysis and interpretation of entomological data for risk assessment, planning, implementation, monitoring and evaluation of vector control interventions
targeted drug administration	Administration of a full treatment course of an antimalarial medicine to individuals at increased risk of malaria infection compared to the general population.
targeted testing and treatment	Parasitological screening of individuals at increased risk of malaria infection compared to the general population and treating those with a malaria positive test result.
testing, malaria	Use of a malaria diagnostic test to determine whether an individual has malaria infection
tolerance	A response in a human or mosquito host to a given quantum of infection, toxicant or drug that is less than expected
transmission intensity	The frequency with which people living in an area are bitten by anopheline mosquitoes carrying human malaria sporozoites
transmission season	Period of the year during which most mosquito-borne transmission of malaria infection occurs
transmission, re-establishment of	Renewed presence of a measurable incidence of locally acquired malaria infection due to repeated cycles of mosquito-borne infections in an area in which transmission had been interrupted
transmission, interruption of	Cessation of mosquito-borne transmission of malaria in a geographical area as a result of the application of antimalarial measures
transmission, perennial	Transmission that occurs throughout the year with no great variation in intensity
transmission, residual	Persistence of malaria transmission following the implementation in time and space of a widely effective malaria programme
transmission, seasonal	Transmission that occurs only during some months of the year and is markedly reduced during other months
transmission, stable	Epidemiological type of malaria transmission characterized by a steady prevalence pattern, with little variation from one year to another except as the result of rapid scaling up of malaria interventions or exceptional environmental changes that affect transmission
transmission, unstable	Epidemiological type of malaria transmission characterized by large variation in incidence patterns from one year to another
trap, mosquito	Device designed for capturing mosquitoes with or without attractant components (light, CO_2, living baits, suction)
treatment failure	Inability to clear malarial parasitaemia or prevent recrudescence after administration of an antimalarial medicine, regardless of whether clinical symptoms are resolved
treatment, anti-relapse	Antimalarial treatment designed to kill hypnozoites and thereby prevent relapses or late primary infections with *P. vivax* or *P. ovale*
treatment, directly observed (DOT)	Treatment administered under the direct observation of a health care worker
treatment, first-line	Treatment recommended in national treatment guidelines as the medicine of choice for treating malaria
treatment, second-line	Treatment used after failure of first-line treatment or in patients who are allergic to or unable to tolerate the first-line treatment
treatment, presumptive	Administration of an antimalarial drug or drugs to people with suspected malaria without testing or before the results of blood examinations are available
treatment, preventive	Intermittent administration of a full therapeutic course of an antimalarial either alone or in combination to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest risk
treatment, radical	Treatment to achieve complete cure. This applies only to vivax and ovale infections and consists of the use of medicines that destroy both blood and liver stages of the parasite.
trophozoite	The stage of development of malaria parasites growing within host red blood cells from the ring stage to just before nuclear division. Trophozoites contain malaria pigment that is visible by microscopy.
uncomplicated malaria	Symptomatic malaria parasitaemia without signs of severity or evidence of vital organ dysfunction

vector	In malaria, adult females of any mosquito species in which *Plasmodium* undergoes its sexual cycle (whereby the mosquito is the definitive host of the parasite) to the infective sporozoite stage (completion of extrinsic development), ready for transmission when a vertebrate host is bitten
vector competence	For malaria, the ability of the mosquito to support completion of malaria parasite development after zygote formation and oocyst formation, development and release of sporozoites that migrate to salivary glands, allowing transmission of viable sporozoites when the infective female mosquito feeds again
vector control	Measures of any kind against malaria-transmitting mosquitoes, intended to limit their ability to transmit the disease
vector susceptibility	The degree to which a mosquito population is susceptible (i.e., not resistant) to insecticides
vector, principal	The species of *Anopheles* mainly responsible for transmitting malaria in any particular circumstance
vector, secondary or subsidiary	Species of *Anopheles* thought to play a lesser role in transmission than the principal vector; capable of maintaining malaria transmission at a reduced level
vectorial capacity	Number of new infections that the population of a given vector would induce per case per day at a given place and time, assuming that the human population is and remains fully susceptible to malaria
vigilance	A function of the public health services for preventing reintroduction of malaria. Vigilance consists of close monitoring for any occurrence of malaria in receptive areas and application of the necessary measures to prevent re-establishment of transmission.

10. Contributors and interests

The Guideline was consolidated for the first time in February 2021, building on previously published guidelines. The consolidation and coordination between the technical areas and GDGs was driven by Dr Pedro Alonso, former Director and Erin Shutes, former Programme Manager of the Global Malaria Programme to ensure consistency in approach and harmonization in the recommendations. The many contributors to the development of recommendations are acknowledged in the sub-sections below according to the evidence reviews of the intervention areas.

Funding
The consolidated WHO Guidelines for malaria, developed by the WHO Global Malaria Programme, were supported by multiple donors including the Bill & Melinda Gates Foundation, the United States Agency for International Development, and the Government of Spain.

The Malaria Vaccine Implementation Programme (MVIP), through which evidence was generated on the use of the RTS,S/AS01 malaria vaccine in routine immunization systems, was made possible through financial support received from Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid.

Platform contribution
WHO would like to acknowledge the MAGIC Evidence Ecosystem Foundation for their support in the consolidation of the Guidelines on the MAGICapp platform.

10.1 Recommendations for vector control

Members of the Guidelines Development Group (GDG) (2019)
The WHO Technical Expert Group on Malaria Vector Control (VCTEG) served as the GDG and included:

- Dr Constance Bart-Plange, Independent Malaria Consultant, Accra, Ghana
- Professor Marc Coosemans, Department of Parasitology, Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium
- Dr Camila Pinto Damasceno, FIOCRUZ Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
- Dr Marcy Erskine, Senior Health Officer (Malaria), International Federation of Red Cross and Red Crescent Societies, Geneva, Switzerland
- Dr Josiane Etang, Organisation de coordination pour la lutte contre les endémies en Afrique centrale, Yaoundé, Cameroon
- Dr John Gimnig (Chair), Entomology Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Jeffrey Hii, Malaria Consortium, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
- Dr Zhou Hong-Ning, Office of Joint Prevention and Control of Malaria/ Dengue, Yunnan Institute of Parasitic Diseases, Shanghai, China
- Dr Hmooda Toto Kafy, Integrated Vector Management Department Manager and Deputy Manager of National Malaria Control Programme, Federal Ministry of Health, Khartoum, Sudan

- Professor Jonathan Lines, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland of Great Britain and Northern Ireland
- Dr Stephen Magesa, Technical Specialist, AIRS Tanzania Project, Abt Associates Inc., Mwanza, United Republic of Tanzania
- Dr Eunice Misiani, Malaria and Other Vector Borne Diseases, National Department of Health, Pretoria, South Africa
- Dr Rajander Singh Sharma, Centre for Medical Entomology and Vector Control National Centre for Disease Control, Ministry of Health and Family Welfare, Delhi, India

Members of the Guidelines Steering Group (2019)

- Dr Rabindra Abeyasinghe, WHO Regional Office for the Western Pacific, Manila, Philippines
- Dr Birkinesh Ameneshewa, WHO Regional Office for Africa, Brazzaville, Congo
- Dr Samira Al-Eryani, WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt
- Dr Haroldo Bezerra, WHO Regional Office for the Americas, Washington DC, United States of America
- Dr Florence Fouque, Special Programme for Research and Training in Tropical Diseases, Geneva, Switzerland
- Dr Jan Kolaczinski, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Dr Tessa Knox, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Mrs Marion Law, Prequalifications Team for Vector Control, Departments of Essential Medicines of Health Products, World Health Organization, Geneva, Switzerland
- Dr Peter Olumese, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Mrs Edith Patouillard, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Dr Nathalie Roebbel, Department of Public Health, Environment and Social Determinants of Health, World Health Organization, Geneva, Switzerland
- Dr Matt Shortus, WHO Country Office, Lao People's Democratic Republic
- Dr Raman Velayudhan, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

Members of the External Review Group (ERG) (2019)

The WHO Malaria Policy Advisory Committee (MPAC) served as the ERG and included:

- Professor Ahmed Adeel, Independent Consultant, United States of America
- Dr Evelyn Ansah, Director, Center for Malaria Research, Institute of Health Research, University of Health and Allied Sciences, Ghana
- Professor Thomas Burkot, Professor and Tropical Leader, Australian Institute of Tropical Health and Medicine, James Cook University, Australia
- Professor Graham Brown, Professor Emeritus, University of Melbourne, Australia
- Dr Gabriel Carrasquilla, Director of ASIESALUD, Fundación de Santa Fe de Bogota, Centre for Health Research, Colombia
- Dr Maureen Coetzee, Director, Wits Research Institute for Malaria, University of Witwatersrand, South Africa
- Professor Umberto d'Alessandro, Director, Medical Research Council Unit, Gambia
- Dr Abdoulaye Djimde, Head, Molecular Epidemiology and Drug Resistance Unit, Malaria Research and Training Center, University of Mali, Mali
- Professor Azra Ghani, Professor in Infectious Diseases, Epidemiology, Centre for Outbreak Analysis and Modelling, Imperial College, United Kingdom of Great Britain and Northern Ireland
- Professor Brian Greenwood, Manson Professor of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Dr Caroline Jones, Senior Social Scientist, KEMRI Wellcome Trust Research Programme, Kenya
- Dr Stephen Kachur, Chief, Malaria Branch, Centers for Disease Control and Prevention, United States of America
- Professor Kevin Marsh (Chair), Director, KEMRI Wellcome Trust Research Programme, Kenya
- Dr Kamini Mendis, Independent Consultant in malaria and tropical medicine, Sri Lanka
- Professor Gao Qi, Senior Professor, Jiangsu Institute of Parasitic Diseases and Suzhou University, China
- Dr Pratap Singhasivanon, Associate Professor, Department of Tropical Hygiene, Mahidol University, Thailand
- Dr Larry Slutsker, Director, Malaria and Neglected Tropical Diseases, Center for Malaria Control and Elimination, PATH, United States of America
- Dr Richard Steketee, Director, Malaria Control and Elimination, PATH, United States of America
- Dr Neena Valecha, Director, National Institute for Malaria Research, India
- Professor Dyann Wirth, Richard Pearson Strong Professor and Chair, Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, United States of America

Systematic review production and management team and GRADE analysis subgroup members (2019)

- Mr Leslie Choi, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Mr Joe Pryce, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Ms Marty Richardson, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr Vittoria Lutje, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr Deirdre Walshe, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United

Kingdom of Great Britain and Northern Ireland
- Prof Paul Garner, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland

Guidelines methodologist (2019)
Dr Joseph Okebe, Guidelines Methodologist, Disease Control and Elimination Team, Medical Research Council Unit, Gambia

Declaration of interests (2019)
Participants in the technical consultations or sessions for development of the Guidelines reported relevant interests. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat, with support from the Office of Compliance, Risk Management and Ethics as needed. WHO was of the opinion that these declarations did not constitute conflicts of interest and that the considered experts could participate in the consultations on the Guidelines subject to the public disclosure of their interests, which was conducted.

The relevant declared interests are summarized as follows:

Dr T. Burkot reported several potential conflicts of interest related to consulting payments, research support and non-monetary support, as follows: 1) consulting with Intellectual Ventures Global Good Fund (IVGGF), the non-profit arm of Intellectual Ventures Laboratory. Work was conducted from October 2014 to March 2015 through James Cook University; 2) consulting with IVGGF for a secondement in 2017 to develop a vector control strategy on mosquito-proof housing and methods to age-grade mosquitoes through James Cook University; 3) consulting with the non-profit Programme for Appropriate Technology in Health (PATH) in 2017 to support grant applications to evaluate new vector control tools in Africa; 4) consulting with IVGGF from 2017 to February 2018 to provide technical support on developing guidelines for testing new vector control strategies, paid directly to Dr Burkot; 5) consulting with PATH from 2017 to February 2018 to provide technical advice on field trials for mosquito-proof housing products paid, directly to Dr Burkot; 6) research support in a supervisory role provided to James Cook University for evaluation of a new malaria diagnostic test from October 2015 to March 2017; 7) research support in a supervisory role provided to James Cook University to undertake a malaria serologic survey in the Solomon Islands until June 2018; and 8) non-monetary support to Vestergaard in a supervisory role to evaluate the impact of insecticide netting on malaria in Solomon Islands.

Dr M. Coetzee reported a potential conflict of interest related to a family member's consulting work with AngloGold Ashanti in 2016 to carry out mosquito surveys and determine insecticide resistance in order to inform vector control strategies by gold mining companies in Africa.

Professor M. Coosemans reported receiving a grant from the Bill & Melinda Gates Foundation for studying the impact of repellents for malaria prevention in Cambodia and also reported receiving repellent products for the study from SC Johnson for work conducted in 2012–2014. He also reported receiving six grants for the evaluation of public health pesticides from WHOPES from 2007, some of which continued until 2018.

Dr J. Hii reported receiving remuneration for consulting services from WHO and from the Ministry of Health of Timor-Leste for work conducted in 2017. He reported holding a grant from SC Johnson that ceased in 2017 for the evaluation of transfluthrin, and receiving travel and accommodation support from Bayer Crop Science to attend the 4th Bayer Vector Control Expert Meeting in 2017. He reported holding a WHO/TDR research grant that focused on studying the magnitude and identifying causes for residual transmission in Thailand and Viet Nam (completed in 2018), and reported a plan to study the impact of socio-ecological systems and resilience (SESR)-based strategies on dengue vector control in schools and neighbouring household communities in Cambodia, which in November 2017 was awaiting ethical approval.

Members of the Guidelines Development Group (GDG) (2021)
- Dr Dorothy Achu, Programme manager, National Malaria Control Programme, Yaoundé, Cameroon
- Prof Basil Brooke, Associate professor, University Witwatersrand/National Institute for Communicable Disease, Johannesburg, South Africa
- Prof Ahmad Ali Enayati, Head, Medical Entomology Department, School of Public Health, Mazandaran University of Medical Sciences, Sari, Islamic Republic of Iran
- Ms Mihirini Hewavitharane, Entomology Technical Manager, PMI VectorLink Project, Abt Associates, Phnom Penh, Cambodia
- Dr Seth Irish, Research entomologist, Centers for Disease Control and Prevention, Atlanta, United States of America
- Professor Fang Jing, Director, Institute for Health Sciences, Kunming Medical University, Yunnan Province, China
- Dr Keziah Malm, Programme manager, National Malaria Control Programme, Accra, Ghana
- Dr Kui Muraya, Social scientist, KEMRI-Wellcome Trust, Nairobi, Kenya
- Prof Martha Quiñones, Professor, Universidad Nacional de Colombia, Bogotá, Colombia
- Dr Christina Rundi, Health director, Sabah Health Department, Ministry of Health, Sabah, Malaysia
- Dr Tanya Russell, Research fellow, James Cook University, Cairns, Australia
- Dr Lucy Tusting, Assistant professor, Faculty of Infectious Tropical Disease, LSHTM, London, United Kingdom of Great Britain and Northern Ireland
- Dr Josh Yukich, Associate professor, Department of Tropical Medicine Tulane University School of Public Health and Tropical Medicine, New Orleans, United States of America

Members of the Guidelines Development Group (GDG) (2022 & 2023)
- Dr Dorothy Achu, Programme manager, National Malaria Control Programme, Yaoundé, Cameroon
- Prof Basil Brooke, Associate professor, University Witwatersrand/National Institute for Communicable Disease, Johannesburg, South Africa
- Prof Ahmad Ali Enayati, Head, Medical Entomology Department, School of Public Health, Mazandaran University

of Medical Sciences, Sari, Islamic Republic of Iran
- Ms Mihirini Hewavitharane, Entomology Technical Manager, PMI VectorLink Project, Abt Associates, Phnom Penh, Cambodia
- Prof Fang Jing, Director, Institute for Health Sciences, Kunming Medical University, Yunnan Province, China
- Dr Keziah Malm, Programme manager, National Malaria Control Programme, Accra, Republic of the Ghana
- Dr Kui Muraya, Social scientist, KEMRI-Wellcome Trust, Nairobi, Kenya
- Prof Martha Quiñones, Professor, Universidad Nacional de Colombia, Bogotá, Colombia
- Dr Tanya Russell, Research fellow, James Cook University, Cairns, Australia
- Dr Lucy Tusting, Assistant professor, Faculty of Infectious Tropical Disease, LSHTM, London, United Kingdom of Great Britain and Northern Ireland
- Dr Charles Wondji, Liverpool School of Tropical Medicine, Liverpool, UK& Centre for Research in Infectious Diseases (CRID), Yaoundé, Cameroon
- Dr Josh Yukich, Associate professor, Department of Tropical Medicine Tulane University School of Public Health and Tropical Medicine, New Orleans, United States of America

Members of the Guidelines Steering Group (2021, 2022 & 2023)
- Dr Samira Al-Eryani, WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt
- Dr Haroldo Bezerra, WHO Regional Office for the Americas, Washington DC, United States of America
- Dr Maurice Bucagu, Family, Women, Children and Adolescents, World Health Organization, Geneva, Switzerland
- Dr Emmanual Chanda, WHO Regional Office for Africa, Brazzaville, Congo
- Dr Florence Fouque, Special Programme for Research and Training in Tropical Diseases, Geneva, Switzerland
- Dr Riffat Hossain, Programme for Health and Migration, World Health Organization, Geneva, Switzerland
- Dr Tessa Knox, WHO Country Office, Vanuatu
- Dr Jan Kolaczinski, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Mrs Marion Law, Prequalification Team for Vector Control, Departments of Essential Medicines of Health Products, World Health Organization, Geneva, Switzerland
- Dr Kim Lindblade, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Dr Katherine Littler, Department of Research for Health, World Health Organization, Geneva, Switzerland
- Dr Ramona Ludolph, Environment, Climate Change and Health, World Health Organization, Geneva, Switzerland
- Dr Edith Patouillard, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Dr Matt Shortus, WHO Country Office, Lao People's Democratic Republic
- Dr Jennifer Stevenson, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Dr Raman Velayudhan, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

Members of the External Review Group (ERG) (2021 & 2022)
- Dr Jenifer Armistead, Malaria Division, United States Agency for International Development (USAID), United States of America
- Prof Maureen Coetzee, University of the Witwatersrand, Africa
- Professor Umberto d'Alessandro, Director, Medical Research Council Unit, Gambia
- Dr Scott Filler, Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland
- Dr Caroline Jones, Senior Social Scientist, KEMRI Wellcome Trust Research Programme, Kenya
- Prof Neil Lobo, University of Notre Dame, United States of America
- Dr Melanie Renshaw, African Leaders Malaria Alliance

Systematic review team members (2021)
- Ms Kallista Chan Department of Disease Control, Faculty of Infectious Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland
- Mr Leslie Choi, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Ms Joanna Furnival-Adams, Department of Disease Control, Faculty of Infectious Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland; ISGlobal, Hospital Clinic – Universitat de Barcelona, Rosello 132, 08036, Kingdom of Spain
- Prof Paul Garner, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Ms Katherine Gleave, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr Jo Leonardi-Bee, University of Nottingham, United Kingdom of Great Britain and Northern Ireland
- Prof Jo Lines, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland
- Dr Elisa Martello, University of Nottingham, United Kingdom of Great Britain and Northern Ireland
- Dr Louisa Messenger, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland
- Dr Lucy Paintain, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland
- Ms Laura Paris, The MENTOR Initiative, Crawley, United Kingdom of Great Britain and Northern Ireland
- Ms Bethanie Pelloquin Department of Disease Control, Faculty of Infectious Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom of

Great Britain and Northern Ireland; School of Tropical Medicine and Global Health, University of Nagasaki, Nagasaki, Japan
- Prof Mark Rowland, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland
- Dr Rebecca Thomas, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr Gowsika Yogeswaran, University of Nottingham, United Kingdom of Great Britain and Northern Ireland

Systematic review team members (2022 & 2023)
- Dr Timothy Hugh Barker, JBI Adelaide GRADE Centre, Faculty of Health and Medical Sciences, The University of Adelaide, SA 5005, Australia
- Dr Jennifer C Stone, JBI Adelaide GRADE Centre, Faculty of Health and Medical Sciences, The University of Adelaide, SA 5005, Australia
- Ms Sabira Hasanoff, JBI Adelaide GRADE Centre, Faculty of Health and Medical Sciences, The University of Adelaide, SA 5005, Australia
- Ms Carrie Price, Albert S. Cook Library, Towson University, Towson, Maryland, United States of America
- Dr Alinune Kabaghe, Training and Research Unit of Excellence, Blantyre, Malawi
- Professor Zachary Munn, JBI Adelaide GRADE Centre, Faculty of Health and Medical Sciences, The University of Adelaide, SA 5005, Australia

Guidelines methodologist and co-chair (2021, 2022 & 2023)
Dr Elie Akl, American University of Beirut, Lebanon

Declaration of interests (2021)
Members of the GDG, the ERG, the methodologist and members of systematic review teams who were commissioned to undertake reviews by WHO were requested to declare any interests related to the topic of the meeting. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed.

One member of the GDG reported interests related to housing improvements for malaria and it was decided that she be recused from discussions on decision-making regarding housing modifications to prevent malaria.

The relevant declared interests for the GDG are summarized as follows:

Dr Lucy Tusting: declared receiving research funding exceeding £5000 within the last 4 years towards studies related to the impact of housing improvements on malaria from the UK Medical Research Council, a topic which was discussed at the GDG meeting. She declared being the principal investigator of this study and the project supports 100% of her income. This support continues to 2022. She also has some unpaid roles relating to housing and malaria, for which she receives travel expenses. She works with a project in the Republic of Uganda, funded by the NIH, analysing data exploring the relationship between housing and malaria. She is also the co-director of the BOVA network (Building Out Vector-Borne Diseases in Africa) from 2017 to date which is an interdisciplinary network focusing on preventing vector-borne diseases such as malaria, dengue and zika disease through improving the built environment. From 2017-2020 she was co-chair of the RBM VCWG's 'Vector-Borne Diseases and the Built Environment Workstream' (formerly 'Housing and Malaria'). She has led key reviews on housing type or improvement and the impact on malaria. The first was a systematic review of housing improvements for malaria control, published in Malaria Journal 2015: Tusting , L.S., Ippolito, M.M., Willey, B.A. *et al.* The evidence for improving housing to reduce malaria: a systematic review and meta-analysis. *Malar J* 14**,** 209 (2015). https://doi.org/10.1186/s12936-015-0724-1. The second and third were analyses of DHS data, studying the relationship between house type and malaria infection in children. Both were published in PLOS Med in 2017 and 2020: Tusting LS, Bottomley C, Gibson H, Kleinschmidt I, Tatem AJ, et al. (2017) Housing Improvements and Malaria Risk in Sub-Saharan Africa: A Multi-Country Analysis of Survey Data. PLOS Medicine 14(2): e1002234. https://doi.org/10.1371/journal.pmed.1002234; Tusting LS, Gething PW, Gibson HS, Greenwood B, Knudsen J, et al. (2020) Housing and child health in sub-Saharan Africa: A cross-sectional analysis. PLOS Medicine 17(3): e1003055. https://doi.org/10.1371/journal.pmed.100305. She was also a guest editor for a Malaria Journal thematic series on Housing and Malaria between 2015 and 2016.

Dr Tusting also was involved in studies and reviews related to larval source management as a vector control tool but all these date to 2015 or earlier and she has not received any support towards work on this topic since and so it was concluded that this did not constitute a conflict of interest.

It was determined that Dr Tusting could participate in all parts of the meeting except for decision-making with respect to recommendations related to housing improvements.

Five members of the External Review Group reported relevant interests; it was assessed that all members could fully participate as the remit of the Review Group was limited to identifying factual errors, providing clarity and commenting on implications for implementation not changing the recommendations formulated by the GDG. It was concluded that their expertise in some of these areas would be valuable, particularly on implementation considerations and factors to be considered associated with gender and social determinants, equity, and human rights.

The relevant declared interests for the ERG are summarized as follows:

Umberto D'Alessandro: reported receiving remuneration for the following activities which were topics of the meeting. He declared receiving research funding exceeding US$ 5000 in the last 4 years on three projects titled 'Can improved housing provide additional protection against clinical malaria over current best practice? A household-randomised controlled study. Supported by the Joint Global Health Trial Scheme (Medical Research Council (MRC), Welcome Trust (WT), Department for International Development (DfID)) and 'Will raised buildings reduce malaria

transmission in sub-Saharan Africa and keep buildings cool?' which is a collaboration with Durham University; and 'Towards the end game: operational research on improving rural housing in sub-Saharan Africa as a strategy to support malaria elimination' also a collaboration with Durham University.

Jennifer Armistead: reported the following projects that she had been involved in in the past 4 years, where funding exceeded £5000 and which concerned topics for discussion during the meeting**;** Monitoring the deployment of PBO synergist ITNs in Ebonyi State, Nigeria, estimating coverage, and impact, funded by PMI; Impact of housing modifications combined with piperonyl butoxide (PBO) long-lasting insecticidal nets (LLINs) on malaria burden in Uganda, a collaboration between CDC, London School of Hygiene & Tropical Medicine, UK and Infectious Disease Research Collaboration, Kampala, Uganda; Determining the feasibility and effectiveness of larviciding, funded by PMI collaboration with PATH.

Maureen Coetzee: reported acting as supervisor for a PhD project to investigate whether integrated spatial information tools could enable targeted urban planning interventions to control malaria and lymphatic filariasis in Dar es Salaam, United Republic of Tanzania. This was a collaboration with Ifakara Health Institute, United Republic of Tanzania; Swiss Tropical & Public Health Institute, Switzerland; Liverpool School of Tropical Medicine, UK. This project investigated housing characteristics that were associated with risk of mosquito biting but did not evaluate the impact of housing modifications on malaria

Caroline Jones: reported being a co-Investigator on a Wellcome Trust Collaborative Award: Improving the efficacy of malaria prevention in an insecticide resistant Africa which aimed to investigate the factors limiting the efficacy of current tools to prevent malaria, largely insecticide-treated nets, and to identify the most cost effective, complementary interventions that would drive malaria transmission towards zero. Although this project could consider interventions under discussion by the ERG, it did not seek to systematically evaluate a particular tool. She also reported being a co-investigator on a DfID/MRC/Wellcome Trust Joint Global Health Trials funded project: Can improved housing provide additional protection against clinical malaria over current best practice? A household-randomized controlled trial.

Neil Lobo: reported being a co-principal investigator on 'Screening mosquito entry points into houses with novel long lasting insecticidal netting to reduce indoor vector densities and mitigate pyrethroid resistance' in collaboration with Durham University.

No interests related to the topics of the meetings were disclosed by the methodologist or systematic review teams.

Declaration of interests (2022 & 2023)
Members of the GDG, the ERG, the methodologist and members of systematic review teams who were commissioned to undertake reviews by WHO were requested to declare any interests related to the topic of the meeting. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed.

The relevant declared interests for the GDG are summarized as follows:

Dr Lucy Tusting declared receiving remuneration for consulting services exceeding US$ 5000 for WHO that ended in October 2022. This agreement was for providing support and input into the development of the WHO Urban Malaria Framework. She also received research funding exceeding US$ 5000 for a Medical Research Council (UK) fellowship that will continue until November 2023. The fellowship is on the role of improved housing on malaria. She has also received a grant from the NovoNordisk Foundation that involves risk mapping of malaria and *Aedes*-borne diseases in Tanzania. The grant runs until 2026.

Charles Wondji declared receiving research support, including grants, collaborations, sponsorships, and other funding from the Innovative Vector Control Consortium (IVCC) exceeding US$ 5000. Ongoing studies aim to evaluate the entomological impact of more recently developed indoor residual spraying (IRS) products, dual active ingredient nets and pyrethroid-PBO nets against insecticide-resistant mosquitoes.

Dr Josh Yukich declared receiving salary support from his university through a project titled 'New Nets' to investigate the cost and cost effectiveness of dual active ingredient nets and pyrethroid- PBO nets. He also declared supervising students engaged in the analysis of the effectiveness of IRS and he has been engaged in similar analyses over the past several years whilst being employed by Tulane university. He is acting as a consultant for the University of California San Francisco to design and develop data collection tools for a cost effectiveness and willingness to pay study that involves topical repellents.

In summary, three members of the GDG declared potential interests. Based on the detailed assessment of the information provided to WHO it was decided that Dr Lucy Tusting could participate in all sessions, while Dr Josh Yukich was to be recused from the decision-making processes where the impact of dual active ingredient nets and topical repellents against malaria were be determined and from the sessions where recommendations were formulated. It was also concluded that Prof Wondji was to be recused from the decision-making processes where the impact of IRS and dual active ingredient nets against malaria were determined and from the sessions where recommendations are formulated.

The relevant declared interests for the ERG are summarized as follows:

Dr Umberto D'Alessandro reported receiving remuneration for being a member of the external scientific advisory board for Medicines for Malaria Venture until December 2018, travel support for a meeting in Geneva in Sept 2017 and Oct 2018, and a donation of dihydroartemisinin piperaquine treatments for malaria for a cluster randomized trial on mass drug administration from Guilin Pharma in 2018. He was also an investigator in a trial on the safety and efficacy of pyronaridine artesunate in asymptomatic malaria-infected individuals.

Jennifer Armistead reported being employed by the US President's Malaria Initiative, who in turn has supported a number of projects in the past 4 years for which funding exceeded US$ 5000 but for which she did not receive any personal funding. The projects focused on the effect of indoor residual spraying on *Anopheles* vector behaviours and their impact on malaria transmission in the northern region of Ghana, an evaluation of pirimiphos-methyl efficacy in experimental huts when sprayed on half the usual surface against natural populations of *Anopheles gambiae* in Ghana, a small-scale field pilot of Partial IRS with pirimiphos-methyl in households in northern Ghana for Malaria Vector Control and evaluating the impact of attractive targeted sugar baits (ATSBs) and indoor residual spraying (IRS) in experimental huts.

Caroline Jones reported receiving research support within the last 4 years that exceeded US$ 5000 for being a co-investigator on UNITAID funded project: Broad One Health Endectocide-based Malaria Intervention in Africa, for being a co-investigator on Wellcome Trust Collaborative Award: Improving the efficacy of malaria prevention in an insecticide resistant Africa, for being a co-investigator on DfID/MRC/Wellcome Trust Joint Global Health Trials funded project: Can improved housing provide additional protection against clinical malaria over current best practice? A household-randomized controlled trial and lastly for being a co-investigator on the Program for Appropriate Technology in Health (PATH) funded project: Dynamics of health care utilization strategies in the context of RTS,S/AS01vaccine introduction: a qualitative longitudinal study [in Kenya].

Neil Lobo reported receiving research funding exceeding US$ 5000 and/or non-monetary support valued at over US$ 1000 overall within the last 4 years towards a project investigating Spatial Repellent Products for Control of Vector-borne Diseases by SC Johnson, and a project on innovative intervention for reducing outdoor malaria transmission by Widder Bros.

Melanie Renshaw reported receiving salary support exceeding US$ 5000 from the African Leaders Malaria Alliance.

In summary, five members of the ERG reported interests; it was, however, judged that none of these were relevant to the recommendations under review and it was decided that all members could fully participate particularly as the remit of the review group was limited to identifying factual errors, providing clarity and commenting on implications for implementation not changing the recommendations formulated by the GDG. It was concluded that their expertise in some of these areas would be valuable, particularly on implementation considerations and factors to be considered associated with gender and social determinants, equity, and human rights.

No interests related to the topics of the meetings were disclosed by the methodologist or systematic review teams.

10.2 Recommendations for chemoprevention

The following outlines the constitution of the Guideline Development Group, Guideline Steering Group, and External Review Group for the chemoprevention recommendations listed below and published in 2022. Also indicated are the contributors to systematic reviews, summaries of contextual factors, AMSTAR-2 Checklist assessments and background papers, as well as the guidelines methodologist. Final compositions of these groups are shown as of the date of finalization of the Guidelines.

Recommendations

- Intermittent preventive treatment of malaria in pregnancy (4.2.1)
- Perennial malaria chemoprevention (4.2.2)
- Seasonal malaria chemoprevention (4.2.3)
- Intermittent preventive treatment of malaria in school-aged children (4.2.4)
- Post-discharge malaria chemoprevention (4.2.5)
- Mass drug administration for burden reduction (4.2.6.1)
- Mass drug administration for burden reduction in emergency settings (4.2.6.2)

Members of the Guideline Development Group (2022)

- Professor Salim Abdulla, Chief Scientist, Ifakara Health Institute, United Republic of Tanzania (Male – Expertise: Malaria research & policy-making)
- Dr Dorothy Achu, Manager, National Malaria Control Programme, Cameroon (Female – Expertise: Malaria control, end-user perspective, service-user, case management & chemoprevention)
- Professor Joseph Amon, Director, Office of Global, Dornsife School of Public Health, Drexel University, United States of America (Male – Expertise: Human rights, epidemiology)
- Dr Anup Anvikar, Scientist, ICMR-National Institute of Malaria Research, India (Male – Expertise: Malaria research, drug resistance/AMR, malaria prevention)
- Dr Matthew Coldiron (PDMC only), Medical Epidemiologist, Epicentre / Médecins Sans Frontières (MSF), United States of America/ France (Male – Expertise: Malaria control in emergency / fragile situations)
- The late Dr Martin De Smet, Senior Health Advisor, Médecins Sans Frontières (MSF), Belgium (Male – Expertise: Malaria control in emergency/fragile situations)
- Dr Corine Karema, Independent Consultant, African Leaders Malaria Alliance (ALMA), Rwanda (Female – Expertise: Malaria control)
- Professor Miriam Laufer, Director, Office of Student Research, University of Maryland School of Medicine, United States of America (Female – Expertise: Malaria drug resistance)
- Mrs Olivia Ngou, Executive Director, Impact Santé Afrique, Cameroon (Female – Expertise: Civil society)
- Professor Melissa Penny, Professor and Unit Head, Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland (Female – Expertise: Mathematical modelling for malaria)
- Dr Francisco Saute, Scientific Director, Manhiça Health

Research Center (CISM), Mozambique (Male – Expertise: Malaria control programming & research)
- The late Dr Samuel Smith, Manager, National Malaria Control Programme, Sierra Leone (Male – Expertise: Malaria control programming)
- Dr Allan Schapira, Visiting Consultant, Bicol University College of Medicine, Phillippines (Male – Expertise: Malaria control and research)
- Professor Robert Snow, Scientist, KEMRI-Wellcome Trust collaboration, Kenya (Male – Expertise: Malaria epidemiology & control)

Members of the Guideline Steering Group (2022)
- Sheick Oumar Coulibaly, Technical Officer, Diagnostic and Laboratory Services, World Health Organization Regional Office for Africa, Brazzaville, Congo
- Mary Hamel, Senior Technical Officer, Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland
- James Kelley, Technical Officer, Malaria and Neglected Tropical Diseases, World Health Organization Regional Office for the Western Pacific, Manila, Philippines
- Kim Lindblade, Team Lead, Elimination, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Özge Tuncalp Mingard, Scientist, Sexual and Reproductive Health and Research, World Health Organization, Geneva, Switzerland
- Laura Nic Lochlainn, Technical Officer, Immunizations, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland
- Sarah Marks, Consultant for the World Health Organization supporting the Responsible Technical Officer
- Abdisalan Noor, Team Leader, Information for Response, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Lynda Ozor, Malaria National Programme Officer, World Health Organization Country Office, Nigeria
- Charlotte Rasmussen, Technical Officer, Diagnostics, Medicines & Resistance, World Health Organization, Geneva, Switzerland
- Lisa Rogers, Technical Officer, Nutrition and Food Safety, World Health Organization, Geneva, Switzerland
- Anthony Solomon, Medical Officer, Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland
- David Schellenberg (Responsible Technical Officer), Science Advisor, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Jackson Sillah, Medical Officer, Tropical and Vector Borne Diseases, World Health Organization Regional Office for Africa, Brazzaville, Congo
- Neena Valecha, Regional Malaria Adviser, World Health Organization Regional Office for South-East Asia, New Delhi, India
- Wilson Were, Medical Officer, Child Health and Development, World Health Organization, Geneva, Switzerland

Members of the External Review Group (2022)
- Professor Umberto d'Alessandro, Director, Medical Research Council Unit, Gambia (Malaria Policy Advisory Group [MPAG] member)
- Mrs Valentina Buj de Lauwerier, Global Malaria and Health Partnerships Advisor, Health Section, Programme Division, UNICEF, New York, United States of America
- Professor Graham Brown, Professor Emeritus (MDA, PMC and SMC only), University of Melbourne, Australia
- Dr Caroline Jones, Senior Social Scientist, KEMRI-Wellcome Trust Research Programme, Kenya (MPAG member)
- Dr Estrella Lasry (MDA, PMC, IPTp, IPTsc, and PDMC only), Senior Disease Advisor Malaria, Technical Advice and Partnerships Department, Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland
- Dr Sussann Nasr (SMC only), Senior Malaria Advisor, Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland
- Dr Harriet Pasquale, HIV/AIDS and STI Program Director, National Ministry of Health, South Sudan
- Dr Richard Steketee, Deputy Coordinator, U.S. President's Malaria Initiative (PMI), United States of America

Contributors to systematic reviews, summaries of contextual factors and AMSTAR-2 Checklist assessments (2022)
Intermittent preventive treatment of malaria in pregnancy (IPTp)

- Jordan Ahn, Emory University, Atlanta, United States of America
- Dr Julie Gutman, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Eva Rodriguez, Emory University, Atlanta, United States of America
- Professor Feiko ter Kuile, Chair in Tropical Epidemiology, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr Anna Maria van Eijk, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland

Perennial Malaria Chemoprevention (PMC) (formerly Intermittent Preventive Treatment in infants or IPTi)

- Dr Christina Carlson, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Laura Steinhardt, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America

Seasonal malaria chemoprevention (SMC)

- Dr Achuyt Bhattarai, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Irene Cavros, Malaria Branch, Division of Parasitic Diseases

and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Julie Gutman, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Julie Thwing, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr John Williamson, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America

Intermittent preventive treatment of malaria in school-aged children (IPTsc)

- Dr Julie Gutman, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Rose Zulliger, President's Malaria Initiative, United States Agency for International Development, Washington DC, United States of America

Post-discharge malaria chemoprevention (PDMC)

- Dr Kalifa Bojang, Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine, Fajara, Gambia
- Dr Aggrey Dhabangi, Makerere University College of Health Sciences, Kampala, Uganda
- Professor Brian Greenwood, Faculty of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland
- Dr Julie Gutman, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Richard Idro, Makerere University College of Health Sciences, Kampala, Uganda
- Dr Chandy John, Ryan White Center for Pediatric Infectious Diseases and Global Health, School of Medicine, Indiana University, Indianapolis, United States of America
- Melf-Jakob Kühl, Centre for International Health (CIH) and Section for Ethics and Health Economics, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
- Siri Lange, Department of Health Promotion and Development, University of Bergen, Bergen, Norway
- Dr Amani Mori, Centre for International Health (CIH) and Section for Ethics and Health Economics, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
- Thandile Nkosi-Gondwe, College of Medicine, University of Malawi, Blantyre, Malawi
- Dr Robert Opoka, Makerere University College of Health Sciences, Kampala, Uganda
- Professir Kamija Phiri, School of Global and Public Health, Kamuzu University of Health Sciences (KUHeS), Blantyre, Malawi
- Carole Khairallah, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr Titus Kwambai, Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya
- Dr Bjarne Robberstad, Section for Ethics and Health Economics, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
- Dr Kasia Stepniewska, Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom of Great Britain and Northern Ireland
- Sarah Svege, Centre for International Health and Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
- Professor Feiko ter Kuile, Chair in Tropical Epidemiology, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr Julie Thwing, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America

MDA for burden reduction

- Marisa Boily, Rollins School of Public Health, Emory University, Atlanta, United States of America
- Alexandra Busbee, Rollins School of Public Health, Emory University, Atlanta, United States of America
- Dr Julie Gutman, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Jimee Hwang, U.S. President's Malaria Initiative, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Monica Shah, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Zachary Schneider, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America

MDA for burden reduction in emergency settings

- Dr Alaine Knipes, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Leah Moriarty, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Dean Sayre, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Monica Shah, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Nelli Westercamp, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America

Preparation of background papers (2022)

- Mr Emmanuel Bache-Bache, Centre for Tropical Medicine and Travel Medicine, Amsterdam UMC, University of Amsterdam, Netherlands (Kingdom of the)
- Professor Martin Grobusch, Head, Centre for Tropical Medicine and Travel Medicine, Amsterdam UMC, University of Amsterdam, Netherlands (Kingdom of the)
- Dr Jasper Littmann, Associate Professor, Bergen Centre for Ethics and Priority Setting, University of Bergen, Norway
- Dr Christopher Plowe, University of Maryland School of Medicine, Baltimore, United States of America

Guidelines methodologist (2022)

Dr Joseph Okebe, Senior Research Associate, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland

Declaration of interests (2022)

Members of the Guideline Development Group (GDG) were requested to declare any interests related to the topic of the meeting. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed.

The relevant declared interests for the GDG are summarized as follows:

Professor Salim Abdulla declared two chemoprevention research support grants his institute receives; he is involved in one of the studies as a technical advisor. The interests were assessed as related to the overall topic of discussion on malaria chemoprevention, with one interest directly related to the topic of PMC. One interest was considered non-personal in nature, academic and financially significant, and the other was considered personal in nature, academic and financially insignificant. Professor Abdulla was allowed to join the discussions as a full member of the GDG.

Professor Joseph Amon declared a research support grant a previous employer received to fund activities related to MDA/ chemoprevention for other diseases. This interest was not current and of a non-personal nature. He was allowed to join the discussions as a full member of the GDG.

The late Dr Martin De Smet declared his employment with an organization that is involved in the use of chemoprevention. This interest was of a non-personal nature and financially significant. He was allowed to join the discussions as a full member of the GDG.

Professor Miriam Laufer declared four research grants. The interests were assessed as related to the overall topic of discussion on malaria chemoprevention, with one interest directly related to the topic of IPT during pregnancy and another interest directly related to the topic of IPT in school children. The four interests were considered non-personal in nature, academic, and financially significant. Professor Laufer was also senior author for the systematic review on IPT in school children that was considered by the GDG, although she did not contribute empirical data to the review. The systematic review on IPT in school children was subjected to a third-party AMSTAR assessment and found to be of good quality. Professor Laufer was allowed to join all GDG discussions as a full member, but was a non-voting and non-chairing participant in discussions on IPT in school children.

Professor Melissa Penny declared financial research support received by her institute related to the overall topic of discussion on malaria chemoprevention, and grants that she held on the broader subject of malaria. These interests were assessed as financially significant, of a non-personal nature and academic. She was able to join the discussions as a full member of the GDG.

Dr Francisco Saute declared involvement in a relevant research project and that his employer is involved in related research studies on malaria. This interest was considered non-personal in nature, academic and financially significant. He was allowed to join the discussions as a full member of the GDG.

Dr Allan Schapira declared his role as Member of a Board of Trustees for an organization working on malaria. He did not receive any remuneration for this role. This interest was assessed as financially insignificant and of a personal nature. Dr Schapira's position on the Board of Trustees was not seen to interfere with the discussions on malaria chemoprevention. He was allowed to join the discussions as a full member of the GDG.

Professor Robert Snow declared his employment and funding for studies on various aspects of malaria but not specifically chemoprevention. This interest was considered non-personal in nature, academic and financially significant. He was allowed to join the discussions as a full member of the GDG.

10.3 Recommendation for malaria vaccines

The following outlines the constitution of the Malaria Policy Advisory Group (MPAG), Strategic Advisory Group of Experts on Immunization (SAGE), the SAGE/MPAG Working Group on Malaria Vaccines, and the External Review Group for the recommendations updated in 2023. Also indicated are members of the systematic review production and management team and GRADE analysis subgroup, as well as the guidelines methodologists. Final compositions of these groups are shown as of the date of finalization of the Guidelines.

Members of the Malaria Policy Advisory Group

- Professor Samira Abdelrahman, Professor of Community Medicine, Faculty of Medicine, University of Gezira, Sudan
- Professor Ahmed Adeel, Professor of Medical Parasitology, College of Medicine, King Saud University, Saudi Arabia
- Emeritus Professor Graham Brown, University of Melbourne, Australia
- Professor Thomas Burkot, Professor and Tropical Leader,

Australian Institute of Tropical Health and Medicine, James Cook University, Cairns, Australia
- Professor Umberto d'Alessandro, Professor of Epidemiology and Director, Medical Research Council Unit, The Gambia at the London School of Hygiene and Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Professor Abdoulaye Djimde, Head, Molecular Epidemiology and Drug Resistance Unit, Faculty of Medicine, University of Mali, Mali
- Professor Chris Drakeley, Department of Infection Biology, London School of Hygiene and Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Professor David Fidock, Director, Center for Malaria Therapeutics and Antimicrobial Resistance, Departments of Microbiology and Immunology and of Medicine (Infectious Diseases), Columbia University Medical Center, United States of America
- Professor Gao Qi, Senior Professor, Jiangsu Institute of Parasitic Diseases, Wuxi, China
- Professor Azra Ghani, Chair in Infectious Disease Epidemiology, Faculty of Medicine, School of Public Health, Imperial College London, United Kingdom of Great Britain and Northern Ireland
- Professor Caroline Jones, Senior Social Scientist, KEMRI-Wellcome Trust Research Programme, Kenya
- Professor S. Patrick Kachur, Columbia University Medical Center, Heilbrunn Department of Population and Family Health, Columbia University Mailman School of Public Health, United States of America
- Professor Evelyn Ansah, Director, Center for Malaria Research, University of Health and Allied Sciences, Ghana
- Dr Nilima Kshirsagar, Emeritus Scientist, Indian Council of Medical Research, India
- Dr Fedros Okumu, Public Health Researcher and Director of Science, Ifakara Health Institute, United Republic of Tanzania
- Dr Arantxa Roca Feltrer, Regional Malaria Director, MACEPA/PATH, Mozambique
- Professor Dyann Wirth, Director, Harvard Life Sciences, Harvard T.H. Chan School of Public Health, United States of America (MPAG Chair)

Members of the Strategic Advisory Group of Experts on Immunization

- Dr Rebecca Grais, Executive Director, Pasteur Network, France
- Dr Sonali Kochhar, Clinical Associate Professor, Department of Global Health, University of Washington, United States of America
- Dr Gabriel Leung, Executive Director, Hong Kong Jockey Club, China, Hong Kong SAR
- Professor Shabir Madhi, Professor of Vaccinology, University of the Witwatersrand, South Africa
- Professor Ziad Memish, Prince Mohammed Bin Abdulaziz Hospital, Ministry of Health, Professor at College of Medicine, Alfaisal University, Saudi Arabia
- Professor Peter McIntyre, Professor, Department of Women's and Children's Health, Dunedin School of Medicine, University of Otago, New Zealand
- Dr Ezzeddine Mohsni, Senior Technical Adviser, Global Health Development, The Eastern Mediterranean Public Health Network, Jordan
- Professor Kim Mulholland, Murdoch Children's Research Institute, University of Melbourne, Australia
- Professor Kathleen Neuzil, Director, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, United States of America
- Dr Hanna Nohynek, Chief Physician, Finnish Institute for Health and Welfare (Thl), Finland (SAGE Chair)
- Dr Folake Olayinka, United States Agency for International Development, Immunization Team Lead, United States of America
- Dr Saad Omer, Dean, Peter O'Donnell Jr. School of Public Health, UT Southwestern Medical Center, United States of America
- Professor Punnee Pitisuttithum, Head, Department of Clinical Tropical Medicine, Mahidol University, Thailand
- Professor Anthony Scott, Wellcome Trust Senior Research Fellow in Clinical Science, KEMRI-Wellcome Trust Research Programme, Kenya, and Professor of Vaccine Epidemiology, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Professor Cristiana Toscano, Professor of Epidemiology and Public Health, Federal University of Goiás, Brazil

Members of the SAGE/MPAG Working Group on Malaria Vaccines

- Professor Nick Andrews, Public Health England, United Kingdom of Great Britain and Northern Ireland
- Emeritus Professor Graham Brown, University of Melbourne, Australia
- Dr Dafrossa Cyrily Lyimo, Independent consultant (and former National Immunization and Vaccine Development Programme Manager), United Republic of Tanzania
- Dr Corine Karema, Independent consultant (and former Director of the Rwanda National Malaria Control Programme), Rwanda
- Dr Eusebio Macete, Centro de Investigação em Saúde de Manhiça, Mozambique (Co-Chair)
- Professor Kim Mulholland, Murdoch Children's Research Institute, Australia
- Professor Kathleen Neuzil, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, United States of America
- Professor Peter Smith, London School of Hygiene and Tropical Medicine, United Kingdom of Great Britain and Northern Ireland (Chair)
- Professor S. Patrick Kachur, Mailman School of Public Health, Columbia University, United States of America

Members of the SAGE Steering Group

- Dr Madhava Ram Balakrishnan, Medicines and Health

Products
- Dr Naor Bar-Zeev, Immunization, Vaccines and Biologicals
- Dr Paul Bloem, Immunization, Vaccines and Biologicals
- Ms Tracey Goodman, Expanded Programme on Immunization
- Dr Mary Hamel, Immunization, Vaccines and Biologicals
- Dr Joachim Hombach, Immunization, Vaccines and Biologicals
- Dr Melanie Marti, Immunization, Vaccines and Biologicals
- Dr Marie-Perre Preziosi, Immunization, Vaccines and Biologicals

Members of the R21 Safety Working Group

- Professor Kathleen Neuzil, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, United States of America (Chair, and SAGE/MPAG Working Group member)
- Professor Dure Samin Akram, Aga Kahn University Hospital, Pakistan (Vice-Chair, and WHO Global Advisory Committee on Vaccine Safety (GACVS) Vice-Chair)
- Dr Rita Helfand, United States Centers for Disease Control and Prevention, United States of America (GACVS Chair)
- Professor Blaise Genton, University of Lausanne, Switzerland (R21/Matrix-M Data and Safety Monitoring Board Chair)
- Professor Beckie N. Tagbo, University of Nigeria (WHO African Advisory Committee on Vaccine Safety Chair)
- Dr Eusebio Macete, Centro de Investigação em Saúde de Manhiça, Mozambique (SAGE/MPAG Working Group member)
- Professor Nick Andrews, Public Health England, United Kingdom of Great Britain and Northern Ireland (SAGE/MPAG Working Group member)
- Dr Nguyen Van Cuong, National Institute of Hygiene and Epidemiology, Viet Nam (GACVS member)
- Professor Kristine Macartney, National Centre for Immunisation Research and Surveillance, University of Sydney, Australia (GACVS member)
- Dr Afework Assefa Mitiku, International Public Health consultant, Ethiopia (GACVS member)

Members of the peer review group (External Review Group)

Members of the peer review group included the Strategic Advisory Group of Experts on Immunization, Malaria Policy Advisory Group, WHO Regional Offices, external subject matter experts, selected national immunization and malaria programme managers, other interested parties (who had not been involved in the process to that point) and industry. Request for peer review from industry is coordinated through the International Federation of Pharmaceutical Manufacturers and Associations and the Developing Countries Vaccine Manufacturers Network. The list of external reviewers is available upon request from the SAGE Secretariat.

Guidelines methodologists and systematic review team

Three methodologists from the Cochrane Response – Gemma Villanueva, Katrin Probyn and Nicholas Henschke – were commissioned to support the development of the malaria vaccine recommendations. They provided a systematic review of evidence, applied the PICO framework to conduct evidence assessments using GRADE, and supported the SAGE/MPAG Working Group in the transparent formulation of evidence-informed recommendations.

Designated writer/editor

Dr Laurence Slutsker drafted and consolidated a full evidence review for the SAGE/MPAG Working Group. WHO contracted Dr Slutsker under an Agreement for Performance of Work (APW).

Declarations of interest

All nine SAGE/MPAG Working Group members updated their Declarations of Interest in advance of the meeting. These were assessed by the WHO Secretariat. Six members reported interests; it was assessed that all members could fully participate. The full summary of interests for the SAGE/MPAG Working Group is available on the WHO Malaria Vaccine Implementation Programme website.

All 15 SAGE members participating in the meeting updated their Declarations of Interest in advance of the meeting. These were assessed by the WHO Secretariat. Eleven SAGE members reported interests and no members recused themselves from the discussion and decision-making during the malaria vaccine session. The full summary of interests for SAGE members is available on the meeting website.

All 19 MPAG members participating in the meeting updated their Declarations of Interest in advance of the meeting. These were assessed by the WHO Secretariat. Thirteen members reported interests and two members reported relevant interests. Two members (Professor Umberto d'Alessandro and Professor Azra Ghani) participated in the meeting under a partial exclusion and were excluded from participating in the decision-making process related to the development of guidelines or a recommendation. It was assessed that the remaining 17 members could fully participate in the meeting. The full summary of interests for MPAG members is available on the meeting website.

- Professor Umberto d'Alessandro, Professor of Epidemiology and Director, Medical Research Council Unit, The Gambia at the London School of Hygiene and Tropical Medicine, United Kingdom of Great Britain and Northern Ireland, declared the following:
  - Employment as a consultant in the development of the M5717 new antimalarial drug for Merck Healthcare KGaA (2022–ongoing). This interest was assessed as personal, non-specific and non-financially significant.
  - Research support as principal investigator in a clinical trial on the safety and efficacy of pyronaridine-artesunate (Pyramax) in asymptomatic malaria-infected individuals. The Medical Research Council Unit, The Gambia, received funding from Medicines for Malaria Venture for this work in 2018–2019. This interest was assessed as non-personal, non-specific and financially significant.

    - Serving as local principal investigator for an EDCTP-funded Phase 1b multi-stage P. falciparum malaria vaccine study to assess the safety and immunogenicity of the blood-stage vaccine candidate RH5.2 virus-like particle) in Matrix-M and the pre-erythrocytic stage vaccine candidate R21 in Matrix-M, both alone and in combination, in adults and infants in the Gambia. This interest was assessed as non-personal, specific and financially significant.
    - Conducting seasonal R21/Matrix-M mass vaccination for malaria elimination with Applied Global Health Research Medical Research Council, UK Research and Innovation. This interest was assessed as non-personal, specific and financially significant.

- Professor Azra Ghani, Infectious Diseases Epidemiology, Imperial College London, United Kingdom of Great Britain and Northern Ireland, declared the following:
    - Consulting – WHO Regional Office for Europe support related to coronavirus disease (COVID-19) vaccination introductions (current). This interest was assessed as personal, non-specific and non-financially significant.
    - Consulting – HSBC panel discussion on the COVID-19 pandemic (current). This interest was assessed as personal, non-specific and non-financially significant.
    - Consulting – Support to a COVID-19 steering group at GSK (2021–2022). This interest was assessed as personal, non-specific and non-financially significant.
    - Research support – Service contract to Imperial College London from the Global Fund for different projects related to modelling impact estimates for malaria, including global scenarios that incorporate RTS,S/AS01 from 2016 to 2019 and in 2021. This interest was assessed as non-personal, specific and financially significant.
    - Research support – Academic grant funding from multiple organizations for work on malaria and COVID-19 research, including Bill & Melinda Gates Foundation, PATH Malaria Vaccine Initiative, Medicines for Malaria Venture, Innovative Vector Control Consortium, Medical Research Council, Wellcome Trust, and National Institutes of Health over three years (current). This included data analysis and modelling of public health impact of routine implementation and assessment of seasonal implementation related to RTS,S/AS01; modelling to support subnational tailoring of malaria interventions; and modelling of elimination focusing on P. knowlesi. This interest was assessed as non-personal, specific and financially significant.
    - Charity trustee (non-monetary) – Malaria No More UK (current). This interest was assessed as personal, non-specific and non-financially significant.
    - Research support – Working with Oxford team in collaboration with the Jenner Institute to undertake public health impact modelling and cost-effectiveness analysis for R21/Matrix-M. This interest was assessed as personal, specific and non-financially significant.

10.4 Recommendations for treatment

Since the first and second editions of the Guidelines were issued in 2006 and 2010, respectively, WHO's methods for preparing guidelines have continued to evolve. The third edition of the *Guidelines for the treatment of malaria* was prepared in accordance with the updated WHO standard methods for guideline development *[1]*. This involved planning, “scoping” and needs assessment, establishment of a GDG, formulation of key questions (PICO questions: population, participants or patients; intervention or indicator; comparator or control; outcome), commissioning of reviews, Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and making recommendations. This method ensures a transparent link between the evidence and the recommendations. The GRADE system is a uniform, widely adopted approach based on explicit methods for formulating and evaluating the strength of recommendations for specific clinical questions on the basis of the robustness of the evidence.

The GDG, co-chaired by Professor Fred Binka and Professor Nick White (other participants are listed below), organized a technical consultation on preparation of the third edition of the Guidelines. Declarations of conflicts of interest were received from all participants. A WHO Guideline Steering Group facilitated the scoping meeting, which was convened in February 2013, to set priorities and identify which sections of the second edition of the Guidelines were to be reviewed and to define potential new recommendations. Draft PICO questions were formulated for collation and review of the evidence. A review of data on pharmacokinetics and pharmacodynamics was considered necessary to support dose recommendations, and a subgroup was formed for this purpose.

After the scoping meeting, the Cochrane Infectious Diseases Group at the Liverpool School of Tropical Medicine in Liverpool, United Kingdom, was commissioned to undertake systematic reviews and to assess the quality of the evidence for each priority question. The reviews involved extensive searches for published and unpublished reports of trials and highly sensitive searches of the Cochrane Infectious Diseases Group trials register, the Cochrane Central Register of Controlled Trials, MEDLINE®, Embase and LILACS. All the reviews have been published on line in the Cochrane Library. When insufficient evidence was available from randomized trials, published reviews of non-randomized studies were considered.

The subgroup on dose recommendations reviewed published studies from MEDLINE® and Embase on the pharmacokinetics and pharmacodynamics of antimalarial medicines. For analyses of pharmacokinetics and simulations of dosing, they used raw clinical and laboratory data from the Worldwide Antimalarial Resistance Network on the concentrations of antimalarial agents in plasma or whole blood measured with validated assays in individual patients. The data had either been included in peer-reviewed publications or been submitted to regulatory authorities

for drug registration. Population pharmacokinetics models were constructed, and the plasma or whole blood concentration profiles of antimalarial medicines were simulated (typically 1000 times) for different weight categories.

The GDG met in two technical meetings, in November 2013 and June 2014, to develop and finalize recommendations based on the GRADE tables constructed on the basis of answers to the PICO questions. The Guidelines were written by a subcommittee of the group. At various times during preparation of the Guidelines, sections of the document or recommendations were reviewed by external experts and users who were not members of the group; these external peer reviewers are listed below. Treatment recommendations were agreed by consensus, supported by systematic reviews and review of information on pharmacokinetics and pharmacodynamics. Areas of disagreement were discussed extensively to reach consensus; voting was not required.

Members of the GDG

- Professor K.I. Barnes, Division of Clinical Pharmacology, University of Cape Town, South Africa
- Professor F. Binka, (*co-Chair*), University of Health and Allied Sciences, Ho, Volta Region, Ghana
- Professor A. Bjorkman, Division of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden
- Professor M.A. Faiz, Dev Care Foundation, Dhaka, Bangladesh
- Professor O. Gaye, Service de Parasitologie, Faculté de Médicine, Université Cheikh Anta Diop, Dakar-Fann, Senegal
- Dr S. Lutalo, King Faisal Hospital, Kigali, Rwanda
- Dr E. Juma, Kenya Medical Research Institute, Centre for Clinical Research, Nairobi, Kenya
- Dr A. McCarthy, Tropical Medicine and International Health Clinic, Division of Infectious Diseases, Ottawa Hospital General Campus, Ottawa, Canada
- Professor O. Mokuolu, Department of Paediatrics, University of Ilorin Teaching Hospital, Ilorin, Nigeria
- Dr D. Sinclair, International Health Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Dr L. Slutsker, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America
- Dr E. Tjitra, National Institute of Health and Development, Ministry of Health, Jakarta, Indonesia
- Dr N. Valecha, National Institute of Malaria Research, New Delhi, India
- Professor N. White (*co-Chair*), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Members of the sub-group on dose recommendations

- Professor K. Barnes, *(co-Chair)*
- Professor F. Binka
- Dr S. Lutalo
- Dr E. Juma
- Professor O. Mokuolu
- Dr S. Parikh, Department of Medicine, Yale University School of Public Health, Connecticut, United States of America
- Dr D. Sinclair
- Dr J. Tarning, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
- Dr D.J. Terlouw, Malawi-Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi
- Professor N. White *(co-Chair)*

Guideline Steering Group

- Dr A. Bosman, Global Malaria Programme, WHO, Geneva, Switzerland
- Dr K. Carter, Malaria Regional Adviser, WHO Regional Office for the Americas, Washington D.C., United States of America
- Dr N.Dhingra-Kumar, Health Systems Policies and Workforce, WHO, Geneva, Switzerland
- Dr M. Gomes, Special Programme for Research and Training in Tropical Diseases, WHO, Geneva, Switzerland
- Dr P.E. Olumese (*Secretary*), Global Malaria Programme WHO, Geneva, Switzerland
- Dr F. Pagnoni, Special Programme for Research and Training in Tropical Diseases, WHO, Geneva, Switzerland
- Dr A.E.C. Rietveld, Global Malaria Programme WHO, Geneva, Switzerland
- Dr P. Ringwald, Global Malaria Programme WHO, Geneva, Switzerland
- Dr M. Warsame, Global Malaria Programme WHO, Geneva, Switzerland
- Dr W. Were, Child and Adolescent Health, WHO, Geneva, Switzerland

External reviewers

- Dr F. ter-Kuile, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr R. McGready, Shoklo Malaria Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
- Professor F. Nosten, Shoklo Malaria Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Guidelines methodologist

Professor P. Garner, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland

Declaration of interests

Participants in the technical consultation for the review of the *Guidelines for the treatment of malaria* and the external expert reviewers of the Guidelines reported relevant interests, in accordance with WHO procedures. These were discussed extensively by the committee. Although it was considered that none of the declared interests had direct relevance to the deliberations or recommendations of the meeting, the panel members with declared interests were excluded from the subcommittees on GRADE and recommendations and the drafting group. The declared interests, as per WHO regulations, were reviewed through the Legal Department of WHO.

Dr K. Barnes reported being a grants co-recipient from the Medicines for Malaria Venture to undertake clinical trials to evaluate antimalarial medicines.

Dr F. Binka reported being a member of the INDEPTH network

that was a recipient of a research grant from the Bill & Melinda Gates Foundation to conduct Phase IV post licensure studies on “Euratesim”.

Dr P. Garner reported receiving a grant from the Department for International Development (UK) to help ensure global guidelines and decisions are based on reliable evidence.

Dr N. Valecha reported serving as an investigator for a clinical trial supported by the Department of Science and Technology India, and Ranbaxy Laboratories Limited. There were no monetary benefits and no conflicts with the subject of this review.

Professor N. White reported being an advisor to all pharmaceutical companies developing new antimalarial medicines. This is done on a pro bono basis; it did not include consultancy fees or any form of remuneration.

Members of the GDG (2022)

- Dr Dorothy Achu, Programme Manager, National Malaria Control Programme, Yaoundé, Cameroon
- Professor Karen Barnes, Clinical Pharmacology, University of Cape Town, South Africa
- Dr Constance Bart-Plange, Independent Malaria Consultant, Accra, Ghana
- Professor Adrianus Dondorp, Deputy Director, Mahidol Oxford Tropical Medicine Research Unit, Mahidol University, Thailand
- Professor Sanjeev Krishna, (Co-chair) Molecular Parasitology and Medicine, St George’s University London, United Kingdom of Great Britain and Northern Ireland
- Professor Marcus Lacerda, Infectious Disease Researcher, Tropical Medicine Foundation
- Dr Miriam Laufer, Director, Office of Student Research, University of Maryland School of Medicine, United States of America
- Professor Rose Leke, Professor, Immunology and Parasitology, Faculty of Medicine and Biomedical Sciences, University of Yaoundé, Cameroon
- Professor Olugbenga Mokuolu, (Co-chair) Professor, Paediatrics & Child Health, Department of Paediatrics, College of Health Sciences, University of Ilorin, Nigeria
- Professor Bernhards Ogutu, Senior Principal Clinical Research Scientist, Kenya Medical Research Institute, Kenya
- Professor Stephen Rogerson, Professor, Department of Infectious Diseases, Doherty Institute, University of Melbourne, Australia
- Professor Philip Rosenthal, Professor, Department of Medicine, University of California, United States of America
- Professor Terrie Taylor, Professor, Department of Osteopathic Medical Specialties, College of Osteopathic Medicine, Michigan State University, United States of America

Members of the Guidelines Steering Group (2022)

- Andrea Bosman, Coordinator, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Maurice Bucagu, Family, Women, Children and Adolescents, World Health Organization, Geneva, Switzerland
- Maria Bustos, Technical Officer, Malaria Control, WHO Country Office, Thailand
- Jane Cunningham, Technical Officer, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Bayo Fatunmbi, Technical Officer, Malaria, WHO Country Office, Uganda
- Elizabeth Juma, WHO Country Office, Ghana
- Roberto Montoya, Regional Malaria Adviser, WHO Regional Office for the Americas, United States of America
- Deus Mubangizi, Coordinator, Prequalification Regulation and Prequalification, Access to Medicines and Health Products, World Health Organization, Geneva, Switzerland
- Peter Olumese, (Secretary) Medical Officer, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Shanthi Pal, Technical Officer, Pharmacovigilance, Regulation and Safety/ Regulation and Prequalification, World Health Organization, Geneva, Switzerland
- Pascal Ringwald, Medical Officer, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Neena Valecha, Regional Malaria Adviser, WHO Regional Office for South-East Asia, India
- Wilson Were, Medical Officer, Child Health and Development HQ/UHL/MCA/CHD, Maternal, Newborn, Child and Adolescent Health and Ageing, World Health Organization, Geneva, Switzerland
- Ghasem Zamani, Regional Malaria Adviser, WHO Regional Office for the Eastern Mediterranean, Egypt

Members of the External Review Group (ERG) (2022)

- Professor Ahmed Adeel, Independent Consultant, United States of America
- Professor Umberto d’Alessandro, Director, Medical Research Council Unit, Gambia

Members of the Systematic Review Team members (2022)

- Stephanie Dellicour, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Martha Chaplin, Liverpool School of Tropical Medicine, Centre for Evidence Synthesis, United Kingdom of Great Britain and Northern Ireland
- Paul Garner, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Centre for Evidence Synthesis, United Kingdom of Great Britain and Northern Ireland
- Patricia Graves, College of Public Health Medical & Vet Sciences, Australian Institute of Tropical Health and Medicine, Australia
- Jenny Hill, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Paul Hine, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Feiko ter Kuile, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Makoto Saito, WorldWide Antimalarial Resistance Network,

Institute of Medical Science, University of Tokyo, Japan
- Kasia Stepniewska, WorldWide Antimalarial Resistance Network, Infectious Disease Data Observatory, Oxford, United Kingdom of Great Britain and Northern Ireland
- Melissa Taylor, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Rebecca Thomas, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland

Guidelines methodologist and co-chair (2022)
Leonila Dans, Independent Methodologist and World Health Organization consultant, Philippines

Declarations of interest (2022)
Members of the GDG, the ERG, the methodologist and members of systematic review teams who were commissioned to undertake reviews by WHO were requested to declare any interests related to the topic of the meeting. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed. Below is a summary of the declared interests of members.

Professor Karen Barnes declared that she is currently serving as staff with Oxford University in the WorldWide Antimalarial Resistance Network, Infectious Disease Data Observatory, receiving around US$ 3000 per month, and her institution University of Cape Town is currently running projects on antimalarial pharmacology translational research with funding from Bill & Melinda Gates Foundation and the South African Ministry of Health of around US$ 450 000. She is not a direct beneficiary of this funding. Although the funding was for studies with antimalarial medicines, , it is not related to the subject of this Guideline. It was judged that none of these research projects or appointments had any direct relationship to the agenda of this meeting. These declarations were assessed as non-personal and non-specific, and of no direct or indirect personal or financial benefit; therefore, they were considered non-significant

Professor Arjen Dondrop declared that, starting in February 2021, he has chaired the Malaria Advisory Council of Novartis, but he does not receive remuneration for this consultancy. In 2014, his research group received a grant from Guilin Pharma (now Fosun) to study intravenous artesunate. His group is currently investigating the efficacy and safety of triple ACTs for uncomplicated falciparum malaria in the context of increasing antimalarial drug resistance. One of the triple ACTs, artemether-lumefantrine-amodiaquine, is provided for free by Fosun Pharma. These declarations were assessed as not directly related to any of the medicines being discussed by this GDG. These declarations were assessed as non-personal and non-specific, and of no direct or indirect personal or financial benefit; therefore, they were considered non-significant.

Professor Lacerda declared institutional grants from Medicines for Malaria Venture and Bill & Melinda Gates Foundation to study the operational feasibility of appropriate *P. vivax* radical cure with tafenoquine or primaquine. These interests were assessed as being of no direct or indirect personal or financial benefit; therefore, they were considered non-significant.

Professor Terrie Taylor declared serving on two advisory boards of Novartis AG and receiving US$ 3125 in 2019; her University and research group has received several rounds of research funding from the United States National Institutes of Health. None of these were directly related to the considerations of the GDG, and it was determined that she could join the discussions of the group. These interests were assessed as non-personal and non-specific.

Recommendations on qualitative near-patients G6PD tests (2024) and semi-quantitative near-patients G6PD tests (2024)
The following outlines the constitution of the Guidelines Development Group, Guidelines Steering Group, and External Review Group for the recommendations published in 2024. Also indicated are members of the systematic review production and management team as well as the guidelines methodologist. Final compositions of these groups are shown as of the date of finalization of the Guidelines.

Members of the GDG (2023–2024)

- Dr Anupkumar Anvikar, Director, National Institute of Medical Research, India
- Pr Angela Devine, Menzies School of Public Health, Australia
- Professor Adrianus Dondorp, Deputy Director, Mahidol Oxford Tropical Medicine Research Unit, Mahidol University, Thailand
- Professor Thomas Douglas, Faculty of Philosophy, University of Oxford, United Kingdom of Great Britain and Northern Ireland
- Dr Kebede Etana, National Malaria Program, Federal Ministry of Health, Ethiopia
- Professor Michelle Gatton, School of Public Health and Social Work, Queenslands University of Technology, Australia
- Dr Rosalind Howes, Senior Scientist, FIND, Switzerland
- Professor Weiiying Jiang, Zhongshan Medicine School, Sun Yat-sen University, China
- Dr Mikashmi Kohli, Senior manager, FIND, Switzerland
- Dr Manisha Madkaikar, Director ICMR-Center for Research, Management and Care of Hemoglobinopathies, India
- Dr Cássio Roberto Leonel Peterka, Director Immunization and Communicable Diseases, Ministry of Health, Brazil
- Professor Ric Price, Menzies School of Health Research and Charles Darwin University, Australia
- Dr Ari Satyagraha, Senior Researcher, Eijkman Research Center for Molecular Biology, Indonesia
- Dr Yemisi TakwoingI, Deputy Director, College of Medical and Dental Sciences, University of Birmingham, United Kingdom of Great Britain and Northern Ireland

Members of the Guidelines Steering Group (2023–2024)

- Maria de la Paz Ade Torrent, Advisor, Department of Communicable Diseases Prevention, Control and Elimination, Washington, PAHO, Washington, United States of America

- Céine Barnadas, Public Health Laboratory Strengthening, Country Readiness Strengthening
- Andrea Bosman (Secretariat), Head Unit, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Anderson Chinorumba, WHO consultant, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Jane Cunningham, Emergency Pandemic Preparedness and Prevention,WHO, Geneva, Switzerland
- James Kellley, Technical Officer, Malaria and Neglected Tropical Diseases, WPRO, Manila, Philippines
- Daniel Ngamijie, Director, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Risintha Premaratne, Regional Malaria Adviser, SEARO, New Dehli, India
- Peter Olumese, Medical Officer, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Anne-Laure Page, Technical Officer, IVD Prequalification. World Health Organization, Geneva, Switzerland
- Silvia Schwarte, Technical Officer, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Jackson Sillah, Medical Officer, Tropical and Vector-borne Diseases, AFRO, Brazzaville, Congo
- Ghasem Zamani, Regional Malaria Adviser, WHO Regional Office for the Eastern Mediterranean, Egypt

Members of the External Review Group (ERG) (2023–2024)

- Dr Dionicia Gamboa, Universidad Peruana Cayetano Heredia, Lima, Peru
- Dr Sandra Incardona, Medical Care Development (MCD) Global Health, France
- Professor Marcus Lacerda, Infectious Disease Researcher, Tropical Medicine Foundation
- Professor Lucio Luzzatto, University of Florence, Italy
- Professor Ivo Mueller, The Walter and Eliza Hall Institute of Medical Research, Melbourne Australia
- Dr Neena Valecha, Independent consultant, former WHO SEARO malaria adviser, New Dehli, India

Members of the Systematic Review Team members (2023–2024)

For the systemic evidence review:

- Dr Praveen Weeratunga, Department of Clinical Medicine, University of Columbo, Sri Lanka
- Dr Germana Bancone, Research Scientist, Shoklo Malaria Research Unit (SMRU), Thailand

For the review of contextual factors:

- Dr Timothy Barker, School of Public Health, University of Adelaide, Australia
- Dr Zachary Munn, School of Public Health, University of Adelaide, Australia

Guidelines methodologist and co-chair (2023-2024)

- Dr Mariska M. Leeflang, Amsterdam University Medical Centers, Amsterdam, Kingdom of the Netherlands

Declarations of interest (2023-2024)

Members of the GDG, the ERG, the methodologist and members of systematic review teams who were commissioned to undertake reviews by WHO were requested to declare any interests related to the topic of the meeting. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed. Below is a summary of the declared interests of members.

Dr Devine declared receiving from Alere, Inc AU$ 2200 to participate on a panel discussion on the occasion of World Malaria Day 2023. This declaration was assessed as personal, financially non-significant and non-specific to the subject of the meeting and, on this basis, considered as non-significant.

Professor Douglas declared receiving from Merk KGaA, Darmstadt approx. £22,000 per year as member of Ethics Advisory Panel of a pharm/biotech company which is developing a new antimalarial medicine. These declarations were assessed as personal, financially significant and non-specific to the subject of the meeting and, on this basis, considered as non-significant.

Two members of the Guidelines Development Group, Dr R. Howes and Dr Mikashmi Kohli were FIND staff, invited in their personal capacity as experts on diagnostics for G6PD, G6PD epidemiology and gender and G6PD. FIND is not investing in the development of G6PD at the time of planning and completion of the GDG work, but in generating evidence to facilitate the implementation of G6PD testing at the point-of-care. On this basis individual who work for FIND were not considered to have a conflict of interest.

Dr Howes declared participation in facilitating a donation of SD Biosensor tests (worth US$ 12,900) to FIND collaborating laboratories which were owning the Analyser. This declaration was assessed as non-personal, financially significant and non-specific to the subject of the meeting and, on this basis, considered as non-significant.

Professor Price declared receiving a grant from BMGF of near US$ I,5 million for research on hemolytic risks after primaquine treatment in G6PD intermediate patients. Professor Price also declared receiving a grant from UNITAID of US$ 5 million to conduct a feasibility study on SD Biosensor (G6PD test) in Indonesia. These declarations were assessed as personal, financially significant and specific to the subject of the meeting. As these conflicts are considered significant, Professor Price did not participate to sessions of the meeting in which the WHO guidelines recommendations were generated.

Dr Satyagraha declared receiving a grant from Menzies School of Health Research of AU$ 10,000 to train as consultant lab technicians on the use of SD Biosensor test for the SCOPE study. Dr Satyagraha also declared receiving a grant from ASEAN of AU$ 50,000 to conduct a field to evaluate a G6PD RDT from Humasis (Republic of Korea). These declarations were assessed as personal, financially significant and specific to the subject of the meeting. As these conflicts are considered significant, Dr Satyagraha did not participate to the entire sessions of the meeting in which the WHO guidelines recommendations were generated.

Recommendations on tafenoquine as anti-relapse treatment of P. vivax (2024) and primaquine as anti-relapse treatment of *P. vivax* and *P. ovale* (2024)

The following outlines the constitution of the Guidelines Development Group, Guidelines Steering Group, and External Review Group for these recommendations, published in 2024. Also indicated are members of the systematic review production and management team as well as the guidelines methodologist. Final compositions of these groups are shown as of the date of finalization of the Guidelines.

Members of the GDG (2023–2024)

- Professor Karen Barnes, Professor of Clinical Pharmacology, University of Cape Town, South Africa
- Professor Adrianus Dondorp, Deputy Director, Mahidol Oxford Tropical Medicine Research Unit, Mahidol University, Thailand
- Dr Anitta Kamara, National malaria control programme, Ministry of Health, Sierra Leone
- Professor Marcus Lacerda, Infectious Disease Researcher, Tropical Medicine Foundation
- Dr Miriam Laufer, Director, Office of Student Research, University of Maryland School of Medicine, United States of America
- Dr Christine Manyando, Tropical Disease Research Centre, Ndola, Zambia
- Professor Olugbenga Mokuolu, (Co-chair) Professor, Paediatrics & Child Health, Department of Paediatrics, College of Health Sciences, University of Ilorin, Nigeria
- Dr Jeanne Rini Poespoprodjo, Pediatrician, The District Hospital, Timia, Papua, Indonesia
- Professor Bernhards Ogutu, Senior Principal Clinical Research Scientist, Kenya Medical Research Institute, Kenya
- Professor Stephen Rogerson, Professor, Department of Infectious Diseases, Doherty Institute, University of Melbourne, Australia
- Professor Philip Rosenthal, Professor, Department of Medicine, University of California, United States of America
- Professor Terrie Taylor, Professor, Department of Osteopathic Medical Specialties, College of Osteopathic Medicine, Michigan State University, United States of America
- Professor Nick White, Faculty of Tropical Medicine, Faculty of Tropical Medicine, University of Oxford, United Kingdom of Great Britain and Northern Ireland

Members of the Guidelines Steering Group (2023–2024)

- Dorothy Achu, Team Lead, Tropical and Vector Borne Diseases, UCN, WHO Africa Regional Office, Brazzaville, Congo
- Andrea Bosman, Coordinator, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Maurice Bucagu, Family, Women, Children and Adolescents, World Health Organization, Geneva, Switzerland
- Maria Bustos, Technical Officer, Malaria Control, WHO Country Office, Thailand
- Jane Cunningham, Technical Officer, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Roberto Montoya, Regional Malaria Adviser, WHO Regional Office for the Americas, United States of America
- Deus Mubangizi, Coordinator, Prequalification Regulation and Prequalification, Access to Medicines and Health Products, World Health Organization, Geneva, Switzerland
- Peter Olumese, (Secretary) Medical Officer, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Shanthi Pal, Technical Officer, Pharmacovigilance, Regulation and Safety/ Regulation and Prequalification, World Health Organization, Geneva, Switzerland
- Risintha Premaratne, Regional Malaria Adviser, WHO Regional Office for the Southeast Asia, India
- Wilson Were, Medical Officer, Child Health and Development HQ/UHL/MCA/CHD, Maternal, Newborn, Child and Adolescent Health and Ageing, World Health Organization, Geneva, Switzerland
- Ghasem Zamani, Regional Malaria Adviser, WHO Regional Office for the Eastern Mediterranean, Egypt

Members of the External Review Group (ERG) (2023–2024)

- Dr Emiliana Tijtra, National Institute of Health Research and Development, Ministry of Health, Jakarta, Indonesia
- Professor Ahmed Adeel, College of Medicine, King Saud University, Saudi Arabia
- Professor Kamini Mendis, Independent expert on malaria epidemiology and chemotherapy

Members of the Systematic Review Team members (2023–2024)

- Dr Kerry Dwan, Centre for Evidence Synthesis, The Cochrane Infectious Disease Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Tilly Fox, Review Synthesis Delivery Specialist, The Cochrane Infectious Disease Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr Robert Commons, Menzies School of Health Research, Charles Darwin University, Australia

Guidelines methodologist and co-chair (2023–2024)

Leonila Dans, Independent Methodologist and World Health Organization consultant, Philippines

Declarations of interest (2023)

Members of the GDG, the ERG, the methodologist and members of systematic review teams who were commissioned to undertake reviews by WHO were requested to declare any interests related to the topic of the meeting. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed. Below is a summary of the declared interests of members.

Professor Karen Barnes declared that she is currently serving as a staff with Oxford University on the WWARN/IDDO receiving approx. US$ 3000 per month and her institution UTC is currently running projects on antimalarial pharmacology translational research with funding from BMGF and South African Ministry of Health to the tune of approx. US$ 381,341. She is not a direct beneficiary of these funding. She also currently serves on the EDTCP antimalarial drug development portfolio oversight committee and has received an honorarium of approx.. € 2,025.00. Though related to malaria chemotherapy, it is not related to the subject of this Guidelines. It is adjudged that none of these research or appointment have any direct relationship to the agenda of this meeting. These declarations were assessed as non-personal and non-specific of no direct or indirect personal nor financially benefits, thus considered as non-significant

Professor Arjen Dondrop declared that starting Feb 2021, he chaired the Malaria Advisory Council of Novartis, for which he did not receive remuneration. His group is currently investigating the efficacy and safety of Triple ACTs for uncomplicated falciparum malaria in the context of increasing antimalarial drug resistance. One of the Triple ACTs, artemether-lumefantrine-amodiaquine, is provided free of cost by Fosun Pharma. These declarations are assessed as not directly related to agenda of this meeting. These declarations were assessed as non-personal and non-specific of no direct or indirect personal nor financially benefits, thus considered as non-significant.

Professor Marcus Lacerda declared institutional grants from MMV and BMGF to study the operational feasibility of appropriate P. vivax radical cure with tafenoquine or primaquine. These interests were assessed as personal, financially significant and specific to the contents of the meeting. On this basis, Professor Lacerda was excluded from the sessions of the GDG dedicated to the development of the recommendations.

Professor Mokuolu declared serving in an advisory capacity to a single meeting of a Novartis meeting in 2019. This declaration was assessed as personal, financially significant and non-specific to the subject of the meeting, and, on this basis, considered as non-significant.

Professor Terrie Taylor declared serving on two advisory boards of Novartis AG and received US$ 5000 in 2022. Her university and research group has received several research funding from the US National Institutes of Health. It is adjudged that none of these research or appointments have any direct relationship to the agenda of this meeting. These declarations were assessed as non-specific of no direct or indirect personal nor financially benefits, thus considered as non-significant.

All other members of the GDG and External Review Group declared no conflict of interest.

10.5 Recommendations for interventions in the final phase of elimination and prevention of re-establishment

The following outlines the constitution of the Guidelines Development Group, Guidelines Steering Group, and External Review Group for the recommendations listed below, published in 2022. Also indicated are members of the systematic review production and management team as well as the guidelines methodologist. Final compositions of these groups are shown as of the date of finalization of the Guidelines.

Recommendations

- Mass drug administration for reduction of transmission of *P. falciparum* in very low to low transmission settings (4.2.6.3)
- Mass drug administration for reduction of transmission of *P. falciparum* in moderate to high transmission settings (4.2.6.4)
- Mass drug administration for reduction of transmission of *P. vivax* (4.2.6.5)
- Mass relapse prevention to reduce transmission of *P. vivax* (4.2.6.6)
- Mass testing and treatment (6.1.1)
- Targeted drug administration (6.2.1)
- Targeted testing and treatment (6.2.2)
- Targeted testing and treatment at points of entry (6.2.3)
- Reactive drug administration (6.3.1)
- Reactive case detection and treatment (6.3.2)
- Reactive indoor residual spraying (6.3.3)

Members of the Guidelines Development Group (2022)

- Dr Jane Achan, Senior Research Advisor, Malaria Consortium, United Kingdom of Great Britain and Northern Ireland (Female – Expertise: Malaria control and case management)
- Dr Mohammed Alzahrani, General Director of Vector-borne & Zoonotic Diseases Department, Public Health Agency, Ministry of Health, Saudi Arabia (Male – Expertise: Malaria elimination programme management)
- Dr Kevin Baird, Director, Eijkman Oxford Clinical Research Unit, University of Oxford, Indonesia (Male – Expertise: Malaria elimination and *P. vivax*)
- Professor Teun Bousema, Radboud University Medical Center, The Netherlands (Male – Expertise: Malaria transmission)

- Dr Marcus Lacerda, Tropical Medicine Foundation Dr Heitor Vieira Dourado, Manaus, Brazil (Male – Expertise: *P. vivax*)
- Associate Professor Dionicia Gamboa, Institute of Tropical Medicine, Alexander von Humboldt, Cayetano Heredia University, Peru (Female – Expertise: Malaria transmission)
- Professor Kevin Marsh (Co-chair), Kenya Academy of Sciences, Kenya (Male – Expertise: Clinical malaria epidemiology)
- Dr Kamini Mendis, Independent Consultant, Sri Lanka (Female – Expertise : Malaria elimination)
- Professor Melissa Penny, Professor and Unit Head, Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland (Female - Expertise: Mathematical modelling for malaria)
- Dr Allan Schapira, Visiting Consultant, Bicol University College of Medicine, Philippines (Male - Expertise: Malaria control and research)
- Dr Siv Sovannaroth, Manager, National Malaria Programme, Cambodia (Male – Expertise : Malaria elimination programme management)
- Dr Chansuda Wongsrichanalai, Consultant, Thailand (Female – Expertise: *P. vivax*)

Members of the Guidelines Steering Group (2022)

- Dr Ebenezer Sheshi Baba, Medical Officer, Tropical and Vector Borne Diseases, WHO Regional Office for Africa, Brazzaville, Congo
- Dr Maurice Bucagu, Medical Officer, Maternal Health, World Health Organization, Geneva, Switzerland
- Dr Jane Cunningham, Technical Officer, Diagnostics, Medicines & Resistance, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Dr Blanca Escribano Ferrer, Medical Officer, Malaria and Neglected Tropical Diseases, WHO Regional Office for the Americas, Washington, DC, United States of America
- Dr Shirin Heidari, Consultant, Gender, Equity and Human Rights, World Health Organization, Geneva, Switzerland
- Kanokporn Kaojaroen, Technical Officer, Health and Migration Programme, World Health Organization, Geneva, Switzerland
- Dr Mika Kawano, Technical Officer, Border Health Risk Dissemination, World Health Organization, Geneva, Switzerland
- Dr James Kelley, Technical Officer, Malaria and Neglected Tropical Diseases, WHO Regional Office for the Western Pacific, Manila, Philippines
- Dr Jan Kolaczinski, Head, Vector Control and Insecticide Resistance Unit, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Dr Kim Lindblade (Responsible Technical Officer), Head, Elimination Unit, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Dr Abdisalan Noor, Head, Information for Response Unit, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Dr Peter Olumese, Medical Officer, Diagnostics, Medicines & Resistance, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Dr Risintha Premaratne, Technical Officer, Malaria Control, WHO Regional Office for South-East Asia, New Delhi, India
- Charlotte Rasmussen, Technical Officer, Diagnostics, Medicines & Resistance, World Health Organization, Geneva, Switzerland
- Dr Pascal Ringwald, Coordinator, Office of the Director, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Dr Anthony Solomon, Medical Officer, Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland
- Dr Ghasem Zamani, Regional Adviser, Malaria and Vector Control, WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt

Members of the External Review Group (2022)

- Dr Gao Qi, Chair of National Malaria Expert Group, Wuxi, China (MPAG member)
- Dr Azra Ghani, Professor, Imperial College, London, United Kingdom of Great Britain and Northern Ireland (MPAG member)
- Dr Jimee Hwang, U.S. President's Malaria Initiative, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Jenarun Jelip, Ministry of Health, Kuala Lumpur, Malaysia
- Dr Roopal Patel, Senior Disease Advisor, Malaria, the Global Fund to Fight AIDS, Tuberculosis and Malaria; Geneva, Switzerland
- Dr Frank Richards, Senior Advisor, Onchocerciasis, Lymphatic Filariasis, Schistosomiasis and Malaria, The Carter Center (Chair of the Malaria Elimination Oversight Committee)
- Dr Francisco Saúte, Director General, Centro de Investigação,em Saúde de Manhiça, Manhiça, Mozambique
- Dr Stephen Vreden, Vice-Chair, National Malaria Elimination Taskforce, Paramaribo, Suriname

Systematic review team members (2022)

- Dr Koya Allen, MESA, Barcelona Institute for Global Health (ISGlobal), University of Barcelona, Spain
- Taiwo Samson Awolola, Entomology Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Beena Bhamani, MESA, ISGlobal, University of Barcelona, Spain
- Dr Achuyt Bhattarai, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
  Marisa Boily, Rollins School of Public Health, Emory University, Atlanta, United States of America
- Alexandra Busbee, Rollins School of Public Health, Emory University, Atlanta, United States of America
- Dr Julie Gutman, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr John Gimnig, Entomology Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Jimee Hwang, U.S. President's Malaria Initiative, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers

for Disease Control and Prevention, Atlanta, United States of America
- Dr Daniel Impoinvil, Entomology Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Amy Large, Rollins School of Public Health, Emory University, Atlanta, United States of America
- Dr Kim Lindblade, Head, Elimination Unit, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Leah Loerinc, School of Medicine, Emory University, Atlanta, GA, United States of America
- Elisabet Martí Coma-Cros, ISGlobal, University of Barcelona, Spain
  Vita Mithi, ISGlobal, University of Barcelona, Spain
- Elizabeth Quincer, School of Medicine, Emory University, Atlanta, GA, United States of America
- Dr Regina Rabinovich, Malaria Elimination Initiative, ISGlobal, University of Barcelona, Spain
- Dr Zachary Schneider, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Elisa Serra, MESA, ISGlobal, University of Barcelona, Spain
- Dr Monica Shah, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Laura Steinhardt, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Amanda Tiffany, Elimination Unit, Global Malaria Programme, World Health Organization, Geneva, Switzserland
- Maria Tusell, ISGlobal, University of Barcelona, Spain
- Dr Nelli Westercamp, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Kate Whitfield, MESA, ISGlobal, University of Barcelona, Spain
- Sarah Zohdy, Entomology Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America

WHO Secretariat (2022)
- Dr Kim Lindblade, Head, Elimination Unit, Global Malaria Programme
- Dr Amanda Tiffany, Epidemiologist, Elimination Unit, Global Malaria Programme
- Dr Li Xiao Hong, Technical Officer, Elimination Unit, Global Malaria Programme
- Selome Tadesse, Assistant, Elimination Unit, Global Malaria Programme
- Laurent Bergeron, Project Officer, Elimination Unit, Global Malaria Programme

Preparation of background papers (2022)
- Dr Gillian Stresman, Assistant Professor, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland

Guidelines methodologist (2022)
- Professor Elie Akl, Department of Medicine, American University of Beirut, Beirut, Lebanon

Declaration of interests (2022)
Members of the Guideline Development Group were requested to declare any interests related to the topic of the meeting. Additionally, The WHO Secretariat conducted due diligence online searches for other interests or public statements that could constitute a potential conflict of interests. Any potential conflicts identified through the diligence search were referred back to the GDG member to update their DOI. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed.

The relevant declared interests for the Guideline Development Group and their management are summarized as follows:

Dr Kevin Baird reported research support for a clinical trial of tafenoquine combined with ACT for radical cure of *P. vivax*. It was determined that these interests do not present a conflict with respect to the meeting but would be disclosed to the GDG members.

Professor Teun Bousema reported research funding related to evaluating the impact of MDA and MTaT on malaria transmission. It was determined that these interests do not present a serious conflict with respect to the meeting but would be disclosed to the GDG members.

Professor Donicia Gamboa reported research support from FIND diagnostics to serve as a co-principle investigator on a study to validate a malaria rapid diagnostic test. It was determined that this interest does not present a serious conflict with respect to the meeting but would be disclosed to the GDG members

Dr Marcus Lacerda reported research interests related to use of tafenoquine, an 8-aminoquinoline, for radical cure of *P. vivax* infections. It was determined that this interest does not present a conflict with respect to the meeting but would be disclosed to GDG members.

Dr Kevin Marsh reported that he is an advisor to several WHO, USAID, Malaria Vaccine Initiative and PATH groups. It was determined that this interest does not present a conflict with respect to the meeting topics but would be disclosed to GDG members.

Dr Kamini Mendis reported that she is the Director of the Board of the Asia Pacific Leaders Malaria Alliance, and that she wrote the following paper published in the Malaria Journal in 2019, on invitation by the journal to participate in a debate series. The specific topics were pre-defined by the journal, and the authors could choose among the topics presented. Mendis K. (2019). Mass drug administration should be implemented as a tool to accelerate elimination: against. Malaria Journal. 18:281. https://doi.org/10.1186/s12936-019-2907-7. As the paper could be perceived as presenting a bias against implementation of MDA,

Dr Mendis was recused from making judgments related to any of the MDA recommendations.

Professor Melissa Penny declared financial research support her institute receives related to the overall topic of discussion on malaria elimination, and grants that she holds on the broader subject of malaria. It was determined that this interest does not present a conflict with respect to the meeting but would be disclosed to GDG members.

Dr Allan Schapira reported that he is on the Board of Trustees of the UK-based charity, Malaria Consortium. It was determined that this interest does not present a conflict with respect to the meeting but would be disclosed to GDG members.

Dr Chansuda Wongsrichanalai reported two interests, a paid consultancy to Medicines for Malaria Venture on radical therapy for *P. vivax* and travel and per diem to attend international *P. vivax* meetings. It was determined that these interests do not present a conflict with respect to the meeting topics but would be disclosed to GDG members.

References

1. WHO Handbook for Guideline Development 2nd edition. Geneva: World Health Organization 2014. Website

2. International travel and health. Geneva: World Health Organization 2012. Website

3. World malaria report 2023. Geneva: World Health Organization 2023. Website

4. Global technical strategy for malaria 2016-2030, 2021 update. Geneva: World Health Organization 2021. Website

5. High burden to high impact: a targeted malaria response. Geneva: World Health Organization 2018. Website

6. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed.) 2008;336(7650):924-6 Pubmed Journal

7. International Covenant on Economic, Social and Cultural Rights. United National General Assembly resolution (21st session) 1966. Website

8. State of inequality: HIV, tuberculosis and malaria. Geneva: World Health Organization 2021. Website

9. A framework for malaria elimination. Geneva: World Health Organization 2017. Website

10. Yekutiel P. Problems of epidemiology in malaria eradication. Bulletin of the World Health Organization 1960;22:669-83 Pubmed Website

11. Cameron E, Battle KE, Bhatt S, Weiss DJ, Bisanzio D, Mappin B, et al. Defining the relationship between infection prevalence and clinical incidence of Plasmodium falciparum malaria. Nature communications 2015;6:8170 Pubmed Journal

12. Guiding principles for prioritizing malaria interventions in resource-constrained country contexts to achieve maximum impact. Geneva: World Health Organization 2024. Website

13. Cox J, Sovannaroth S, Dy Soley L, Ngor P, Mellor S, Roca-Feltrer A. Novel approaches to risk stratification to support malaria elimination: an example from Cambodia. Malaria journal 2014;13:371 Pubmed Journal

14. A research agenda for malaria eradication: monitoring, evaluation, and surveillance. PLoS medicine 2011;8(1):e1000400 Pubmed Journal

15. Investing to overcome the global impact of neglected tropical diseases. Geneva: World Health Organization 2015. Website

16. Global vector control response 2017–2030. World Health Organization, Geneva 2017. Website

17. Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature 2015;526(7572):207-211 Pubmed Journal

18. Framework for a national vector control needs assessment. Geneva: World Health Organization 2017. Website

19. Kafy HT, Ismail BA, Mnzava AP, Lines J, Abdin MSE, Eltaher JS, et al. Impact of insecticide resistance in Anopheles arabiensis on malaria incidence and prevalence in Sudan and the costs of mitigation. Proceedings of the National Academy of Sciences of the United States of America 2017;114(52):E11267-E11275 Pubmed Journal

20. Kleinschmidt I, Bradley J, Knox TB, Mnzava AP, Kafy HT, Mbogo C, et al. Implications of insecticide resistance for malaria vector control with long-lasting insecticidal nets: a WHO-coordinated, prospective, international, observational cohort study. The Lancet. Infectious diseases 2018;18(6):640-649 Pubmed Journal

21. Global plan for insecticide resistance management in malaria vectors. Geneva: World Health Organization 2012. Website

22. Manual for monitoring insecticide resistance in mosquito vectors and selecting appropriate interventions. Geneva: World Health Organization 2022. Website

23. Framework for a national plan for monitoring and management of insecticide resistance in malaria vectors. Geneva: World Health Organization 2017. Website

24. Lissenden N, Kont MD, Essandoh J, Ismail HM, Churcher TS, Lambert B, et al. Review and Meta-Analysis of the Evidence for Choosing between Specific Pyrethroids for Programmatic Purposes. Insects 2021;12(9):826 Pubmed Journal

25. Insecticide-treated nets for malaria transmission control in areas with insecticide-resistant mosquito populations: preferred product characteristics. Geneva: World Health Organization 2021. Website

26. REX Consortium. Heterogeneity of selection and the evolution of resistance. Trends in ecology & evolution 2013;28(2):110-8 Pubmed Journal

27. Sternberg ED, Thomas MB. Insights from agriculture for the management of insecticide resistance in disease vectors. Evolutionary applications 2018;11(4):404-414 Pubmed Journal

28. Huijben S, Paaijmans KP. Putting evolution in elimination: Winning our ongoing battle with evolving malaria mosquitoes and parasites. Evolutionary applications 2018;11(4):415-430 Pubmed Journal

29. South A, Hastings IM. Insecticide resistance evolution with mixtures and sequences: a model-based explanation. Malaria journal 2018;17(1):80 Pubmed Journal

30. Malaria surveillance, monitoring and evaluation: a reference manual. Geneva: World Health Organization 2018. Website

31. Yukich JO, Lindblade K, Kolaczinski J. Receptivity to malaria: meaning and measurement. Malaria journal 2022;21(1):145 Pubmed Journal

32. Guidance note on the control of residual malaria parasite transmission. Geneva: World Health Organization 2014. Website

33. World Health Assembly. Global vector control response: an integrated approach for the control of vector-borne diseases. Geneva: World Health Organization 2017;70 Website

34. Ethical issues associated with vector-borne diseases. Report of a scoping meeting, 23–24 February 2017. Geneva: World Health Organization 2017. Website

35. Ethics and vector-borne diseases: WHO guidance. Geneva: World Health Organization 2020. Website

36. Conteh L, Shuford K, Agboraw E, Kont M, Kolaczinski J, Patouillard E. Costs and Cost-Effectiveness of Malaria Control Interventions: A Systematic Literature Review. Value in Health 2021;24(8):1213-1222 Journal Website

37. ter Kuile FO, Terlouw DJ, Phillips-Howard PA, Hawley WA, Friedman JF, Kolczak MS, et al. Impact of permethrin-treated bed nets on malaria and all-cause morbidity in young children in an area of intense perennial malaria transmission in western Kenya: cross-sectional survey. The American journal of tropical medicine and hygiene 2003;68(4 Suppl):100-7 Pubmed Website

38. Gimnig JE, Kolczak MS, Hightower AW, Vulule JM, Schoute E, Kamau L, et al. Effect of permethrin-treated bed nets on the spatial distribution of malaria vectors in western Kenya. The American journal of tropical medicine and hygiene 2003;68(4 Suppl):115-20 Pubmed Website

39. Gimnig JE, Vulule JM, Lo TQ, Kamau L, Kolczak MS, Phillips-Howard PA, et al. Impact of permethrin-treated bed nets on entomologic indices in an area of intense year-round malaria transmission. The American journal of tropical medicine and hygiene 2003;68(4 Suppl):16-22 Pubmed Website

40. Phillips-Howard PA, Nahlen BL, Kolczak MS, Hightower AW, ter Kuile FO, Alaii JA, et al. Efficacy of permethrin-treated bed nets in the prevention of mortality in young children in an area of high perennial malaria transmission in western Kenya. The American journal of tropical medicine and hygiene 2003;68(4 Suppl):23-9 Pubmed Website

41. Hawley WA, Phillips-Howard PA, ter Kuile FO, Terlouw DJ, Vulule JM, Ombok M, et al. Community-wide effects of permethrin-treated bed nets on child mortality and malaria morbidity in western Kenya. The American journal of tropical medicine and hygiene 2003;68(4 Suppl):121-7 Pubmed Website

42. D'Alessandro U, Olaleye BO, McGuire W, Langerock P, Bennett S, Aikins MK, et al. Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme. Lancet (London, England) 1995;345(8948):479-83 Pubmed Website

43. Quiñones ML, Lines J, Thomson MC, Jawara M, Greenwood BM. Permethrin-treated bed nets do not have a 'mass-killing effect' on village populations of Anopheles gambiae s.l. in The Gambia. Transactions of the Royal Society of Tropical Medicine and Hygiene 92(4):373-8 Pubmed Website

44. Snow RW, Lindsay SW, Hayes RJ, Greenwood BM. Permethrin-treated bed nets (mosquito nets) prevent malaria in Gambian children. Transactions of The Royal Society of Tropical Medicine and Hygiene 1988;82(6):838-842 Pubmed Journal Website

45. Russell TL, Lwetoijera DW, Maliti D, Chipwaza B, Kihonda J, Charlwood JD, et al. Impact of promoting longer-lasting insecticide treatment of bed nets upon malaria transmission in a rural Tanzanian setting with pre-existing high coverage of untreated nets. Malaria journal 2010;9:187 Pubmed Journal

46. Govella NJ, Okumu FO, Killeen GF. Insecticide-treated nets can reduce malaria transmission by mosquitoes which feed outdoors. The American journal of tropical medicine and hygiene 2010;82(3):415-9 Pubmed Journal

47. Birget PLG, Koella JC. An Epidemiological Model of the Effects of Insecticide-Treated Bed Nets on Malaria Transmission. PloS one 2015;10(12):e0144173 Pubmed Journal

48. Guidelines for testing mosquito adulticides for indoor residual spraying and treatment of mosquito nets. Geneva: World Health Organization 2006. Website

49. Indoor residual surface treatments for malaria transmission control in areas with insecticide-resistant mosquito populations: preferred product characteristics. Geneva: World Health Organization 2022. Website

50. Data requirements and protocol for determining non-inferiority of insecticide-treated net and indoor residual spraying products within an established WHO policy class. Geneva: World Health Organization 2019. Website

51. Malaria control in humanitarian emergencies: an inter-agency field handbook, 2nd ed. Geneva: World Health Organization 2013. Website

52. Dolan G., ter Kuile FO, Jacoutot V., White NJ, Luxemburger C., Malankirii L., et al. Bed nets for the prevention of malaria and anaemia in pregnancy. Transactions of The Royal Society of Tropical Medicine and Hygiene 1993;87(6):620-626 Pubmed Journal Website

53. Luxemburger C., Perea W.A., Delmas G., Pruja C., Pecoul B., Moren A.. Permethrin-impregnated bed nets for the prevention of malaria in schoolchildren on the Thai-Burmese border. Transactions of The Royal Society of Tropical Medicine and Hygiene 1994;88(2):155-159 Pubmed Journal Website

54. Rowland M, Bouma M, Ducornez D, Durrani N, Rozendaal J, Schapira A, et al. Pyrethroid-impregnated bed nets for personal protection against malaria for Afghan refugees. Transactions of The Royal Society of Tropical Medicine and Hygiene 1996;90(4):357-361 Pubmed Journal Website

55. Rowland M, Hewitt S, Durrani N, Bano N, Wirtz R. Transmission and control of vivax malaria in Afghan refugee settlements in Pakistan. Transactions of The Royal Society of Tropical Medicine and Hygiene 1997;91(3):252-255 Pubmed Journal Website

56. Rowland M, Mahmood P, Iqbal J, Carneiro I, Chavasse D. Indoor residual spraying with alphacypermethrin controls malaria in Pakistan: a community-randomized trial. Tropical Medicine & International Health 2000;5(7):472-481 Pubmed Journal Website

57. Smithuis FM, Kyaw MK, Phe UO, van der Broek I, Katterman N, Rogers C, et al. The effect of insecticide-treated bed nets on the incidence and prevalence of malaria in children in an area of unstable seasonal transmission in western Myanmar. Malaria Journal 2013;12(1):363 Pubmed Journal Website

58. Messenger LA, Furnival-Adams J, Pelloquin B, Rowland M. Vector control for malaria prevention during humanitarian emergencies: protocol for a systematic review and meta-analysis. BMJ Open 2021/07/27;11(7):e046325-e046325 Pubmed Journal Website

59. Pryce J, Richardson M, Lengeler C. Insecticide-treated nets for preventing malaria. Cochrane Database of Systematic Reviews 2018.(11) Pubmed Journal Website

60. Technical consultation on determining non-inferiority of vector control products within an established class: Report of a virtual meeting 31 August–2 September 2021. Geneva: World Health Organization 2021. Website

61. Staedke SG, Gonahasa S, Dorsey G, Kamya MR, Maiteki-Sebuguzi C, Lynd A, et al. Effect of long-lasting insecticidal nets with and without piperonyl butoxide on malaria indicators in Uganda (LLINEUP): a pragmatic, cluster-randomised trial embedded in a national LLIN distribution campaign. The Lancet 2020;395(10232):1292-1303 Pubmed Journal Website

62. Protopopoff N, Mosha JF, Lukole E, Charlwood JD, Wright A, Mwalimu CD, et al. Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial. Lancet (London, England) 2018;391(10130):1577-1588 Pubmed Journal

63. Gleave K, Lissenden N, Richardson M, Choi L, Ranson H. Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. The Cochrane Database of Systematic Reviews 2021;5:CD012776 Pubmed Journal

64. Mosha JF, Kulkarni MA, Lukole E, Matowo NS, Pitt C, Messenger LA, et al. Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial. Lancet (London, England) 2022;399(10331):1227-1241 Pubmed Journal

65. Guidance on the prioritization of insecticide-treated nets in situations where resources are limited. Geneva: World Health Organization 2023. Website

66. Accrombessi M, Cook J, Dangbenon E, Yovogan B, Akpovi H, Sovi A, et al. Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets (LLINs) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial. Lancet (London, England) 2023;401(10375):435-446 Pubmed Journal

67. Tiono AB, Ouédraogo A, Ouattara D, Bougouma EC, Coulibaly S, Diarra A, et al. Efficacy of Olyset Duo, a bednet containing pyriproxyfen and permethrin, versus a permethrin-only net against clinical malaria in an area with highly pyrethroid-resistant vectors in rural Burkina Faso: a cluster-randomised controlled trial. Lancet (London, England) 2018;392(10147):569-580 Pubmed Journal

68. Achieving and maintaining universal coverage with long-lasting insecticidal nets for malaria control. Geneva: World Health Organization 2017. Website

69. WHO recommendations on the sound management of old long-lasting insecticidal nets. Geneva: World Health Organization 2014. Website

70. Operational manual on indoor residual spraying: control of vectors of malaria, Aedes-borne diseases, Chagas disease, leishmaniases and lymphatic filariasis. Geneva: World Health Organization 2023. Website

71. Stockholm Convention on Persistent Organic Pollutants (POPS). United Nations Environment Programme 2018. Website

72. Meeting report on the WHO Evidence Review Group on assessing comparative effectiveness of new vector control tools. Geneva: World Health Organization 2017. Website

73. Indoor residual spraying : use of indoor residual spraying for scaling up global malaria control and elimination : WHO position statement. Geneva: World Health Organization 2006. Website

74. WHO Expert Committee on Malaria (1956 ; Athens, Greece). WHO Expert Committee on Malaria, Athens, 20-28 June 1956 : sixth report. World Health Organization. https://apps.who.int/iris/handle/10665/64537. Geneva: World Health Organization 1956.

75. Abuaku B, Ahorlu C, Psychas P, Ricks P, Oppong S, Mensah S, et al. Impact of indoor residual spraying on malaria parasitaemia in the Bunkpurugu-Yunyoo District in northern Ghana. Parasites & vectors 2018;11(1):555 Pubmed Journal

76. Tseng LF, Chang WC, Ferreira MC, Wu CH, Rampão HS, Lien JC. Rapid control of malaria by means of indoor residual spraying of alphacypermethrin in the Democratic Republic of São Tomé and Príncipe. The American journal of tropical medicine and hygiene 2008;78(2):248-50 Pubmed

77. Keating J, Yukich JO, Miller JM, Scates S, Hamainza B, Eisele TP, et al. Retrospective evaluation of the effectiveness of indoor residual spray with pirimiphos-methyl (Actellic) on malaria transmission in Zambia. Malaria journal 2021;20(1):173 Pubmed Journal

78. Namuganga JF, Epstein A, Nankabirwa JI, Mpimbaza A, Kiggundu M, Sserwanga A, et al. The impact of stopping and starting indoor residual spraying on malaria burden in Uganda. Nature communications 2021;12(1):2635 Pubmed Journal

79. Gimnig JE, Otieno P, Were V, Marwanga D, Abong'o D, Wiegand R, et al. The Effect of Indoor Residual Spraying on the Prevalence of Malaria Parasite Infection, Clinical Malaria and Anemia in an Area of Perennial Transmission and Moderate Coverage of Insecticide Treated Nets in Western Kenya. PloS one 2016;11(1):e0145282 Pubmed Journal

80. Curtis CF, Maxwell CA, Finch RJ, Njunwa KJ. A comparison of use of a pyrethroid either for house spraying or for bednet treatment against malaria vectors. Tropical medicine & international health : TM & IH 1998;3(8):619-31 Pubmed

81. Misra SP, Webber R, Lines J, Jaffar S, Bradley DJ. Malaria control: bednets or spraying? Spray versus treated nets using deltamethrin--a community randomized trial in India. Transactions of the Royal Society of Tropical Medicine and Hygiene 1999;93(5):456-7 Pubmed

82. Abong'o B, Gimnig JE, Torr SJ, Longman B, Omoke D, Muchoki M, et al. Impact of indoor residual spraying with pirimiphos-methyl (Actellic 300CS) on entomological indicators of transmission and malaria case burden in Migori County, western Kenya. Scientific reports 2020;10(1):4518 Pubmed Journal

83. Hailu A, Lindtjørn B, Deressa W, Gari T, Loha E, Robberstad B. Cost-effectiveness of a combined intervention of long lasting insecticidal nets and indoor residual spraying compared with each intervention alone for malaria prevention in Ethiopia. Cost effectiveness and resource allocation : C/E 2018;16:61 Pubmed Journal

84. Loha E, Deressa W, Gari T, Balkew M, Kenea O, Solomon T, et al. Long-lasting insecticidal nets and indoor residual spraying may not be sufficient to eliminate malaria in a low malaria incidence area: results from a cluster randomized controlled trial in Ethiopia. Malaria journal 2019;18(1):141 Pubmed Journal

85. Longman B, Won N, Aghajanyan A, Sanchez A. PMI IRS country programs: 2021 comparative cost analysis. Rockville, MD. PMI VectorLink Project, Abt Associates Inc. 2022. Website

86. Gunasekaran K, Sahu SS, Jambulingam P, Das PK. DDT indoor residual spray, still an effective tool to control Anopheles fluviatilis-transmitted Plasmodium falciparum malaria in India. Tropical medicine & international health : TM & IH 2005;10(2):160-8 Pubmed

87. Data requirements and methods to support the evaluation of new vector control products. Geneva: World Health Organization,2017 Website

88. Technical consultation to assess comparative efficacy of vector control products: meeting report, 5 and 9 June 2023. Geneva: World Health Organization 2023; Website

89. WHO malaria policy advisory group (MPAG) meeting report, 18–20 April 2023. Geneva: World Health Organization 2023 Website

90. Bhatia MR, Fox-Rushby J, Mills A. Cost-effectiveness of malaria control interventions when malaria mortality is low: insecticide-treated nets versus in-house residual spraying in India. Social science & medicine (1982) 2004;59(3):525-39 Pubmed

91. Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. The Cochrane database of systematic reviews 2010;(4):CD006657 Pubmed Journal

92. Charlwood J.D, Qassim M, Elnsur E.I, Donnelly M, Petrarca V, Billingsley P.F, et al. The impact of indoor residual spraying with malathion on malaria in refugee camps in eastern Sudan. Acta Tropica 2001;80(1):1-8 Pubmed Journal Website

93. Mashauri FM, Kinung'hi SM, Kaatano GM, Magesa SM, Kishamawe C, Mwanga JR, et al. Impact of indoor residual spraying of lambda-cyhalothrin on malaria prevalence and anemia in an epidemic-prone district of Muleba, north-western Tanzania. The American journal of tropical medicine and hygiene 2013;88(5):841-9 Pubmed Journal

94. Guyatt HL, Corlett SK, Robinson TP, Ochola SA, Snow RW. Malaria prevention in highland Kenya: indoor residual house-spraying vs. insecticide-treated bednets. Tropical medicine & international health : TM & IH 2002;7(4):298-303 Pubmed

95. Rowland M, Hewitt S, Durrani N. Prevalence of malaria in Afghan refugee villages in Pakistan sprayed with lambdacyhalothrin or malathion. Transactions of the Royal Society of Tropical Medicine and Hygiene 88(4):378-9 Pubmed

96. Wahid S, Stresman GH, Kamal SS, Sepulveda N, Kleinschmidt I, Bousema T, et al. Heterogeneous malaria transmission in long-term Afghan refugee populations: a cross-sectional study in five refugee camps in northern Pakistan. Malaria journal 2016;15:245 Pubmed Journal

97. Choi L, Pryce J, Garner P. Indoor residual spraying for preventing malaria in communities using insecticide-treated nets. The Cochrane database of systematic reviews 2019;(5):CD012688 Pubmed Journal Website

98. WHO Guidance for countries on combining indoor residual spraying and long-lasting insecticidal nets. Geneva: World Health Organization 2014 . Website

99. Risks associated with scale-back of vector control after malaria transmission has been reduced. Information note. Geneva: World Health Organization 2015. Website

100. Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ. Mosquito repellents for malaria prevention. The Cochrane database of systematic reviews 2018;(2):CD011595 Pubmed Journal Website

101. Gabaldón Figueira JC, Wagah MG, Adipo LB, Wanjiku C, Maia MF. Topical repellents for malaria prevention. The Cochrane Database of Systematic Reviews 2023; (8):CD015422 Journal Website

102. WHO Housing and health guidelines. Geneva: World Health Organization 2018. Website

103. Keeping the vector out: housing improvements for vector control and sustainable development. Geneva: World Health Organization 2017. Website

104. Tusting LS, Bottomley C, Gibson H, Kleinschmidt I, Tatem AJ, Lindsay SW, et al. Housing Improvements and Malaria Risk in Sub-Saharan Africa: A Multi-Country Analysis of Survey Data. PLoS medicine 2017;14(2):e1002234 Pubmed Journal

105. Larval source management: a supplementary measure for malaria vector control. An operational manual. Geneva: World Health Organization 2013. Website

106. Choi L, Majambere S, Wilson AL. Larviciding to prevent malaria transmission. The Cochrane database of systematic reviews 2019;(8):CD012736 Pubmed Journal Website

107. Walshe DP, Garner P, Adeel AA, Pyke GH, Burkot TR. Larvivorous fish for preventing malaria transmission. The Cochrane database of systematic reviews 2017;(12):CD008090 Pubmed Journal Website

108. Pryce J, Choi L, Richardson M, Malone D. Insecticide space spraying for preventing malaria transmission. The Cochrane database of systematic reviews 2018;(11):CD012689 Pubmed Journal Website

109. Furnival-Adams JA, Olanga EA, Napier M, Garner M. House modifications for preventing malaria. The Cochrane database of systematic reviews 2021;(1):CD013398 Pubmed Journal Website

110. Getawen SK, Ashine T, Massebo F, Woldeyes D, Lindtjørn B. Exploring the impact of house screening intervention on entomological indices and incidence of malaria in Arba Minch town, southwest Ethiopia: A randomized control trial. Acta tropica 2018;181:84-94 Pubmed Journal

111. Kirby MJ, Ameh D, Bottomley C, Green C, Jawara M, Milligan PJ, et al. Effect of two different house screening interventions on exposure to malaria vectors and on anaemia in children in The Gambia: a randomised controlled trial. Lancet (London, England) 2009;374(9694):998-1009 Pubmed Journal

112. Barreaux AMG, Oumbouke WA, Brou N, Tia IZ, Ahoua Alou LP, Doudou DT, et al. The role of human and mosquito behaviour in the efficacy of a house-based intervention. Philosophical transactions of the Royal Society of London. Series B, Biological sciences 2021;376(1818):20190815 Pubmed Journal

113. Global surveillance, prevention and control of chronic respiratory diseases : a comprehensive approach. Geneva: World Health Organization 2007. Website

114. Exposure to household air pollution. Geneva: World Health Organization 2021. Website

115. Guidelines for indoor air quality: household fuel combustion. Geneva: World Health Organization 2014. Website

116. Sundell J, Levin H, Nazaroff WW, Cain WS, Fisk WJ, Grimsrud DT, et al. Ventilation rates and health: multidisciplinary review of the scientific literature. Indoor air 2011;21(3):191-204 Pubmed Journal

117. Knudsen JB, Pinder M, Jatta E, Jawara M, Yousuf MA, Søndergaard AT, et al. Measuring ventilation in different typologies of rural Gambian houses: a pilot experimental study. Malaria journal 2020;19(1):273 Pubmed Journal

118. Jatta E, Jawara M, Bradley J, Jeffries D, Kandeh B, Knudsen JB, et al. How house design affects malaria mosquito density, temperature, and relative humidity: an experimental study in rural Gambia. The Lancet Planetary Health 2018;2(11):e498-e508 Pubmed Journal Website

119. Norms, standards and processes underpinning development of WHO recommendations on vector control. Geneva: World Health Organization 2020. Website

120. Sicuri E, Bardají A, Nhampossa T, Maixenchs M, Nhacolo A, Nhalungo D, et al. Cost-effectiveness of intermittent preventive treatment of malaria in pregnancy in southern Mozambique. PloS one 2010;5(10):e13407 Pubmed Journal

121. Fernandes S, Sicuri E, Kayentao K, van Eijk AM, Hill J, Webster J, et al. Cost-effectiveness of two versus three or more doses of intermittent preventive treatment for malaria during pregnancy in sub-Saharan Africa: a modelling study of meta-analysis and cost data. The Lancet. Global health 2015;3(3):e143-53 Pubmed Journal

122. Hansen KS, Ndyomugyenyi R, Magnussen P, Clarke SE. Cost-effectiveness analysis of three health interventions to prevent malaria in pregnancy in an area of low transmission in Uganda. International health 2012;4(1):38-46 Pubmed Journal

123. Diengou NH, Cumber SN, Nkfusai CN, Mbinyui MS, Viyoff VZ, Bede F, et al. Factors associated with the uptake of intermittent preventive treatment of malaria in pregnancy in the Bamenda health districts, Cameroon. The Pan African medical journal 2020;35:42 Pubmed Journal

124. Nekaka R, Nteziyaremye J, Oboth P, Iramiot JS, Wandabwa J. Malaria preventive practices and delivery outcomes: A cross-sectional study of parturient women in a tertiary hospital in Eastern Uganda. PloS one 2020;15(8):e0237407 Pubmed Journal

125. Ngapanya S, Mikomangwa W, Bwire G, Kilonzi M, Mlyuka H, Mutagonda R, et al. Uptake of Intermittent Preventive Therapy Among Pregnant Women Living in Dar es Salaam, Tanzania: a Descriptive Cross-sectional Study. SN Comprehensive Clinical Medicine 2020;2:408-413 Journal Website

126. Onyebuchi AK, Lawani LO, Iyoke CA, Onoh CR, Okeke NE. Adherence to intermittent preventive treatment for malaria with sulphadoxine-pyrimethamine and outcome of pregnancy among parturients in South East Nigeria. Patient preference and adherence 2014;8:447-52 Pubmed Journal

127. Moberg J, Oxman AD, Rosenbaum S, Schünemann HJ, Guyatt G, Flottorp S, et al. The GRADE Evidence to Decision (EtD) framework for health system and public health decisions. Health research policy and systems 2018;16(1):45 Pubmed Journal

128. WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP)SP. Geneva: World Health Organization 2014. Website

129. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization 2016. Website

130. Community deployment of intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine a field guide. Geneva: World Health Organization 2024. Website

131. Esu EB, Oringanje C, Meremikwu MM. Intermittent preventive treatment for malaria in infants. The Cochrane database of systematic reviews 2021;7:CD011525 Pubmed Journal

132. Kobbe R, Kreuzberg C, Adjei S, Thompson B, Langefeld I, Thompson PA, et al. A randomized controlled trial of extended intermittent preventive antimalarial treatment in infants. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2007;45(1):16-25 Pubmed

133. Mockenhaupt FP, Reither K, Zanger P, Roepcke F, Danquah I, Saad E, et al. Intermittent preventive treatment in infants as a means of malaria control: a randomized, double-blind, placebo-controlled trial in northern Ghana. Antimicrobial agents and chemotherapy 2007;51(9):3273-81 Pubmed

134. Grobusch MP, Lell B, Schwarz NG, Gabor J, Dornemann J, Potschke M, et al. Intermittent preventive treatment against malaria in infants in Gabon--a randomized, double-blind, placebo-controlled trial. The Journal of infectious diseases 2007;196(11):1595-602 Pubmed

135. Bigira V, Kapisi J, Clark TD, Kinara S, Mwangwa F, Muhindo MK, et al. Protective efficacy and safety of three antimalarial regimens for the prevention of malaria in young Ugandan children: a randomized controlled trial. PLoS medicine 2014;11(8):e1001689 Pubmed Journal

136. Griffin JT, Cairns M, Ghani AC, Roper C, Schellenberg D, Carneiro I, et al. Protective efficacy of intermittent preventive treatment of malaria in infants (IPTi) using sulfadoxine-pyrimethamine and parasite resistance. PloS one 2010;5(9):e12618 Pubmed Journal

137. Lahuerta M, Sutton R, Mansaray A, Eleeza O, Gleason B, Akinjeji A, et al. Evaluation of health system readiness and coverage of intermittent preventive treatment of malaria in infants (IPTi) in Kambia district to inform national scale-up in Sierra Leone. Malaria journal 2021;20(1):74 Pubmed Journal

138. Manzi F, Schellenberg J, Hamis Y, Mushi AK, Shirima K, Mwita A, et al. Intermittent preventive treatment for malaria and anaemia control in Tanzanian infants; the development and implementation of a public health strategy. Transactions of the Royal Society of Tropical Medicine and Hygiene 2009;103(1):79-86 Pubmed Journal

139. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Clinical research ed.) 2017;358:j4008 Pubmed

Journal

140. Intermittent preventive treatment for infants using sulfadoxine-pyrimethamine (SP-IPTi) for malaria control in Africa: implementation field guide. Geneva: World Health Organization 2011. Website

141. Paton RS, Kamau A, Akech S, Agweyu A, Ogero M, Mwandawiro C, et al. Malaria infection and severe disease risks in Africa. Science (New York, N.Y.) 2021;373(6557):926-931 Pubmed Journal

142. Issiaka D, Barry A, Tounkara M, Traore T, Diarra I, Kone D, et al. Determining the optimal mode for delivery of seasonal malaria chemoprevention in Mali. American Journal of Tropical Medicine and Hygiene 2015;93(4 Supplement):496 Website

143. Barry A, Issiaka D, Traore T, Mahamar A, Diarra B, Sagara I, et al. Optimal mode for delivery of seasonal malaria chemoprevention in Ouelessebougou, Mali: A cluster randomized trial. PloS one 2018;13(3):e0193296 Pubmed Journal

144. Ceesay S, Hubbard E, Bojang K, Kandeh B, Kolley O, Jah H, et al. Implementation of seasonal malaria chemoprevention in The Gambia. American Journal of Tropical Medicine and Hygiene 2016;95(5 Supplement 1) Website

145. Effectiveness of seasonal malaria chemoprevention at scale in west and central Africa: an observational study. Lancet (London, England) 2020;396(10265):1829-1840 Pubmed Journal

146. Seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine in children: A field guide. Second edition. Geneva: World Health Organization; 2023 Website

147. Clarke SE, Jukes MC, Njagi JK, Khasakhala L, Cundill B, Otido J, et al. Effect of intermittent preventive treatment of malaria on health and education in schoolchildren: a cluster-randomised, double-blind, placebo-controlled trial. Lancet (London, England) 2008;372(9633):127-138 Pubmed Journal

148. Nankabirwa J, Cundill B, Clarke S, Kabatereine N, Rosenthal PJ, Dorsey G, et al. Efficacy, safety, and tolerability of three regimens for prevention of malaria: a randomized, placebo-controlled trial in Ugandan schoolchildren. PloS one 2010;5(10):e13438 Pubmed Journal

149. Matangila JR, Doua JY, Mitashi P, da Luz RI, Lutumba P, Van Geertruyden JP. Efficacy and safety of intermittent preventive treatment in schoolchildren with sulfadoxine/pyrimethamine (SP) and SP plus piperaquine in Democratic Republic of the Congo: a randomised controlled trial. International journal of antimicrobial agents 2017;49(3):339-347 Pubmed Journal

150. Cohee LM, Opondo C, Clarke SE, Halliday KE, Cano J, Shipper AG, et al. Preventive malaria treatment among school-aged children in sub-Saharan Africa: a systematic review and meta-analyses. The Lancet. Global health 2020;8(12):e1499-e1511 Pubmed Journal

151. Audibert C, Tchouatieu A-M. Perception of Malaria Chemoprevention Interventions in Infants and Children in Eight Sub-Saharan African Countries: An End User Perspective Study. Tropical medicine and infectious disease 2021;6(2) Pubmed Journal

152. Maccario R, Rouhani S, Drake T, Nagy A, Bamadio M, Diarra S, et al. Cost analysis of a school-based comprehensive malaria program in primary schools in Sikasso region, Mali. BMC public health 2017;17(1):572 Pubmed Journal

153. Temperley M, Mueller DH, Njagi JK, Akhwale W, Clarke SE, Jukes MCH, et al. Costs and cost-effectiveness of delivering intermittent preventive treatment through schools in western Kenya. Malaria journal 2008;7:196 Pubmed Journal

154. Maiga H, Opondo C, Chico RM, Cohee LM, Sagara I, Traore OB, et al. Overall and gender-specific effects of intermittent preventive treatment of malaria with artemisinin-based combination therapies among schoolchildren in Mali: a three-group open label randomized controlled trial. American Journal of Tropical Medicine & Hygiene 2022. Pubmed Journal

155. Rohner F, Zimmermann MB, Amon RJ, Vounatsou P, Tschannen AB, N'goran EK, et al. In a randomized controlled trial of iron fortification, anthelmintic treatment, and intermittent preventive treatment of malaria for anemia control in Ivorian children, only anthelmintic treatment shows modest benefit. The Journal of nutrition 2010;140(3):635-41 Pubmed Journal

156. Cohee LM, Chilombe M, Ngwira A, Jemu SK, Mathanga DP, Laufer MK. Pilot Study of the Addition of Mass Treatment for Malaria to Existing School-Based Programs to Treat Neglected Tropical Diseases. The American journal of tropical medicine and hygiene

2018;98(1):95-99 Pubmed Journal

157. Staedke SG, Maiteki-Sebuguzi C, Rehman AM, Kigozi SP, Gonahasa S, Okiring J, et al. Assessment of community-level effects of intermittent preventive treatment for malaria in schoolchildren in Jinja, Uganda (START-IPT trial): a cluster-randomised trial. The Lancet. Global health 2018;6(6):e668-e679 Pubmed Journal

158. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: World Health Organization 2011. Website

159. Phiri K, Esan M, van Hensbroek MB, Khairallah C, Faragher B, ter Kuile FO. Intermittent preventive therapy for malaria with monthly artemether-lumefantrine for the post-discharge management of severe anaemia in children aged 4-59 months in southern Malawi: a multicentre, randomised, placebo-controlled trial. The Lancet. Infectious diseases 2012;12(3):191-200 Pubmed Journal

160. Kwambai TK, Dhabangi A, Idro R, Opoka R, Watson V, Kariuki S, et al. Malaria Chemoprevention in the Postdischarge Management of Severe Anemia. The New England journal of medicine 2020;383(23):2242-2254 Pubmed Journal

161. Bojang KA, Milligan PJM, Conway DJ, Sisay-Joof F, Jallow M, Nwakanma DC, et al. Prevention of the recurrence of anaemia in Gambian children following discharge from hospital. PloS one 2010;5(6):e11227 Pubmed Journal

162. Nkosi-Gondwe T, Robberstad B, Blomberg B, Phiri KS, Lange S. Introducing post-discharge malaria chemoprevention (PMC) for management of severe anemia in Malawian children: a qualitative study of community health workers' perceptions and motivation. BMC health services research 2018;18(1):984 Pubmed Journal

163. Nkosi-Gondwe T, Robberstad B, Mukaka M, Idro R, Opoka RO, Banda S, et al. Adherence to community versus facility-based delivery of monthly malaria chemoprevention with dihydroartemisinin-piperaquine for the post-discharge management of severe anemia in Malawian children: A cluster randomized trial. PloS one 2021;16(9):e0255769 Pubmed Journal

164. Svege S, Kaunda B, Robberstad B, Nkosi-Gondwe T, Phiri KS, Lange S. Post-discharge malaria chemoprevention (PMC) in Malawi: caregivers` acceptance and preferences with regard to delivery methods. BMC health services research 2018;18(1):544 Pubmed Journal

165. Nadia J, Lu F. Historical experiences on mass drug administration for malaria control and elimination, its challenges and China's experience: a narrative review. Acta tropica 2022;225:106209 Pubmed Journal

166. Mass drug administration for falciparum malaria: a practical field manual. Geneva: World Health Organization 2017. Website

167. Shattock AJ, Johnson HC, Sim SY, Carter A, Lambach P, Hutubessy RCW, et al. Contribution of vaccination to improved survival and health: modelling 50 years of the Expanded Programme on Immunization. Lancet (London, England) 2024;403(10441):2307-2316 Pubmed Journal

168. WHO Immunization Data Portal. Website

169. WHO review of malaria vaccine clinical development. Geneva: World Health Organization 2024. Website

170. Good MF. Our impasse in developing a malaria vaccine. Cellular and molecular life sciences : CMLS 2011;68(7):1105-13 Pubmed Journal

171. Minassian AM, Silk SE, Barrett JR, Nielsen CM, Miura K, Diouf A, et al. Reduced blood-stage malaria growth and immune correlates in humans following RH5 vaccination. Med (New York, N.Y.) 2021;2(6):701-719.e19 Pubmed Journal

172. Safety and immunogenicity of Pfs25M-EPA/AS01 and Pfs230D1M-EPA/AS01 vaccines, transmission blocking vaccines against Plasmodium falciparum, at full and fractional dosing in adults in Mali. Website

173. Draper SJ, Angov E, Horii T, Miller LH, Srinivasan P, Theisen M, et al. Recent advances in recombinant protein-based malaria vaccines. Vaccine 2015;33(52):7433-43 Pubmed Journal

174. BioNTech SE. Safety and immune responses after vaccination with an investigational RNA-based vaccine against malaria

(NCT05581641). U.S National Library of Medicine Website

175. BioNTech SE. A clinical trial to evaluate the safety, efficacy, and immune responses after vaccination with an investigational RNA-based vaccine against malaria. U.S. National Library of Medicine Website

176. Adjuvant development for vaccines and for autoimmune and allergic diseases. Washington (DC): Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) 2020. Website

177. Guidelines on the quality, safety and efficacy of recombinant malaria vaccines targeting the pre-erythrocytic and blood stages of Plasmodium falciparum, Annex 3, TRS No 980. Geneva: World Health Organization 2014. Website

178. Malaria vaccine: WHO position paper - May 2024. Weekly Epidemiological Record,Vol. 99, No. 19, pp. 225-248. 10 May 2024. Geneva: World Health Organization 2024. Website

179. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet (London, England) 2015;386(9988):31-45 Pubmed Journal

180. Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites. PLoS medicine 2014;11(7):e1001685 Pubmed Journal

181. Tinto H, Otieno W, Gesase S, Sorgho H, Otieno L, Liheluka E, et al. Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised controlled trial. The Lancet. Infectious diseases 2019;19(8):821-832 Pubmed Journal

182. Datoo MS, Dicko A, Tinto H, Ouédraogo J-B, Hamaluba M, Olotu A, et al. Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: a multicentre, double-blind, randomised, phase 3 trial. Lancet (London, England) 2024;403(10426):533-544 Pubmed Journal

183. Chandramohan D, Zongo I, Sagara I, Cairns M, Yerbanga R-S, Diarra M, et al. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. The New England journal of medicine 2021;385(11):1005-1017 Pubmed Journal

184. Schmit N, Topazian HM, Natama HM, Bellamy D, Traoré O, Somé MA, et al. The public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine: a mathematical modelling study. The Lancet. Infectious diseases 2024;24(5):465-475 Pubmed Journal

185. Mosquirix: Opinion on medicine for use outside EU. European Medicines Agency 2015. Website

186. Prequalification of Medical Products: Mosquirix. Geneva: World Health Organization 2022. Website

187. Prequalification of Medical Products: R21 Malaria. Geneva: World Health Organization 2023. Website

188. Asante KP, Mathanga DP, Milligan P, Akech S, Oduro A, Mwapasa V, et al. Feasibility, safety, and impact of the RTS,S/AS01E malaria vaccine when implemented through national immunisation programmes: evaluation of cluster-randomised introduction of the vaccine in Ghana, Kenya, and Malawi. Lancet (London, England) 2024;403(10437):1660-1670 Pubmed Journal

189. Vekemans J, Guerra Y, Lievens M, Benns S, Lapierre D, Leach A, et al. Pooled analysis of safety data from pediatric Phase II RTS,S/AS malaria candidate vaccine trials. Human vaccines 2011;7(12):1309-16 Pubmed Journal

190. Baral R, Levin A, Odero C, Pecenka C, Tanko Bawa J, Antwi-Agyei KO, et al. Cost of introducing and delivering RTS,S/AS01 malaria vaccine within the malaria vaccine implementation program. (Supplementary material, Appendix 3). Vaccine 2023;41(8):1496-1502 Pubmed Journal

191. Dicko A, Ouedraogo J-B, Zongo I, Sagara I, Cairns M, Yerbanga RS, et al. Seasonal vaccination with RTS,S/AS01E vaccine with or without seasonal malaria chemoprevention in children up to the age of 5 years in Burkina Faso and Mali: a double-blind, randomised, controlled, phase 3 trial. The Lancet. Infectious diseases 2024;24(1):75-86 Pubmed Journal

192. Samuels AM, Ansong D, Kariuki SK, Adjei S, Bollaerts A, Ockenhouse C, et al. Efficacy of RTS,S/AS01E malaria vaccine

administered according to different full, fractional, and delayed third or early fourth dose regimens in children aged 5-17 months in Ghana and Kenya: an open-label, phase 2b, randomised controlled trial. The Lancet. Infectious diseases 2022;22(9):1329-1342 Pubmed Journal

193. Westercamp N, Osei-Tutu L, Schuerman L, Kariuki SK, Bollaerts A, Lee CK, et al. Could Less Be More? Accounting for Fractional-Dose Regimens and Different Number of Vaccine Doses When Measuring the Impact of the RTS,S/AS01E Malaria Vaccine. The Journal of infectious diseases 2024;230(2):e486-e495 Pubmed Journal

194. Kintampo Health Research Centre. Strengthening the Evidence for Policy on the RTS,S/AS01 Malaria Vaccine (MVPE-CC). U.S. National Library of Medicine Website

195. Asante KP, Abdulla S, Agnandji S, Lyimo J, Vekemans J, Soulanoudjingar S, et al. Safety and efficacy of the RTS,S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. The Lancet. Infectious diseases 2011;11(10):741-9 Pubmed Journal

196. Agnandji ST, Asante KP, Lyimo J, Vekemans J, Soulanoudjingar SS, Owusu R, et al. Evaluation of the safety and immunogenicity of the RTS,S/AS01E malaria candidate vaccine when integrated in the expanded program of immunization. The Journal of infectious diseases 2010;202(7):1076-87 Pubmed Journal

197. University of Oxford. Assessment of safety and immunogenicity of a single vial presentation of R21/Matrix-M and co-administration with EPI vaccines. U.S National Library of Medicine Website

198. University of Oxford. Assessment of safety and immunogenicity of R21/Matrix-M in African children living with HIV. U.S. National Library of Medicine Website

199. Datoo MS, Natama MH, Somé A, Traoré O, Rouamba T, Bellamy D, et al. Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. Lancet 2021;397(10287):1809-1818 Pubmed Journal Website

200. Milligan P, Fogelson A. Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 46 months after the vaccine was introduced (unpublished evidence). Geneva: World Health Organization 2024. Website

201. Milligan P, Moore K. Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced (unpublished evidence). 2021;V1.3 6 Sept 2021 Website

202. Malaria case management: operations manual. Geneva: World Health Organization 2009. Website

203. Integrated management of childhood illness for high HIV settings: chart booklet. Geneva: World Health Organization 2008. Website

204. Universal access to malaria diagnostic testing - an operational manual. Geneva: World Health Organization 2011. Website

205. Malaria diagnosis: memorandum from a WHO meeting. Bulletin of the World Health Organization 1988;66(5):575-94 Pubmed

206. Malaria microscopy quality assurance manual, version 2. Geneva: World Health Organization 2016. Website

207. Kawamoto F, Billingsley PF. Rapid diagnosis of malaria by fluorescence microscopy. Parasitology today (Personal ed.) 1992;8(2):69-71 Pubmed

208. Malaria diagnosis: new perspectives. Geneva: World Health Organization 2003. Website

209. Malaria rapid diagnosis: making it work. Meeting report. World Health Organization. Regional Office for the Western Pacific 2003. Website

210. The use of rapid diagnostic tests. World Health Organization. Regional Office for the Western Pacific 2004. Website

211. Transporting, storing and handling malaria rapid diagnostic tests in health clinics. Geneva: World Health Organization 2009. Website

212. Malaria rapid diagnostic test performance. Results of WHO product testing of malaria RDTs: round 8. Geneva: World Health Organization 2018. Website

213. False-negative RDT results and implications of new reports of P. falciparum hrp2/3 gene deletions. Geneva: World Health Organization 2017. Website

214. Abba K, Deeks JJ, Olliaro P, Naing C-M, Jackson SM, Takwoingi Y, et al. Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. The Cochrane database of systematic reviews 2011;(7):CD008122 Pubmed Journal

215. Thiam S, Thior M, Faye B, Ndiop M, Diouf ML, Diouf MB, et al. Major reduction in anti-malarial drug consumption in Senegal after nation-wide introduction of malaria rapid diagnostic tests. PloS one 2011;6(4):e18419 Pubmed Journal

216. Voller A. The immunodiagnosis of malaria. In: Wernsdorfer WH, McGregor I, editors. Malaria. Principles and Practice of Malariology. Edinburgh: Churchill Livingstone 1988;1:815-827 Website

217. Bates I, Iboro J, Barnish G. Challenges in monitoring the impact of interventions against malaria using diagnostics. In: Reducing malaria's burden. Evidence of effectiveness for decision-makers. Global Health Council, Washington D.C. 2003;33-39 Website

218. WHO Evidence review group on malaria diagnosis in low transmission settings. Meeting Report. Geneva: World Health Organization 2012. Website

219. Good procurement practices for artemisinin-based antimalarial medicines. Geneva: World Health Organization 2010. Website

220. Sinclair D, Zani B, Donegan S, Olliaro P, Garner P. Artemisinin-based combination therapy for treating uncomplicated malaria. The Cochrane database of systematic reviews 2009;(3):CD007483 Pubmed Journal

221. Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated Plasmodium falciparum malaria. The Cochrane database of systematic reviews 2014;(1):CD010927 Pubmed Journal

222. Tarning J, Zongo I, Somé FA, Rouamba N, Parikh S, Rosenthal PJ, et al. Population pharmacokinetics and pharmacodynamics of piperaquine in children with uncomplicated falciparum malaria. Clinical pharmacology and therapeutics 2012;91(3):497-505 Pubmed Journal

223. Tona Lutete G, Mombo-Ngoma G, Assi S-B, Bigoga JD, Koukouikila-Koussounda F, Ntamabyaliro NY, et al. Pyronaridine-artesunate real-world safety, tolerability, and effectiveness in malaria patients in 5 African countries: A single-arm, open-label, cohort event monitoring study. PLoS medicine 2021;18(6):e1003669 Pubmed Journal

224. Pryce J, Taylor M, Fox T, Hine P. Pyronaridine-artesunate for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database Syst Rev 2022;6(6) Pubmed Journal

225. . The effect of dosing regimens on the antimalarial efficacy of dihydroartemisinin-piperaquine: a pooled analysis of individual patient data. PLoS medicine 2013;10(12):e1001564; discussion e1001564 Pubmed Journal

226. Graves PM, Gelband H, Garner P. Primaquine or other 8-aminoquinoline for reducing P. falciparum transmission. The Cochrane database of systematic reviews 2014;(6):CD008152 Pubmed Journal

227. White NJ, Qiao LG, Qi G, Luzzatto L. Rationale for recommending a lower dose of primaquine as a Plasmodium falciparum gametocytocide in populations where G6PD deficiency is common. Malaria journal 2012;11:418 Pubmed Journal

228. Recht J, Ashley E, White N. Safety of 8-aminoquinoline antimalarial medicines. World Health Organization, Geneva 2014. Website

229. Gilder ME, Hanpithakphong W, Hoglund RM, Tarning J, Win HH, Hilda N, et al. Primaquine pharmacokinetics in lactating women and breastfed infant exposures. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2018;67(7):1000-1007 Pubmed Journal

230. Policy brief on single-dose primaquine as a gametocytocide in Plasmodium falciparum malaria. Geneva: World Health Organization

2015. Website

231. Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, et al. Epidemiology and burden of malaria in pregnancy. The Lancet. Infectious diseases 2007;7(2):93-104 Pubmed

232. Accrombessi M, Yovo E, Fievet N, Cottrell G, Agbota G, Gartner A, et al. Effects of Malaria in the First Trimester of Pregnancy on Poor Maternal and Birth Outcomes in Benin. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2019;69(8):1385-1393 Pubmed Journal

233. Walker PGT, ter Kuile FO, Garske T, Menendez C, Ghani AC. Estimated risk of placental infection and low birthweight attributable to Plasmodium falciparum malaria in Africa in 2010: a modelling study. The Lancet. Global health 2014;2(8):e460-7 Pubmed Journal

234. Antimalarial studies on Qinghaosu. Chinese medical journal 1979;92(12):811-6 Pubmed

235. White TEK, Bushdid PB, Ritter S, Laffan SB, Clark RL. Artesunate-induced depletion of embryonic erythroblasts precedes embryolethality and teratogenicity in vivo. Birth defects research. Part B, Developmental and reproductive toxicology 2006;77(5):413-29 Pubmed

236. Saito M, Mansoor R, Kennon K, Anvikar AR, Ashley EA, Chandramohan D, et al. Efficacy and tolerability of artemisinin-based and quinine-based treatments for uncomplicated falciparum malaria in pregnancy: a systematic review and individual patient data meta-analysis. The Lancet. Infectious diseases 2020;20(8):943-952 Pubmed Journal

237. Burger RJ, van Eijk AM, Bussink M, Hill J, Ter Kuile FO. Artemisinin-Based Combination Therapy Versus Quinine or Other Combinations for Treatment of Uncomplicated Plasmodium falciparum Malaria in the Second and Third Trimester of Pregnancy: A Systematic Review and Meta-Analysis. Open forum infectious diseases 2016;3(1):ofv170 Pubmed Journal

238. Clark RL, Arima A, Makori N, Nakata Y, Bernard F, Gristwood W, et al. Artesunate: developmental toxicity and toxicokinetics in monkeys. Birth defects research. Part B, Developmental and reproductive toxicology 2008;83(4):418-34 Pubmed Journal

239. Clark RL. Embryotoxicity of the artemisinin antimalarials and potential consequences for use in women in the first trimester. Reproductive toxicology (Elmsford, N.Y.) 2009;28(3):285-96 Pubmed Journal

240. Clark RL. Teratogen update: Malaria in pregnancy and the use of antimalarial drugs in the first trimester. Birth defects research 2020;112(18):1403-1449 Pubmed Journal

241. Moore KA, Simpson JA, Scoullar MJL, McGready R, Fowkes FJI. Quantification of the association between malaria in pregnancy and stillbirth: a systematic review and meta-analysis. The Lancet. Global health 2017;5(11):e1101-e1112 Pubmed Journal

242. Saito M, McGready R, Titnto H, Rouamba T, Mosha D, Rulisa S, et al. Pregnancy outcomes after first-trimester treatment with artemisinin derivatives versus non-artemisinin antimalarials: a systematic review and individual patient data meta-analysis. The Lancet In Press 2022 . Journal

243. Dellicour S, Sevene E, McGready R, Tinto H, Mosha D, Manyando C, et al. First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-analysis of observational studies. PLoS medicine 2017;14(5):e1002290 Pubmed Journal

244. Mitchell AA. Special considerations in studies of drug induced birth defects. In: Strom BL, editor. Pharmacoepidemiology, 3rd edition. Chichester: Wiley 2000;749-763

245. Heinonen OP, Shapiro S, Slone D. Birth defects and drugs in pregnancy. Littleton: Publishing Sciences Group 1977.

246. PREGACT Study Group, Pekyi D, Ampromfi AA, Tinto H, Traoré-Coulibaly M, Tahita MC, et al. Four Artemisinin-Based Treatments in African Pregnant Women with Malaria. The New England journal of medicine 2016;374(10):913-27 Pubmed Journal

247. Pell C, Straus L, Andrew EVW, Meñaca A, Pool R. Social and cultural factors affecting uptake of interventions for malaria in pregnancy in Africa: a systematic review of the qualitative research. PloS one 2011;6(7):e22452 Pubmed Journal

248. Achan J, Talisuna AO, Erhart A, Yeka A, Tibenderana JK, Baliraine FN, et al. Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. Malaria journal 2011;10:144 Pubmed Journal

249. Adegnika AA, Breitling LP, Agnandji ST, Chai SK, Schütte D, Oyakhirome S, et al. Effectiveness of quinine monotherapy for the treatment of Plasmodium falciparum infection in pregnant women in Lambaréné, Gabon. The American journal of tropical medicine and hygiene 2005;73(2):263-6 Pubmed

250. Al Khaja KAJ, Sequeira RP. Drug treatment and prevention of malaria in pregnancy: a critical review of the guidelines. Malaria journal 2021;20(1):62 Pubmed Journal

251. Hill J, D'Mello-Guyett L, Hoyt J, van Eijk AM, ter Kuile FO, Webster J. Women's access and provider practices for the case management of malaria during pregnancy: a systematic review and meta-analysis. PLoS medicine 2014;11(8):e1001688 Pubmed Journal

252. Tests for glucose-6-phosphate dehydrogenase activity: target product profiles. Geneva: World Health Organization; 2022 Website

253. Riley C, Dellicour S, Ouma P, Kioko U, ter Kuile FO, Omar A, et al. Knowledge and Adherence to the National Guidelines for Malaria Case Management in Pregnancy among Healthcare Providers and Drug Outlet Dispensers in Rural, Western Kenya. PloS one 2016;11(1):e0145616 Pubmed Journal

254. Rao VB, Jensen TO, Jimenez BC, Robays JO, Lasry E, Sterk E, et al. Malaria in pregnancy: a call for a safe, efficient, and patient-centred approach to first-trimester treatment. The Lancet. Global health 2018;6(6):e607-e608 Pubmed Journal

255. Gething PW, Elyazar IRF, Moyes CL, Smith DL, Battle KE, Guerra CA, et al. A long neglected world malaria map: Plasmodium vivax endemicity in 2010. PLoS neglected tropical diseases 2012;6(9):e1814 Pubmed Journal

256. Mendis K, Sina BJ, Marchesini P, Carter R. The neglected burden of Plasmodium vivax malaria. The American journal of tropical medicine and hygiene 64(1-2 Suppl):97-106 Pubmed

257. Singh B, Kim Sung L, Matusop A, Radhakrishnan A, Shamsul SSG, Cox-Singh J, et al. A large focus of naturally acquired Plasmodium knowlesi infections in human beings. Lancet (London, England) 2004;363(9414):1017-24 Pubmed

258. Sutherland CJ, Tanomsing N, Nolder D, Oguike M, Jennison C, Pukrittayakamee S, et al. Two nonrecombining sympatric forms of the human malaria parasite Plasmodium ovale occur globally. The Journal of infectious diseases 2010;201(10):1544-50 Pubmed Journal

259. Douglas NM, Lampah DA, Kenangalem E, Simpson JA, Poespoprodjo JR, Sugiarto P, et al. Major burden of severe anemia from non-falciparum malaria species in Southern Papua: a hospital-based surveillance study. PLoS medicine 2013;10(12):e1001575; discussion e1001575 Pubmed Journal

260. Poespoprodjo JR, Fobia W, Kenangalem E, Lampah DA, Hasanuddin A, Warikar N, et al. Vivax malaria: a major cause of morbidity in early infancy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2009;48(12):1704-12 Pubmed Journal

261. Genton B, D'Acremont V, Rare L, Baea K, Reeder JC, Alpers MP, et al. Plasmodium vivax and mixed infections are associated with severe malaria in children: a prospective cohort study from Papua New Guinea. PLoS medicine 2008;5(6):e127 Pubmed Journal

262. Kochar DK, Das A, Kochar SK, Saxena V, Sirohi P, Garg S, et al. Severe Plasmodium vivax malaria: a report on serial cases from Bikaner in northwestern India. The American journal of tropical medicine and hygiene 2009;80(2):194-8 Pubmed

263. Alexandre MA, Ferreira CO, Siqueira AM, Magalhães BL, Mourão MPG, Lacerda MV, et al. Severe Plasmodium vivax malaria, Brazilian Amazon. Emerging infectious diseases 2010;16(10):1611-4 Pubmed Journal

264. Nosten F, McGready R, Simpson JA, Thwai KL, Balkan S, Cho T, et al. Effects of Plasmodium vivax malaria in pregnancy. Lancet (London, England) 1999;354(9178):546-9 Pubmed

265. William T, Menon J, Rajahram G, Chan L, Ma G, Donaldson S, et al. Severe Plasmodium knowlesi malaria in a tertiary care hospital, Sabah, Malaysia. Emerging infectious diseases 2011;17(7):1248-55 Pubmed Journal

266. Barber BE, William T, Grigg MJ, Menon J, Auburn S, Marfurt J, et al. A prospective comparative study of knowlesi, falciparum, and vivax malaria in Sabah, Malaysia: high proportion with severe disease from Plasmodium knowlesi and Plasmodium vivax but no mortality with early referral and artesunate therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;56(3):383-97 Pubmed Journal

267. Grigg MJ, William T, Barber BE, Parameswaran U, Bird E, Piera K, et al. Combining parasite lactate dehydrogenase-based and histidine-rich protein 2-based rapid tests to improve specificity for diagnosis of malaria Due to Plasmodium knowlesi and other Plasmodium species in Sabah, Malaysia. Journal of clinical microbiology 2014;52(6):2053-60 Pubmed Journal

268. Gogtay N, Kannan S, Thatte UM, Olliaro PL, Sinclair D. Artemisinin-based combination therapy for treating uncomplicated Plasmodium vivax malaria. The Cochrane database of systematic reviews 2013;(10):CD008492 Pubmed Journal

269. Testing for G6PD deficiency for safe use of primaquine in radical cure of P. vivax and P. ovale (Policy brief). Geneva: World Health Organization 2016. Website

270. Guide to G6PD deficiency rapid diagnostic testing to support P. vivax radical cure. World Health Organization, Geneva 2018. Website

271. WHO Scientific Group on the Standardization of Procedures for the Study of Glucose-6-Phosphate Dehydrogenase & World Health Organization. Standardization of procedures for the study of glucose-6-phosphate dehydrogenase : report of a WHO Scientific Group [meeting held in Geneva from 5 to 10 December 1966]. Geneva: World Health Organization, 1967 Website

272. Rodrigo C, Rajapakse S, Fernando D. Tafenoquine for preventing relapse in people with Plasmodium vivax malaria. The Cochrane database of systematic reviews 2020;9(9):CD010458 Pubmed Journal

273. Llanos-Cuentas A, Lacerda MVG, Hien TT, Vélez ID, Namaik-Larp C, Chu CS, et al. Tafenoquine versus Primaquine to Prevent Relapse of Plasmodium vivax Malaria. The New England journal of medicine 2019;380(3):229-241 Pubmed Journal

274. Price DJ, Nekkab N, Monteiro WM, Villela DAM, Simpson JA, Lacerda MVG, et al. Tafenoquine following G6PD screening versus primaquine for the treatment of vivax malaria in Brazil: A cost-effectiveness analysis using a transmission model. PLoS medicine 2024;21(1):e1004255 Pubmed Journal

275. Brito M, Rufatto R, Murta F, Sampaio V, Balieiro P, Baía-Silva D, et al. Operational feasibility of Plasmodium vivax radical cure with tafenoquine or primaquine following point-of-care, quantitative glucose-6-phosphate dehydrogenase testing in the Brazilian Amazon: a real-life retrospective analysis. The Lancet. Global health 2024;12(3):e467-e477 Pubmed Journal

276. Commons RJ, Rajasekhar M, Edler P, Abreha T, Awab GR, Baird JK, et al. Effect of primaquine dose on the risk of recurrence in patients with uncomplicated Plasmodium vivax: a systematic review and individual patient data meta-analysis. The Lancet. Infectious diseases 2024;24(2):172-183 Pubmed Journal

277. Verma R, Commons RJ, Gupta A, Rahi M, Nitika, Bharti PK, et al. Safety and efficacy of primaquine in patients with Plasmodium vivax malaria from South Asia: a systematic review and individual patient data meta-analysis. BMJ global health 2023;8(12) Pubmed Journal

278. Mehdipour P, Rajasekhar M, Dini S, Zaloumis S, Abreha T, Adam I, et al. Effect of adherence to primaquine on the risk of Plasmodium vivax recurrence: a WorldWide Antimalarial Resistance Network systematic review and individual patient data meta-analysis. Malaria journal 2023;22(1):306 Pubmed Journal

279. Devine A, Battle KE, Meagher N, Howes RE, Dini S, Gething PW, et al. Global economic costs due to vivax malaria and the potential impact of its radical cure: A modelling study. PLoS medicine 2021;18(6):e1003614 Pubmed Journal

280. Rajasekhar M, Simpson JA, Ley B, Edler P, Chu CS, Abreha T, et al. Primaquine dose and the risk of haemolysis in patients with uncomplicated Plasmodium vivax malaria: a systematic review and individual patient data meta-analysis. The Lancet. Infectious diseases 2024;24(2):184-195 Pubmed Journal

281. Galappaththy GNL, Tharyan P, Kirubakaran R. Primaquine for preventing relapse in people with Plasmodium vivax malaria treated with chloroquine. The Cochrane database of systematic reviews 2013;(10):CD004389 Pubmed Journal

282. Milligan R, Daher A, Villanueva G, Bergman H, Graves P. Primaquine alternative dosing schedules for preventing malaria relapse in people with Plasmodium vivax. Cochrane Database Syst Rev 2020. Pubmed Journal

283. Commons RJ, Simpson JA, Thriemer K, Chu CS, Douglas NM, Abreha T, et al. The haematological consequences of Plasmodium vivax malaria after chloroquine treatment with and without primaquine: a WorldWide Antimalarial Resistance Network systematic review and individual patient data meta-analysis. BMC medicine 2019;17(1):151 Pubmed Journal

284. Radeva-Petrova D, Kayentao K, ter Kuile FO, Sinclair D, Garner P. Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment. The Cochrane database of systematic reviews 2014;(10):CD000169 Pubmed Journal

285. Information note on delayed haemolytic anaemia following treatment with artesunate. Geneva: World Health Organization 2013. Website

286. Sinclair D, Donegan S, Isba R, Lalloo DG. Artesunate versus quinine for treating severe malaria. The Cochrane database of systematic reviews 2012;(6):CD005967 Pubmed Journal

287. Pre-referral treatment with rectal artesunate of children with suspected severe malaria: a field guide. Geneva: World Health Organization Website

288. Hendriksen ICE, Mtove G, Kent A, Gesase S, Reyburn H, Lemnge MM, et al. Population pharmacokinetics of intramuscular artesunate in African children with severe malaria: implications for a practical dosing regimen. Clinical pharmacology and therapeutics 2013;93(5):443-50 Pubmed Journal

289. Zaloumis SG, Tarning J, Krishna S, Price RN, White NJ, Davis TME, et al. Population pharmacokinetics of intravenous artesunate: a pooled analysis of individual data from patients with severe malaria. CPT: pharmacometrics & systems pharmacology 2014;3:e145 Pubmed Journal

290. Esu E, Effa EE, Opie ON, Uwaoma A, Meremikwu MM. Artemether for severe malaria. The Cochrane database of systematic reviews 2014;(9):CD010678 Pubmed Journal

291. Okebe J, Eisenhut M. Pre-referral rectal artesunate for severe malaria. The Cochrane database of systematic reviews 2014;(5):CD009964 Pubmed Journal

292. The use of rectal artesunate as a pre-referral treatment for severe Plasmodium falciparum malaria, 2023 update. Geneva: World Health Organization, 2023 Website

293. Management of severe malaria - A practical handbook, 3rd edition. Geneva: World Health Organization 2013. Website

294. Prequalification programme: A United Nations programme managed by WHO. Geneva: World Health Organization 2009. Website

295. Methods for surveillance of antimalarial drug efficacy. Geneva: World Health Organization 2009. Website

296. Methods and techniques for clinical trials on antimalarial drug efficacy: Genotyping to identify parasite populations. World Health Organization, Geneva 2008. Website

297. Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010-2019). Geneva: World Health Organization 2020. Website

298. Ajayi IO, Browne EN, Bateganya F, Yar D, Happi C, Falade CO, et al. Effectiveness of artemisinin-based combination therapy used in the context of home management of malaria: a report from three study sites in sub-Saharan Africa. Malaria journal 2008;7:190 Pubmed Journal

299. A practical handbook on the pharmacovigilance of antimalarial medicines. Geneva: World Health Organization 2008. Website

300. Stresman G, Whittaker C, Slater HC, Bousema T, Cook J. Quantifying Plasmodium falciparum infections clustering within households

to inform household-based intervention strategies for malaria control programs: An observational study and meta-analysis from 41 malaria-endemic countries. PLoS medicine 2020;17(10):e1003370 Pubmed Journal

301. Sandfort M, Vantaux A, Kim S, Obadia T, Pepey A, Gardais S, et al. Forest malaria in Cambodia: the occupational and spatial clustering of Plasmodium vivax and Plasmodium falciparum infection risk in a cross-sectional survey in Mondulkiri province, Cambodia. Malaria journal 2020;19(1):413 Pubmed Journal

302. Smith C, Whittaker M. Malaria elimination without stigmatization: a note of caution about the use of terminology in elimination settings. Malaria journal 2014;13:377 Pubmed Journal

303. International health regulations (2005) - 3rd ed. Geneva: World Health Organization 2016. Website

304. Communicable disease surveillance and response systems: guide to monitoring and evaluating. Geneva: World Health Organization 2006. Website

305. WHO technical brief for countries preparing malaria funding requests for the Global Fund (2020-2022). Geneva: World Health Organization 2020. Website

306. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. [GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction]. Gaceta sanitaria 32(2):166.e1-166.e10 Pubmed Journal

307. GRADE Handbook: Introduction to GRADE Handbook. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group 2013. Website

308. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2020;192(32):E901-E906 Pubmed Journal

309. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. Journal of clinical epidemiology 2020;119:126-135 Pubmed Journal

310. Meeting of Strategic Advisory Group of Experts on Immunization, October 2021: conclusions and recommendations. Weekly Epidemiological Record 2021;96(50):613-632 Website

311. 20th meeting of the Malaria Policy Advisory Group (MPAG). Geneva: World Health Organization 2021. Website

312. WHO malaria terminology, 2021 update. Geneva: World Health Organization 2021. Website

313. Domingo GJ, Satyagraha AW, Anvikar A, Baird K, Bancone G, Bansil P, et al. G6PD testing in support of treatment and elimination of malaria: recommendations for evaluation of G6PD tests. Malaria journal 2013;12:391 Pubmed Journal

Annex: All evidence profiles, sorted by sections

1. Abbreviations

2. Executive summary

2.1. Guideline translations

3. Introduction

4. Prevention

4.1. Vector control

4.1.1. Interventions recommended for large-scale deployment

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Pyrethroid-only nets or curtains

Comparator: No nets or curtains

Summary

Of the 23 included studies, 21 were cluster RCTs (six with households as the cluster and 15 with villages as the cluster) and two were individual RCTs; 12 studies compared ITNs with untreated nets, and 11 studies compared ITNs with no nets. Based on WHO regions, 12 studies were conducted in Africa (Burkina Faso, Côte d'Ivoire, Cameroon, Gambia [two studies], Ghana, Kenya [three studies], Madagascar, Sierra Leone and the United Republic of Tanzania), six in the Americas (Venezuela [Bolivarian Republic of], Colombia, Ecuador, Nicaragua and Peru [two studies]), four in South-East Asia (India, Myanmar, Thailand [two studies]) and one in the Eastern Mediterranean (Pakistan).

Pyrethroid-only nets or curtains versus no ITNs or curtains:
Pyrethroid-only nets or curtains reduce the child mortality from all causes compared to no nets or curtains.
(Rate ratio: 0.83; 95% CI: 0.77–0.89; five studies; high-certainty evidence)
Pyrethroid-only nets or curtains reduce the incidence of uncomplicated episodes of *P. falciparum* malaria compared to no nets or curtains.
(Rate ratio: 0.54; 95% CI: 0.48–0.60; five studies; high-certainty evidence)
Pyrethroid-only nets or curtains reduce the prevalence of *P. falciparum* malaria compared to no nets or curtains
(Rate ratio: 0.69; 95% CI: 0.54–0.89; five studies; high-certainty evidence)
Pyrethroid-only nets or curtains probably reduce the incidence of uncomplicated episodes of *P. vivax* malaria compared to no nets or curtains.
(Rate ratio: 0.61 95% CI 0.48 - 0.77, two studies, moderate-certainty evidence)
Pyrethroid-only nets or curtains may have little or no effect on *P. vivax* prevalence malaria compared to no nets or curtains.
(Risk ratio: 1.00; 95% CI: 0.75–1.34; two studies; low-certainty evidence)
Pyrethroid-only nets or curtains reduce the incidence of severe malaria episodes compared to no nets or curtains.
(Rate ratio: 0.56; 95% CI: 0.38–0.82; two studies; high-certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** No nets or curtains	**Intervention** Pyrethroid-treated nets or curtains	**Certainty of the evidence** (Quality of evidence)	**Summary**
Child all-cause mortality	Relative risk 0.83 (CI 95% 0.77 — 0.89) Based on data from 129,714 participants in 5 studies. (Randomized controlled)	33 per 1000 Difference:	27 per 1000 **6 fewer per 1000** (CI 95% 8 fewer — 4 fewer)	High	Pyrethroid-only nets or curtains reduce the child mortality from all causes compared to no nets or curtains.
P. falciparum uncomplicated episodes (incidence)	Relative risk 0.54 (CI 95% 0.48 — 0.6) Based on data from 32,699 participants in 5 studies. (Randomized controlled)	178 per 1000 Difference:	96 per 1000 **82 fewer per 1000** (CI 95% 93 fewer — 71 fewer)	High	Pyrethroid-only nets or curtains reduce the incidence of uncomplicated episodes of P. falciparum malaria compared to no nets or curtains.
P. falciparum uncomplicated episodes	Relative risk 0.44 (CI 95% 0.31 — 0.62) Based on data from 10,964 participants in 2	137 per 1000	60 per 1000	Moderate Due to serious indirectness [1]	Pyrethroid-only nets or curtains probably reduce the incidence of uncomplicated episodes of

Outcome Timeframe	**Study results and measurements**	**Comparator** No nets or curtains	**Intervention** Pyrethroid-treated nets or curtains	**Certainty of the evidence** (Quality of evidence)	**Summary**
(cumulative incidence)	studies. (Randomized controlled)	Difference:	**77 fewer per 1000** (CI 95% 95 fewer — 52 fewer)		P. falciparum malaria compared to no nets or curtains.
P. falciparum prevalence	Relative risk 0.69 (CI 95% 0.54 — 0.89) Based on data from 17,860 participants in 5 studies. (Randomized controlled)	120 per 1000 Difference:	83 per 1000 **37 fewer per 1000** (CI 95% 55 fewer — 13 fewer)	High	Pyrethroid-only nets or curtains reduce the prevalence of P. falciparum malaria compared to no nets or curtains.
P. vivax uncomplicated episodes (cumulative incidence)	Relative risk 0.61 (CI 95% 0.48 — 0.77) Based on data from 10,972 participants in 2 studies. (Randomized controlled)	149 per 1000 Difference:	91 per 1000 **58 fewer per 1000** (CI 95% 77 fewer — 34 fewer)	Moderate Due to serious indirectness [2]	Pyrethroid-only nets or curtains probably reduce the incidence of uncomplicated episodes of P. vivax malaria compared to no nets or curtains.
P. vivax prevalence	Relative risk 1 (CI 95% 0.75 — 1.34) Based on data from 9,900 participants in 2 studies. (Randomized controlled)	130 per 1000 Difference:	130 per 1000 **0 fewer per 1000** (CI 95% 32 fewer — 44 more)	Low Due to serious indirectness and serious imprecision [3]	Pyrethroid-only nets or curtains may have little or no effect on P. vivax prevalence malaria compared to no nets or curtains.
Any Plasmodium spp. uncomplicated episodes (incidence)	Relative risk 0.5 (CI 95% 0.28 — 0.9) Based on data from 5,512 participants in 1 studies. (Randomized controlled)	256 per 1000 Difference:	128 per 1000 **128 fewer per 1000** (CI 95% 184 fewer — 26 fewer)	Low Due to very serious indirectness [4]	Pyrethroid-only nets or curtains probably reduce the incidence of uncomplicated episodes of malaria compared to no nets or curtains.
Severe malaria episodes	Relative risk 0.56 (CI 95% 0.38 — 0.82) Based on data from 31,173 participants in 2 studies. (Randomized controlled)	15 per 1000 Difference:	8 per 1000 **7 fewer per 1000** (CI 95% 9 fewer — 3 fewer)	High	Pyrethroid-only nets or curtains reduce the incidence of severe malaria episodes compared to no nets or curtains.

1, 2. **Inconsistency: no serious. Indirectness: serious. Imprecision: no serious. Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: serious. Imprecision: serious. Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: very serious. Imprecision: no serious. Publication bias: no serious.**

References

59. Pryce J, Richardson M, Lengeler C. Insecticide-treated nets for preventing malaria. Cochrane Database of Systematic Reviews 2018.(11) Pubmed Journal Website

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Pyrethroid-only nets or curtains

Comparator: Untreated nets or curtains

Summary

Of the 23 included studies, 21 were cluster RCTs (six with households as the cluster and 15 with villages as the cluster) and two were individual RCTs; 12 studies compared ITNs with untreated nets, and 11 studies compared ITNs with no nets. Based on WHO regions, 12 studies were conducted in Africa (Burkina Faso, Côte d'Ivoire, Cameroon, Gambia (two studies), Ghana, Kenya (three studies), Madagascar, Sierra Leone, United Republic of Tanzania), six in the Americas (Colombia, Ecuador, Nicaragua (two studies), Peru and Venezuela [Bolivarian Republic of]) and four in South-East Asia (India, Myanmar, Thailand [two studies]) and one in the Eastern Mediterranean (Pakistan).

Pyrethroid-only nets or curtains versus untreated nets or curtains:
Pyrethroid-only nets or curtains probably reduce all-cause child mortality compared to untreated nets or curtains.
(Rate ratio: 0.67; 95% CI (0.36–1.23); two studies; moderate certainty evidence)
Pyrethroid-only nets or curtains reduce the incidence of uncomplicated *P. falciparum* malaria episodes compared to untreated nets or curtains.
(Rate ratio: 0.58; 95% CI (0.43–0.79); five studies; high certainty evidence)
Pyrethroid-only nets or curtains reduce the prevalence of *P. falciparum* malaria compared to untreated nets or curtains.
(Risk ratio: 0.81; 95% CI (0.68–0.97); four studies; high certainty evidence)
Pyrethroid-only nets or curtains may reduce the incidence of uncomplicated *P. vivax* malaria episodes compared to untreated nets or curtains.
(Rate ratio: 0.73; 95% CI (0.51–1.05); three studies; low certainty evidence)
he evidence is very uncertain about the effect of pyrethroid-only nets or curtains on *P. vivax* prevalence compared to untreated nets or curtains.
(Risk ratio: 0.52; 95% CI (0.13–2.04); two studies; very low certainty evidence)

Note: The panel reviewed an earlier report of the systematic review at the time of the meeting where figures varied slightly to those published in the final summary of findings tables. However, the interpretation of the findings and certainty of evidence were no different.

Outcome Timeframe	**Study results and measurements**	**Comparator** Untreated nets or curtains	**Intervention** Pyrethroid-only nets or curtains	**Certainty of the evidence** (Quality of evidence)	**Summary**
All-cause mortality	Relative risk 0.67 (CI 95% 0.36 — 1.23) Based on data from 32,721 participants in 2 studies. (Randomized controlled)	19 per 1000 Difference:	13 per 1000 **6 fewer per 1000** (CI 95% 12 fewer — 4 more)	Moderate Due to serious imprecision [1]	Pyrethroid-only nets or curtains probably reduce all-cause child mortality compared to untreated nets or curtains.
P. falciparum uncomplicated episodes	Relative risk 0.58 (CI 95% 0.43 — 0.79) Based on data from 2,084 participants in 5 studies. (Randomized controlled)	180 per 1000 Difference:	104 per 1000 **76 fewer per 1000** (CI 95% 103 fewer — 38 fewer)	High	Pyrethroid-only nets or curtains reduce the incidence of uncomplicated P. falciparum malaria episodes compared to untreated nets or curtains.
P. falciparum prevalence	Relative risk 0.81 (CI 95% 0.68 — 0.97) Based on data from 300 participants in 4 studies. (Randomized controlled)	85 per 1000 Difference:	69 per 1000 **16 fewer per 1000** (CI 95% 27 fewer — 3 fewer)	High	Pyrethroid-only nets or curtains reduce the prevalence of P. falciparum malaria compared to untreated nets or curtains.

Outcome Timeframe	**Study results and measurements**	**Comparator** Untreated nets or curtains	**Intervention** Pyrethroid-only nets or curtains	**Certainty of the evidence** (Quality of evidence)	**Summary**
P. vivax uncomplicated episodes	Relative risk 0.73 (CI 95% 0.51 — 1.05) Based on data from 1,771 participants in 3 studies. (Randomized controlled)	143 per 1000 Difference:	104 per 1000 **39 fewer per 1000** (CI 95% 70 fewer — 7 more)	Low Due to serious indirectness, Due to serious imprecision [2]	Pyrethroid-only nets or curtains may reduce the incidence of uncomplicated P. vivax malaria episodes compared to untreated nets or curtains.
P. vivax uncomplicated episodes (cumulative incidence)	Relative risk 0.58 (CI 95% 0.3 — 1.14) Based on data from 17,910 participants in 3 studies. (Randomized controlled)	168 per 1000 Difference:	97 per 1000 **71 fewer per 1000** (CI 95% 118 fewer — 23 more)	Low Due to serious imprecision, Due to serious inconsistency [3]	Pyrethroid-only nets or curtains may reduce the incidence of uncomplicated P. vivax malaria episodes compared to untreated nets or curtains.
P. vivax prevalence	Relative risk 0.52 (CI 95% 0.13 — 2.04) Based on data from 300 participants in 1 studies. (Randomized controlled)	85 per 1000 Difference:	44 per 1000 **41 fewer per 1000** (CI 95% 74 fewer — 88 more)	Very low Due to very serious imprecision, Due to very serious indirectness [4]	The evidence is very uncertain about the effect of pyrethroid-only nets or curtains on P. vivax prevalence compared to untreated nets or curtains.
Any Plasmodium spp. uncomplicated episodes (cumulative incidence)	Relative risk 0.47 (CI 95% 0.17 — 1.28) Based on data from 7,082 participants in 2 studies. (Randomized controlled)	69 per 1000 Difference:	32 per 1000 **37 fewer per 1000** (CI 95% 57 fewer — 19 more)	Moderate Due to serious imprecision [5]	Pyrethroid-only nets or curtains probably reduce the incidence of uncomplicated malaria episodes compared to untreated nets or curtains.
Any Plasmodium spp. prevalence	Relative risk 0.17 (CI 95% 0.05 — 0.53) Based on data from 691 participants in 1 studies. (Randomized controlled)	104 per 1000 Difference:	18 per 1000 **86 fewer per 1000** (CI 95% 99 fewer — 49 fewer)	Very low Due to serious imprecision, Due to very serious indirectness [6]	The evidence is very uncertain about the effect of pyrethroid-only nets or curtains on Plasmodium prevalence compared to untreated nets or curtains.

1, 5. **Imprecision: serious.**
2. **Indirectness: serious. Imprecision: serious.**
3. **Inconsistency: serious. Imprecision: serious.**
4. **Indirectness: very serious. Imprecision: very serious.**
6. **Indirectness: very serious. Imprecision: serious.**

References

59. Pryce J, Richardson M, Lengeler C. Insecticide-treated nets for preventing malaria. Cochrane Database of Systematic Reviews 2018.(11) Pubmed Journal Website

Clinical question/ PICO

Population: Adults and children in areas with ongoing malaria transmission and high insecticide resistance

Intervention: ITNs treated with both piperonyl butoxide (PBO) and pyrethroid

Comparator: ITNs treated with pyrethroid only

Summary

Two cRCTs from Uganda and the United Republic of Tanzania were included in the review.

Pyrethroid-PBO ITNs versus pyrethroid-only LLINs:
Pyrethroid-PBO ITNs reduce malaria parasite prevalence at 4- to 6-month follow-up compared to pyrethroid-only LLINs.
(Odds ratio:0.74; 95% CI (0.62 to 0.89); two studies; high certainty evidence)
Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence at 9- to 12-month follow-up compared to pyrethroid-only LLINs.
(Odds ratio: 0.72; 95% CI (0.61–0.86); two studies; moderate certainty evidence)
Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence at 16- to 18-month follow-up compared to pyrethroid-only LLINs
(Odds ratio: 0.88; 95% CI (0.74–1.04); two studies; moderate certainty evidence)
Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence at 21- to 25-month follow-up compared to pyrethroid-only LLINs
(Odds ratio:0.79; 95% CI (0.67 to 0.95); two studies; moderate certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only LLINs	**Intervention** Pyrethroid-PBO ITNs	**Certainty of the evidence** (Quality of evidence)	**Summary**
Parasite prevalence - 4 to 6 months	Odds ratio 0.74 (CI 95% 0.62 — 0.89) Based on data from 11,582 participants in 2 studies. (Randomized controlled)	254 per 1000 Difference:	201 per 1000 **53 fewer per 1000** (CI 95% 80 fewer — 21 fewer)	High	Pyrethroid-PBO ITNs reduce malaria parasite prevalence in areas of high insecticide resistance at 4- to 6-month follow-up compared to pyrethroid-only LLINs.
Parasite prevalence - 9 to 12 months	Odds ratio 0.72 (CI 95% 0.61 — 0.86) Based on data from 11,370 participants in 2 studies. (Randomized controlled)	224 per 1000 Difference:	172 per 1000 **52 fewer per 1000** (CI 95% 74 fewer — 25 fewer)	Moderate Due to serious inconsistency [1]	Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence in areas of high insecticide resistance at 9- to 12-month follow-up compared to pyrethroid-only LLINs.
Parasite prevalence - 16 to 18 months	Odds ratio 0.88 (CI 95% 0.74 — 1.04) Based on data from 11,822 participants in 2 studies. (Randomized controlled)	248 per 1000 Difference:	225 per 1000 **23 fewer per 1000** (CI 95% 52 fewer — 7 more)	Moderate Due to serious inconsistency [2]	Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence in areas of high insecticide resistance at 16- to 18-month follow-up compared to pyrethroid-only LLINs.
Parasite prevalence - 21 to 25 months	Odds ratio 0.79 (CI 95% 0.67 — 0.95) Based on data from 10,603 participants in 2 studies. (Randomized controlled)	350 per 1000 Difference:	298 per 1000 **52 fewer per 1000** (CI 95% 85 fewer — 12 fewer)	Moderate Due to serious inconsistency [3]	Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence in areas of high insecticide resistance at 21- to 25-month follow-up compared to pyrethroid-only LLINs.

1, 2, 3. **Inconsistency: serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

References

63. Gleave K, Lissenden N, Richardson M, Choi L, Ranson H. Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. The Cochrane Database of Systematic Reviews 2021;5:CD012776 Pubmed Journal

Clinical question/ PICO

Population: Adults and children in areas with ongoing malaria transmission and high insecticide resistance

Intervention: ITNs treated with both piperonyl butoxide (PBO) and pyrethroid

Comparator: ITNs treated with pyrethroid only

Summary

Ten experimental hut trials from Benin, Burkina Faso, Cameroon, Côte d'Ivoire and United Republic of Tanzania were included in the review.

Pyrethroid-PBO ITNs vs pyrethroid-only LLINs
In highly pyrethroid-resistant areas:
Mosquito mortality is higher with unwashed pyrethroid-PBO ITNs compared to unwashed pyrethroid-only LLINs (Risk ratio: 1.84; 95% CI: 1.60–2.11; five trials; high-certainty evidence)
It is not known if mosquito mortality is higher with washed pyrethroid-PBO ITNs compared to washed pyrethroid-only LLINs (Risk ratio: 1.20; 95% CI: 0.88–1.63; four trials, very low-certainty evidence)
Blood-feeding success is decreased with unwashed pyrethroid-PBO ITNs compared to unwashed pyrethroid-only LLINs (Risk ratio: 0.60; 95% CI: 0.50–0.71; four trials, high-certainty evidence)
Blood-feeding success is decreased with washed pyrethroid-PBO ITNs compared to washed pyrethroid-only LLINs (Risk ratio: 0.81; 95% CI: 0.72–0.92; three trials; high-certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only LLINs	**Intervention** Pyrethroid-PBO ITNs	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mosquito mortality - Unwashed nets	Relative risk 1.84 (CI 95% 1.6 — 2.11) Based on data from 4,896 participants in studies. [1]	238 per 1000 Difference:	438 per 1000 **200 more per 1000** (CI 95% 143 more — 264 more)	High Not downgraded for imprecision: both best- and worst-case scenarios in this situation are important effects	Unwashed pyrethroid-PBO ITNs results in higher mosquito mortality with unwashed pyrethroid-PBO ITNs compared to unwashed pyrethroid-only LLINs .
Mosquito mortality - Washed nets	Relative risk 1.2 (CI 95% 0.88 — 1.63) Based on data from 3,101 participants in studies. [2]	201 per 1000 Difference:	242 per 1000 **40 more per 1000** (CI 95% 24 fewer — 127 more)	Very low Due to imprecision and inconsistency	The evidence is very uncertain about the effect of washed pyrethroid-PBO ITNs on mosquito mortality compared to washed pyrethroid-only LLINs
Mosquito blood-feeding success - Unwashed nets	Relative risk 0.6 (CI 95% 0.5 — 0.71) Based on data from 4,458 participants in studies. [3]	438 per 1000 Difference:	263 per 1000 **175 fewer per 1000** (CI 95% 219 fewer — 127 fewer)	High	Unwashed pyrethroid-PBO ITNs results in lower mosquito blood-feeding success compared to unwashed pyrethroid-only LLINs.
Mosquito blood-feeding success - Washed nets	Relative risk 0.81 (CI 95% 0.72 — 0.92) Based on data from 2,676 participants in studies. [4]	494 per 1000 Difference:	400 per 1000 **94 fewer per 1000** (CI 95% 138 fewer — 40 fewer)	High	Washed pyrethroid-PBO ITNs results in lower mosquito blood-feeding success compared to washed pyrethroid-only LLINs.

1, 2, 3, 4. Systematic review [63]

References

63. Gleave K, Lissenden N, Richardson M, Choi L, Ranson H. Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. The Cochrane Database of Systematic Reviews 2021;5:CD012776 Pubmed Journal

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Pyrethroid-chlorfenapyr ITNs for prevention of malaria

Comparator: Pyrethroid-only ITNs for prevention of malaria

Summary

The systematic review [Barker *et al unpublished evidence*] included two RCTs, one from Benin *[66]* and one from the United Republic of Tanzania *[64]* that compared the epidemiological impact against malaria of pyrethroid-chlorfenapyr ITNs (alphacypermethrin-chlorfenapyr) against pyrethroid-only LLINs (alphacypermethrin). Both trials were conducted in areas of high malaria transmission and pyrethroid-resistance. The review provided high to moderate certainty evidence that incidence of clinical malaria was lower in areas where pyrethroid-chlorfenapyr ITNs were deployed than in those with pyrethroid-only LLINs, at one and two years after ITN deployment (one-year incidence rate ratio (IRR): 0.44; 95% CI: 0.37–0.52; two-year IRR: 0.57; 95% CI: 0.51–0.63). The review also provided high certainty evidence that prevalence of malaria infection was lower where pyrethroid-chlorfenapyr ITNs were deployed than in those with pyrethroid-only LLINs, at several time points after ITN deployment (six-month relative risk (RR): 0.50; 95% CI: 0.43–0.59; 12-month RR: 0.78; 95% CI: 0.72–0.85; 18-month RR: 075; 95% CI: 0.70–0.80; 24-month RR: 0.56; 95% CI: 0.50–0.63).

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only ITNs	**Intervention** Pyrethroid-chlorfenapyr ITNs	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria case incidence (overall)	Rate ratio 0.72 (CI 95% 0.67 — 0.78) Based on data from 61,183 participants in 2 studies. (Randomized controlled)	678 per 1000 Difference:	487 per 1000 **190 fewer per 1000** (CI 95% 224 fewer — 149 fewer)	Moderate Due to serious inconsistency [1]	2000-person years (2 RCTs) Length of time observed: <1 month to 24 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Malaria case incidence (1-year post-intervention)	Rate ratio 0.44 (CI 95% 0.37 — 0.52) Based on data from 61,183 participants in 2 studies. (Randomized controlled)	487 per 1000 Difference:	213 per 1000 **272 fewer per 1000** (CI 95% 307 fewer — 234 fewer)	High	2000-person years (2 RCTs) Length of time observed: <1 month to 12 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Malaria case incidence (2-years post-intervention)	Rate ratio 0.57 (CI 95% 0.51 — 0.63) Based on data from 61,183 participants in 2 studies.	815 per 1000 Difference:	465 per 1000 **351 fewer per 1000** (CI 95% 400 fewer — 302 fewer)	High	2000 (2 RCTs) Length of time observed: 12 months to 24 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Parasite prevalence (6-months follow-up)	Relative risk 0.5 (CI 95% 0.43 — 0.59) Based on data from 2,249 participants in 1 studies. (Randomized controlled)	312 per 1000 Difference:	156 per 1000 **156 fewer per 1000** (CI 95% 178 fewer — 128 fewer)	High	

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only ITNs	**Intervention** Pyrethroid-chlorfenapyr ITNs	**Certainty of the evidence** (Quality of evidence)	**Summary**
Parasite prevalence (12-months follow-up)	Relative risk 0.78 (CI 95% 0.72 — 0.85) Based on data from 2,473 participants in 1 studies. (Randomized controlled)	523 per 1000 Difference:	409 per 1000 **115 fewer per 1000** (CI 95% 147 fewer — 78 fewer)	High	
Parasite prevalence (18-months follow-up)	Relative risk 0.75 (CI 95% 0.7 — 0.85) Based on data from 5,445 participants in 2 studies. (Randomized controlled)	448 per 1000 Difference:	338 per 1000 **112 fewer per 1000** (CI 95% 135 fewer — 90 fewer)	High	
Parasite prevalence (24-months follow-up)	Relative risk 0.56 (CI 95% 0.5 — 0.63) Based on data from 2,471 participants in 1 studies. (Randomized controlled)	458 per 1000 Difference:	256 per 1000 **201 fewer per 1000** (CI 95% 229 fewer — 169 fewer)	High	

1. **Inconsistency: serious.** Point estimates vary widely (from 0.49 to 0.87 with no overlap of confidence intervals). This heterogeneity appears to be unexplained but important (chi2, p <0.0001, I2 = 98%). But may not impact on a recommendation for the intervention. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

References

64. Mosha JF, Kulkarni MA, Lukole E, Matowo NS, Pitt C, Messenger LA, et al. Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial. Lancet (London, England) 2022;399(10331):1227-1241 Pubmed Journal

66. Accrombessi M, Cook J, Dangbenon E, Yovogan B, Akpovi H, Sovi A, et al. Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets (LLINs) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial. Lancet (London, England) 2023;401(10375):435-446 Pubmed Journal

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Pyrethroid-chlorfenapyr ITNs for prevention of malaria

Comparator: Pyrethroid-PBO ITNs for prevention of malaria

Summary

The review [Barker *et al unpublished evidence*] compared the epidemiological impact against malaria of pyrethroid-chlorfenapyr ITNs against pyrethroid-PBO ITNs (permethrin-piperonyl butoxide), based on one RCT *[64]* in the United Republic of Tanzania. The review provided high to low certainty evidence that incidence of clinical malaria was lower in areas where pyrethroid-chlorfenapyr ITNs were deployed than in those with pyrethroid-PBO ITNs, at two years after ITN deployment, but possibly not at one year post-deployment (one-year IRR: 0.98; 95% CI: 0.71–1.36; two-year IRR: 0.65; 95% CI: 0.55–0.77). The review also provided high to moderate certainty evidence that prevalence of malaria infection was generally

lower where pyrethroid-chlorfenapyr ITNs were deployed, compared to those with pyrethroid-only LLINs, at several time points after ITN deployment (12-month RR: 0.81; 95% CI: 0.68–0.98; 18-month RR: 0.94; 95% CI: 0.86–1.04; 24-month RR: 0.63; 95% CI: 0.56–0.71).

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-PBO nets for prevention of malaria	**Intervention** Pyrethroid-chlorfenapyr nets for prevention of malaria	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria case incidence (overall)	Rate ratio 0.68 (CI 95% 0.59 — 0.79) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	333 per 1000 Difference:	227 per 1000 **107 fewer per 1000** (CI 95% 137 fewer — 70 fewer)	High	2000-person years (1 RCT) Length of time observed: <1 month to 24 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Malaria case incidence (1-year post-intervention)	Rate ratio 0.98 (CI 95% 0.71 — 1.36) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	133 per 1000 Difference:	131 per 1000 **3 fewer per 1000** (CI 95% 39 fewer — 48 more)	Low Due to very serious imprecision [1]	2000-person years (1 RCT) Length of time observed: <1 month to 12 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Malaria case incidence (2-years post-intervention)	Rate ratio 0.65 (CI 95% 0.55 — 0.77) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	483 per 1000 Difference:	315 per 1000 **155 fewer per 1000** (CI 95% 198 fewer — 101 fewer)	High	2000-person years (1 RCT) Length of time observed: 12 months to 24 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Parasite prevalence (12-months follow-up)	Relative risk 0.81 (CI 95% 0.68 — 0.98) Based on data from 2,197 participants in 1 studies. (Randomized controlled)	192 per 1000 Difference:	156 per 1000 **37 fewer per 1000** (CI 95% 62 fewer — 4 fewer)	Moderate Due to serious imprecision [2]	
Parasite prevalence (18-months follow up)	Relative risk 0.94 (CI 95% 0.86 — 1.04) Based on data from 2,406 participants in 1 studies. (Randomized controlled)	433 per 1000 Difference:	409 per 1000 **26 fewer per 1000** (CI 95% 61 fewer — 17 more)	Moderate Due to serious imprecision [3]	
Parasite prevalence	Relative risk 0.63 (CI 95% 0.56 — 0.71)	407 per 1000	256 per 1000	High	

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-PBO nets for prevention of malaria	**Intervention** Pyrethroid-chlorfenapyr nets for prevention of malaria	**Certainty of the evidence** (Quality of evidence)	**Summary**
(24-months follow-up)	Based on data from 2,531 participants in 1 studies. (Randomized controlled)	Difference:	**150 fewer per 1000** (CI 95% 179 fewer — 118 fewer)		

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Confidence intervals are very wide (39 fewer to 48 more) and may have crossed many important decision-making threshold (including line of no effect). **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (62 fewer to 4 fewer) and may have crossed many important decision-making threshold. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (from 61 fewer to 17 more) and may have crossed many important decision-making threshold (including line of no effect). **Publication bias: no serious.**

References

64. Mosha JF, Kulkarni MA, Lukole E, Matowo NS, Pitt C, Messenger LA, et al. Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial. Lancet (London, England) 2022;399(10331):1227-1241 Pubmed Journal

66. Accrombessi M, Cook J, Dangbenon E, Yovogan B, Akpovi H, Sovi A, et al. Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets (LLINs) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial. Lancet (London, England) 2023;401(10375):435-446 Pubmed Journal

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Pyrethroid-pyriproxyfen nets for prevention of malaria

Comparator: Pyrethroid-only nets for prevention of malaria

Summary

The systematic review [Barker *et al unpublished evidence*] included three trials from Benin *[66]*, Burkina Faso *[67]* and the United Republic of Tanzania *[64]* that compared the epidemiological impact against malaria of pyrethroid-pyriproxyfen ITNs (either alphacypermethrin-pyriproxyfen or permethrin-pyriproxyfen) against that of pyrethroid-only LLINs (either permethrin or alphacypermethrin). All three trials were conducted in areas of high malaria transmission and pyrethroid-resistance. The review provided high-certainty evidence that incidence of clinical malaria was lower in areas where pyrethroid-pyriproxyfen ITNs were deployed, compared to where pyrethroid-only LLINs were deployed, at one and two years after ITN deployment (one-year incidence rate ratio (IRR): 0.81; 95% CI: 0.70–0.93; two-year IRR: 0.87; 95% CI: 0.80–0.95). The review also provided moderate to high certainty evidence that prevalence of malaria infection was lower in areas where pyrethroid-pyriproxyfen ITNs were deployed than in those where pyrethroid-only LLINs were deployed, at some, but not all, time points after ITN deployment (six-month relative risk (RR): 0.96; 95% CI: 0.85–1.08; 12-month RR: 0.70; 95% CI: 0.60–0.80; 18-month RR: 0.98; 95% CI: 0.92–1.04; 24-month RR: 0.82; 95% CI: 0.75–0.90).

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only nets for prevention of malaria	**Intervention** Pyrethroid-pyriproxyfen nets for prevention of malaria	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria case incidence (overall)	Rate ratio 0.9 (CI 95% 0.73 — 1.13) Based on data from 63,163 participants in 3 studies. (Randomized controlled)	1,037 per 1000 Difference:	929 per 1000 **104 fewer per 1000** (CI 95% 280 fewer — 135 more)	Low	2000-person years (3 RCTs); Length of time observed: 5 months to 24 months; Based on data from at least 63,163 participants (2 studies); Absolute calculation performed manually as GRADEPro cannot calculate using IRR.
Malaria case incidence (1-year post-intervention)	Rate ratio 0.66 (CI 95% 0.47 — 0.85) Based on data from 61,183 participants in 2 studies. (Randomized controlled)	487 per 1000 Difference:	393 per 1000 **166 fewer per 1000** (CI 95% 258 fewer — 73 fewer)	High	2000 person-years; (2 RCTs); Length of time observed: < 1 month to 12 months; Based on data from at least 61 183 participants (1 study); Absolute calculation performed manually as GRADEPro cannot calculate using IRR.
Malaria case incidence (2-year post-intervention)	Rate ratio 0.94 (CI 95% 0.75 — 1.17) Based on data from 61,183 participants in 2 studies. (Randomized controlled)	815 per 1000 Difference:	715 per 1000 **49 fewer per 1000** (CI 95% 204 fewer — 138 more)	Moderate	2000 (2 RCTs); Length of time observed: 12 months to 24 months; Based on data from at least 61,183 participants (1 study); Absolute calculation performed manually as GRADEPro cannot calculate using IRR.
Parasite prevalence (6-months follow-up)	Relative risk 0.92 (CI 95% 0.63 — 1.34) Based on data from 2,934 participants in 1 studies. (Randomized controlled)	280 per 1000 Difference:	269 per 1000 **22 fewer per 1000** (CI 95% 104 fewer — 95 more)	Moderate Due to serious imprecision [1]	
Parasite prevalence (12-months follow-up)	Relative risk 0.69 (CI 95% 0.46 — 1.04) Based on data from 2,192 participants in 1 studies. (Randomized controlled)	312 per 1000 Difference:	217 per 1000 **93 fewer per 1000** (CI 95% 168 fewer — 12 more)	Moderate	
Parasite prevalence (18-months follow-up)	Relative risk 0.97 (CI 95% 0.76 — 1.26) Based on data from 5,337 participants in 2 studies. (Randomized controlled)	448 per 1000 Difference:	438 per 1000 **13 fewer per 1000** (CI 95% 108 fewer — 116 more)	Low Due to serious imprecision [2]	
Parasite prevalence	Relative risk 0.77 (CI 95% 0.54 — 1.16)	458	375	Moderate	

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only nets for prevention of malaria	**Intervention** Pyrethroid-pyriproxyfen nets for prevention of malaria	**Certainty of the evidence** (Quality of evidence)	**Summary**
(24-months follow-up)	Based on data from 2,457 participants in 1 studies. (Randomized controlled)	per 1000 Difference:	per 1000 **105 fewer per 1000** (CI 95% 192 fewer — 13 more)		

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (from 42 fewer to 22 more) and may have crossed many important decision-making thresholds (including line of no effect). **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (from 36 fewer to 18 more) and may have crossed many important decision-making thresholds (including line of no effect). **Publication bias: no serious.**

References

64. Mosha JF, Kulkarni MA, Lukole E, Matowo NS, Pitt C, Messenger LA, et al. Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial. Lancet (London, England) 2022;399(10331):1227-1241 Pubmed Journal

66. Accrombessi M, Cook J, Dangbenon E, Yovogan B, Akpovi H, Sovi A, et al. Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets (LLINs) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial. Lancet (London, England) 2023;401(10375):435-446 Pubmed Journal

67. Tiono AB, Ouédraogo A, Ouattara D, Bougouma EC, Coulibaly S, Diarra A, et al. Efficacy of Olyset Duo, a bednet containing pyriproxyfen and permethrin, versus a permethrin-only net against clinical malaria in an area with highly pyrethroid-resistant vectors in rural Burkina Faso: a cluster-randomised controlled trial. Lancet (London, England) 2018;392(10147):569-580 Pubmed Journal

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Pyrethroid-pyriproxyfen nets for prevention of malaria

Comparator: Pyrethroid-PBO nets for prevention of malaria

Summary

The review [Barker *et al unpublished evidence*] compared pyrethroid-pyriproxyfen ITNs (alphacypermethrin-pyriproxyfen) to pyrethroid-PBO ITNs (permethrin-piperonyl butoxide) in terms of their epidemiological impact against malaria, based on only one trial *[64]* conducted in the United Republic of Tanzania. The review provided high to moderate certainty evidence that incidence of clinical malaria was higher at one year after ITN deployment (IRR: 2.04; 95% CI: 1.55–2.68) in areas where pyrethroid-pyriproxyfen ITNs were deployed that in those where pyrethroid-PBO ITNs were deployed; there was little or no effect on malaria incidence two years post-deployment (IRR: 1.10; 95% CI: 0.95–1.27). The review also provided high- to moderate-certainty evidence that pyrethroid-pyriproxyfen only performed as well as, or worse than, pyrethroid-PBO ITNs in reducing prevalence of malaria infection at all time points after ITN deployment (12-month RR: 1.13; 95% CI: 0.95–1.33; 18-month RR: 1.17; 95% CI: 1.07–1.27; 24-month RR: 0.88; 95% CI: 0.75–1.03).

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-PBO nets for prevention of malaria	**Intervention** Pyrethroid-pyriproxyfen nets for prevention of malaria	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria case incidence (overall)	Rate ratio 1.25 (CI 95% 1.1 — 1.41) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	333 per 1000 Difference:	416 per 1000 **83 more per 1000** (CI 95% 33 more — 137 more)	High	2000-person years (1 RCT); Length of time observed: <1 month to 24 months; Based on data from at least 61,183 participants (1 study); Absolute calculation performed manually as GRADEPro cannot calculate using IRR.
Malaria case incidence (1-year post-intervention)	Rate ratio 2.04 (CI 95% 1.55 — 2.68) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	131 per 1000 Difference:	266 per 1000 **136 more per 1000** (CI 95% 72 more — 220 more)	High	2000-person years (1 RCT) Length of time observed: <1 month to 12 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Malaria case incidence (2-years post-intervention)	Rate ratio 1.1 (CI 95% 0.95 — 1.27) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	483 per 1000 Difference:	531 per 1000 **48 more per 1000** (CI 95% 24 fewer — 130 more)	Moderate Due to serious imprecision [1]	2000-person years (1 RCT) Length of time observed: 12 months to 24 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Parasite prevalence (12-months follow-up)	Relative risk 1.13 (CI 95% 0.95 — 1.33) Based on data from 2,140 participants in 1 studies. (Randomized controlled)	192 per 1000 Difference:	217 per 1000 **25 more per 1000** (CI 95% 10 fewer — 63 more)	Moderate Due to serious imprecision [2]	
Parasite prevalence (18-months follow-up)	Relative risk 1.17 (CI 95% 1.07 — 1.27) Based on data from 2,313 participants in 1 studies. (Randomized controlled)	433 per 1000 Difference:	506 per 1000 **74 more per 1000** (CI 95% 30 more — 117 more)	High	
Parasite prevalence (24-months follow-up)	Odds ratio 0.88 (CI 95% 0.75 — 1.03) Based on data from 2,517 participants in studies. (Randomized controlled)	407 per 1000 Difference:	375 per 1000 **30 fewer per 1000** (CI 95% 67 fewer — 7 more)	Moderate Due to serious imprecision [3]	

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are very wide (from 24

fewer 130 more) and may have crossed many important decision-making thresholds (including line of no effect). **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (from 10 fewer to 63 more) and may have crossed many important decision-making thresholds (including line of no effect). **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (from 67 fewer to 7 more) and may have crossed many important decision-making thresholds (including line of no effect). **Publication bias: no serious.**

References

64. Mosha JF, Kulkarni MA, Lukole E, Matowo NS, Pitt C, Messenger LA, et al. Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial. Lancet (London, England) 2022;399(10331):1227-1241 Pubmed Journal

66. Accrombessi M, Cook J, Dangbenon E, Yovogan B, Akpovi H, Sovi A, et al. Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets (LLINs) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial. Lancet (London, England) 2023;401(10375):435-446 Pubmed Journal

67. Tiono AB, Ouédraogo A, Ouattara D, Bougouma EC, Coulibaly S, Diarra A, et al. Efficacy of Olyset Duo, a bednet containing pyriproxyfen and permethrin, versus a permethrin-only net against clinical malaria in an area with highly pyrethroid-resistant vectors in rural Burkina Faso: a cluster-randomised controlled trial. Lancet (London, England) 2018;392(10147):569-580 Pubmed Journal

Clinical question/ PICO

Population: Refugees and IDP adults and children affected by humanitarian emergencies living in areas with ongoing malaria transmission

Intervention: Insecticide-treated nets

Comparator: No insecticide-treated nets

Summary

Of the four included ITN studies, two were cluster RCTs (one with households as the cluster and one with villages as the cluster) and two were individual-level RCTs. The two individual-level RCTs were conducted on the Myanmar–Thailand border, the village-level RCT was conducted in Myanmar and the household-level RCT was performed in Pakistan.

ITNs versus no ITNs:
ITNs reduce *P. falciparum* case incidence compared to no nets
(Rate ratio: 0.55; 95% CI: 0.37–0.79; four studies; high-certainty evidence)
ITNs reduce *P. falciparum* prevalence compared to no nets
(Rate ratio: 0.60; 95% CI: 0.40–0.88; two studies; high-certainty evidence)
ITNs likely reduce *P. vivax* case incidence compared to no nets
(Rate ratio: 0.69; 95% CI: 0.51–0.94; three studies; moderate-certainty evidence)
ITNs may have little or no effect on the prevalence of *P. vivax* compared to no nets
(Risk ratio: 1.00; 95% CI: 0.75–1.34; two studies; low-certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** no ITNs	**Intervention** ITNs	**Certainty of the evidence** (Quality of evidence)	**Summary**
P. falciparum case incidence	Relative risk 0.55 (CI 95% 0.37 — 0.79) Based on data from 3,200 participants in 4 studies.	70 per 1000 Difference:	39 per 1000 **31 fewer per 1000**	High	ITNs reduce P. falciparum case incidence compared to no ITNs.

Outcome Timeframe	**Study results and measurements**	**Comparator** no ITNs	**Intervention** ITNs	**Certainty of the evidence** (Quality of evidence)	**Summary**
			(CI 95% 44 fewer — 15 fewer)		
P. falciparum prevalence	Relative risk 0.6 (CI 95% 0.4 — 0.88) Based on data from 2,079 participants in 2 studies.	37 per 1000 Difference:	22 per 1000 **15 fewer per 1000** (CI 95% 22 fewer — 4 fewer)	High	ITNs reduce P. falciparum prevalence compared to no ITNs.
P. vivax case incidence	Relative risk 0.69 (CI 95% 0.51 — 0.94) Based on data from 2,997 participants in 3 studies.	116 per 1000 Difference:	80 per 1000 **36 fewer per 1000** (CI 95% 57 fewer — 7 fewer)	Moderate Due to serious imprecision [1]	ITNs probably reduce P. vivax case incidence compared to no ITNs.
P. vivax prevalence	Relative risk 1 (CI 95% 0.75 — 1.34) Based on data from 2,079 participants in 2 studies.	99 per 1000 Difference:	99 per 1000 **0 fewer per 1000** (CI 95% 25 fewer — 34 more)	Low Due to very serious imprecision [2]	ITNs may result in little to no difference in P. vivax prevalence compared to no ITNs.

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**

References

58. Messenger LA, Furnival-Adams J, Pelloquin B, Rowland M. Vector control for malaria prevention during humanitarian emergencies: protocol for a systematic review and meta-analysis. BMJ Open 2021/07/27;11(7):e046325-e046325 Pubmed Journal Website

Clinical question/ PICO

Population: Adults and children in areas with ongoing malaria transmission

Intervention: Indoor residual spraying

Comparator: No indoor residual spraying

Summary

The systematic review (Stone *et al unpublished evidence*) included 10 studies comparing IRS to no vector control: five RCTs, one quasi-experimental study, and four controlled before-and-after studies. Studies were conducted in Afghanistan, Ethiopia *[84]*, India *[86][90]*, Kenya *[82][94]*, Pakistan *[56]*, Sudan *[92]* and the United Republic of Tanzania *[93][80]* which covered a range of transmissions levels from high to low.

The review provided very low-certainty evidence that there was little or no effect of IRS on malaria incidence compared to no spraying (IRR: 0.90; 95% CI: 0.63–1.29). The review also provided very low-certainty evidence that all-age malaria parasite prevalence was lower in IRS study areas than in those without IRS. The post-IRS period during which the impact was measured varied across different studies, and thus a summary RR could not be estimated. However, individual studies

reported the RR of malaria infection as 0.70 (95% CI: 0.65–0.75) one month after application and as 0.68 (95% CI: 0.66–0.70) one year after deployment compared to no IRS.

Outcome Timeframe	**Study results and measurements**	**Comparator** No IRS	**Intervention** IRS	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria, incidence rate (children under 5 years)	Rate ratio 0.9 (CI 95% 0.7 — 1.16) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	139 per 1000 Difference:	138 per 1000 **14 fewer per 1000** (CI 95% 42 fewer — 22 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [1]	The evidence is very uncertain about the effect of IRS on malaria incidence in children under 5 years of age compared to no IRS.
Malaria, incidence rate (all ages) follow-up: range 3-6 months	Rate ratio 0.9 (CI 95% 0.63 — 1.29) Based on data from 2,000 participants in 4 studies. (Randomized controlled)	57 per 1000 Difference:	38 per 1000 **6 fewer per 1000** (CI 95% 21 fewer — 17 more)	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision [2]	The evidence is very uncertain about the effect of IRS on malaria incidence compared to no IRS when followed up for three to six months.
Malaria, point prevalence (children under 6) follow-up: mean 3 months	Relative risk 0.95 (CI 95% 0.68 — 1.32) Based on data from 423 participants in 1 studies. (Randomized controlled)	270 per 1000 Difference:	256 per 1000 **14 fewer per 1000** (CI 95% 86 fewer — 86 more)	Low Due to serious risk of bias, Due to serious imprecision [3]	IRS may have little to no impact on malaria prevalence compared to no IRS in children under 6 years of age when followed up for three months.
Deaths, incidence rate (all ages) follow-up: mean 3 months	Rate ratio 0.4 (CI 95% 0.2 — 0.8) Based on data from 200,000 participants in 1 studies.	25 per 100.000 Difference:	10 per 100.000 **0 fewer per 100.000** (CI 95% 20 fewer — 5 fewer)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [4]	The evidence is very uncertain about the effect of IRS on all-cause deaths compared to no IRS when followed up for three months.
Malaria, point prevalence (all ages) (nRCT and controlled before-and-after data) follow-up: range 1-12 months	Based on data from 7,179 participants in 4 studies. (Observational (non-randomized))	Gunasekaran tested participants for malaria infection approximately four months post IRS. The risk of malaria infection in the sprayed group was 0.31 (95% CI 0.27 to 0.35) relative to the unsprayed group. Guyatt tested participants for malaria infection at approximately two months after IRS. The risk of malaria infection in the sprayed group relative to the unsprayed group was 0.25 (95% CI 0.15 to 0.42). Mashauri examined participants for malaria infection six months post IRS. The risk of malaria infection was 0.56 (95% CI 0.41 to 0.76) for those in the sprayed group compared with those in the unsprayed group. Ramachandra tested for malaria infection		Very low Due to very serious risk of bias [5]	The evidence is very uncertain about the effect of IRS on malaria prevalence compared to no IRS when followed up for one to 12 months.

Outcome Timeframe	**Study results and measurements**	**Comparator** No IRS	**Intervention** IRS	**Certainty of the evidence** (Quality of evidence)	**Summary**
		approximately one month post IRS. The risk of malaria infection in the sprayed group was 0.70 (95% CI 0.65 to 0.75) compared with the unsprayed group.			
Malaria, point prevalence (children under 5) (nRCT and controlled before-and-after data) follow-up: range 6-12 months	Based on data from 497 participants in 2 studies. (Observational (non-randomized))	Guyatt tested participants for malaria infection approximately two months after IRS. The risk of malaria infection in the sprayed group relative to the unsprayed group was 0.28 (95% CI: 0.10–0.77). Mashauri examined participants for malaria infection six months post-IRS. The risk of malaria infection was 0.19 (95% CI: 0.07–0.48) for those in the sprayed group compared to those in the unsprayed group.		Very low Due to very serious risk of bias [6]	The evidence is very uncertain about the effect of IRS on malaria prevalence in children under 5 years of age compared to no IRS when followed up from six months to 12 months.
Malaria, point prevalence (children 5-15 years) follow-up: range 3-6 months	Based on data from 2,752 participants in 2 studies. (Randomized controlled)	Curtis examined children over 6 years of age approximately three months post-IRS (first quarter of 1996, spraying in December 1995). The risk of malaria infection in the sprayed cohort relative to the unsprayed cohort was 1.10 (95% CI: 0.94–1.29). Rowland examined children between 5 and 15 years of age three months post-IRS. The risk of malaria infection in the sprayed cohort relative to the unsprayed cohort was 0.15 (95% CI: 0.06–0.37).		Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [7]	The evidence is very uncertain about the effect of IRS on malaria prevalence in children aged 5 to 15 years compared to no IRS when followed up from three months to six months.
Malaria, point prevalence (children aged 5-15 years) (nRCT and controlled before-and-after data) follow-up: range 6-12 months	Based on data from 907 participants in 2 studies. (Observational (non-randomized))	Guyatt tested participants for malaria infection approximately two months after IRS. The risk of malaria infection in the sprayed group relative to the unsprayed group was 0.32 (95% CI: 0.16–0.65). Mashauri examined participants for malaria infection six months post-IRS. The risk of malaria infection was 0.60 (95% CI: 0.42–0.87) for those in the sprayed group compared to those in the unsprayed group.		Very low Due to very serious risk of bias, Due to serious imprecision [8]	The evidence is very uncertain about the effect of IRS on malaria prevalence in children aged 5 to 15 years compared to no IRS when followed up from six months to 12 months.
Malaria, point prevalence (aged 15+ years) (nRCT and controlled before-and-after data) follow-up: range 6-12 months	Based on data from 916 participants in 2 studies. (Observational (non-randomized))	Guyatt tested participants for malaria infection approximately two months after IRS. The risk of malaria infection in the sprayed group relative to the unsprayed group was 0.17 (95% CI: 0.07–0.43). Mashauri examined participants for malaria infection six months post-IRS. The risk of malaria infection was 1.26 (95% CI: 0.57–2.76) for those in the sprayed group compared to those in the unsprayed group.		Very low Due to very serious risk of bias, Due to serious imprecision [9]	The evidence is very uncertain about the effect of IRS on malaria prevalence in those aged 15 years or older compared to no IRS when followed up from six months to 12 months.
Death, incidence rate (children under 5 years)	Based on data from 2,000 participants in 1 studies. (Randomized controlled)	There were no deaths in children under 5 years in the treated camps within three		Very low Due to serious risk of bias, Due to serious	The evidence is very uncertain about the effect of IRS on all-cause deaths in children under 5 years

Outcome Timeframe	**Study results and measurements**	**Comparator** No IRS	**Intervention** IRS	**Certainty of the evidence** (Quality of evidence)	**Summary**
follow-up: mean 3 months		months following IRS. Confidence intervals could not be estimated.		indirectness, Due to serious imprecision [10]	of age compared to no IRS when followed up for 3 months.

1. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Inconsistency: serious. Indirectness: serious. Imprecision: serious.**
3. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.**
4. **Risk of Bias: serious.** Randomisation method unclear and missing outcome data in most studies. **Inconsistency: no serious. Indirectness: serious.** Charlwood data is from refugee camps. **Imprecision: serious.** Low event rates. The optimal information size for this study was 9955466 and was not met. **Publication bias: no serious.**
5. **Risk of Bias: very serious.** Confounding not addressed, deviations from intended interventions, bias due to missing data. As confounding is not addressed AND no randomization, downgraded three levels to extremely serious..
6. **Risk of Bias: very serious.** Confounding not addressed. As confounding is not addressed AND no randomisation, downgraded 3 levels to extremely serious. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.**
7. **Risk of Bias: serious. Inconsistency: serious. Indirectness: no serious. Imprecision: serious.**
8, 9. **Risk of Bias: very serious.** Confounding not addressed. As confounding is not addressed AND no randomisation, downgraded 3 levels to extremely serious. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.**
10. **Risk of Bias: serious.** Randomisation method unclear and missing outcome data in most studies. **Inconsistency: no serious. Indirectness: serious.** Charlwood data is from refugee camps. **Imprecision: serious.** Low event rates. CI could not be calculated.

Clinical question/ PICO

Population: Refugees and IDP adults and children affected by humanitarian emergencies living in areas with ongoing malaria transmission

Intervention: Indoor residual spraying

Comparator: No indoor residual spraying

Summary

Of the four included IRS studies, one was a cluster RCT at the village-level and three were observational studies (one controlled before-after, one before-after and one cross-sectional). The cRCT was conducted in Sudan and the three observational studies were undertaken in Pakistan.

IRS versus no IRS:
The evidence is very uncertain about the effect of IRS on *P. falciparum* incidence compared to no IRS
(Incidence rate ratio: 0.57; 95% CI: 0.53–0.61; one before-after study; very low-certainty evidence)
IRS may result in little to no difference in *P. falciparum* prevalence compared to no IRS
(Rate ratio: 1.31; 95% CI: 0.91–1.88; one cRCT; low-certainty evidence)
The evidence is very uncertain about the effect of IRS on *P. vivax* incidence compared to no IRS
(Incidence rate ratio: 0.51; 95% CI: 0.49–0.52; one before-after study; very low-certainty evidence)
The evidence is very uncertain about the effect of IRS on *P. vivax* prevalence compared to no IRS
(Odds ratio: 0.74; 95% CI: 0.25–2.14; one controlled before-after study and one cross-sectional study; very low-certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** no IRS	**Intervention** IRS	**Certainty of the evidence** (Quality of evidence)	**Summary**
P. falciparum incidence	Relative risk 0.57 (CI 95% 0.53 — 0.61) Based on data from 480,377 participants in 1 studies.	7 per 1000 Difference:	4 per 1000 **3 fewer per 1000** (CI 95% 3 fewer — 3 fewer)	Very low	The evidence is very uncertain about the effect of IRS on P. falciparum incidence compared to no IRS.
P. falciparum prevalence	Relative risk 1.31 (CI 95% 0.91 — 1.88) Based on data from 278 participants in 1 studies.	257 per 1000 Difference:	337 per 1000 **80 more per 1000** (CI 95% 23 fewer — 226 more)	Low Due to very serious imprecision.	IRS may result in little to no difference in P. falciparum prevalence compared to no IRS.
P. vivax incidence	Relative risk 0.51 (CI 95% 0.49 — 0.52) Based on data from 480,372 participants in 1 studies.	57 per 1000 Difference:	29 per 1000 **28 fewer per 1000** (CI 95% 29 fewer — 27 fewer)	Very low Due to serious risk of bias; due to serious indirectness. Upgraded because all plausible confounding would reduce the demonstrated effect.	The evidence is very uncertain about the effect of IRS on P. vivax incidence compared to no IRS.
P. vivax prevalence	Odds ratio 0.74 (CI 95% 0.25 — 2.14) Based on data from 4,708 participants in 2 studies.	78 per 1000 Difference:	59 per 1000 **19 fewer per 1000** (CI 95% 57 fewer — 75 more)	Very low Due to serious inconsistency; due to serious indirectness; due to serious imprecision. Upgraded because all plausible confounding would reduce demonstrated effect.	The evidence is very uncertain about the effect of IRS on P. vivax prevalence compared to no IRS.

References

58. Messenger LA, Furnival-Adams J, Pelloquin B, Rowland M. Vector control for malaria prevention during humanitarian emergencies: protocol for a systematic review and meta-analysis. BMJ Open 2021/07/27;11(7):e046325-e046325 Pubmed Journal Website

4.1.2. Co-deploying ITNs and IRS

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs)

Comparator: ITNs

Summary

Four RCTs were included in the systematic review. Studies were conducted in Benin, Eritrea, Gambia and the United Republic of Tanzania.

IRS and ITNs vs ITNs
IRS in addition to ITNs probably has little or no effect on malaria incidence compared to ITNs alone
(Rate ratio: 1.17; 95% CI (0.92–1.46); two studies; moderate certainty evidence)
IRS in addition to ITNs may have little or no effect on parasite prevalence compared to ITNs alone
(Odds ratio: 1.04; 95% CI (0.73–1.48); four studies; low certainty evidence)
It is unknown whether IRS in addition to ITNs reduces the EIR compared to ITNs alone
(Rate ratio: 0.57; 95% CI (0.26–1.25); two studies; very low certainty evidence)
IRS in addition to ITNs probably has little or no effect on anaemia prevalence compared to ITNs alone
(Odds ratio: 1.04; 95% CI (0.83–1.30); two studies; moderate certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** ITNs	**Intervention** Pyrethroid-like IRS plus ITNs	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria incidence	Relative risk 1.17 (CI 95% 0.92 — 1.46) Based on data from 5,249 participants in 2 studies. (Randomized controlled)	600 per 1000 Difference:	700 per 1000 **100 more per 1000** (CI 95% 50 fewer — 280 more)	Moderate Due to serious imprecision [1]	IRS using pyrethroid-like insecticides in addition to pyrethroid ITNs probably has little or no effect on malaria incidence compared to pyrethroid ITNs alone.
Malaria prevalence	Odds ratio 1.04 (CI 95% 0.73 — 1.48) Based on data from 34,530 participants in 4 studies. (Randomized controlled)	180 per 1000 Difference:	190 per 1000 **10 more per 1000** (CI 95% 40 fewer — 70 more)	Low Due to serious inconsistency, Due to serious imprecision [2]	IRS using pyrethroid-like insecticides in addition to pyrethroid ITNs may have little or no effect on parasite prevalence compared to pyrethroid ITNs alone
Entomological inoculation rate	Relative risk 0.57 (CI 95% 0.26 — 1.25) Based on data from participants in 2 studies. (Randomized controlled)	1,170 per 1000 Difference:	670 per 1000 **500 fewer per 1000** (CI 95% 870 fewer — 290 fewer)	Very low Due to serious inconsistency, Due to very serious imprecision [3]	The evidence is very uncertain about the effect of IRS using pyrethroid-like insecticides in addition to pyrethroid ITNs on EIR compared to pyrethroid ITNs alone.
Anaemia prevalence (haemoglobin <8g/dl)	Odds ratio 1.04 (CI 95% 0.83 — 1.3) Based on data from 12,940 participants in 2 studies. (Randomized controlled)	50 per 1000 Difference:	50 per 1000 **0 fewer per 1000** (CI 95% 10 fewer — 10 more)	Moderate Due to serious imprecision [4]	IRS using pyrethroid-like insecticides in addition to pyrethroid ITNs probably has little or no effect on anaemia prevalence compared to pyrethroid ITNs alone

1, 4. **Imprecision: serious.**

2. **Inconsistency: serious. Imprecision: serious.**
3. **Inconsistency: serious. Imprecision: very serious.**

References

97. Choi L, Pryce J, Garner P. Indoor residual spraying for preventing malaria in communities using insecticide-treated nets. The Cochrane database of systematic reviews 2019;(5):CD012688 Pubmed Journal Website

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: IRS

Comparator: ITNs

Summary

The systematic review included one RCT from the United Republic of Tanzania that reported the effect of IRS compared to ITNs on malaria in an area of intense malaria transmission and another study from India that investigated the epidemiological impact of IRS in an area with unstable malaria.

IRS versus ITNs in areas with intense transmission:
IRS may reduce malaria incidence compared to ITNs
(Rate ratio: 0.88; 95% CI (0.78–0.98); one study; low certainty evidence)
There may be little or no difference between IRS and ITNs in terms of parasite prevalence
(Risk ratio: 1.06; 95% CI (0.91–1.22); one study; very low certainty evidence)

IRS versus ITNs in areas with unstable transmission:
IRS may increase malaria incidence compared to ITNs
(Rate ratio: 1.48; 95% CI (1.37–1.60); one study; low certainty evidence)
IRS may increase parasite prevalence compared to ITNs
(Risk ratio: 1.70; 95% CI (1.18–2.44); one study; low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** ITNs	**Intervention** IRS	**Certainty of the evidence** (Quality of evidence)	**Summary**
Incidence of malaria in children under 5 years in areas of intense malaria transmission	Relative risk 0.88 (CI 95% 0.78 — 0.98) Based on data from 818 participants in 1 studies. (Randomized controlled)	630 per 1000 Difference:	550 per 1000 **80 fewer per 1000** (CI 95% 140 fewer — 10 fewer)	Low Due to serious indirectness, Due to serious imprecision [1]	IRS may reduce P. falciparum incidence compared to no ITNs in areas of intense malaria transmission.
Parasite prevalence in children under 5 years in areas of intense malaria transmission	Relative risk 1.06 (CI 95% 0.91 — 1.22) Based on data from 449 participants in 1 studies. (Randomized controlled)	600 per 1000 Difference:	640 per 1000 **40 more per 1000** (CI 95% 50 fewer — 140 more)	Low Due to serious indirectness, Due to serious imprecision [2]	IRS may result in little to no difference in parasite prevalence compared to ITNs in areas of intense malaria transmission.

Outcome Timeframe	**Study results and measurements**	**Comparator** ITNs	**Intervention** IRS	**Certainty of the evidence** (Quality of evidence)	**Summary**
Incidence of malaria in all ages in areas of unstable malaria	Relative risk 1.48 (CI 95% 1.37 — 1.6) Based on data from 88,100 participants in 1 studies. (Randomized controlled)	20 per 1000 Difference:	30 per 1000 **10 more per 1000** (CI 95% 10 more — 20 more)	Low Due to serious imprecision, Due to serious indirectness [3]	IRS may increase incidence of malaria compared to ITNs in areas of unstable malaria.
Parasite prevalence in all ages in areas of unstable malaria	Relative risk 1.7 (CI 95% 1.18 — 2.44) Based on data from 52,934 participants in 1 studies. (Randomized controlled)	2 per 1000 Difference:	3 per 1000 **1 more per 1000** (CI 95% 0 fewer — 3 more)	Low Due to serious indirectness, Due to serious imprecision [4]	IRS may result in little to no difference in parasite prevalence compared to ITNs in areas of unstable malaria.

1, 2, 3, 4. **Indirectness: serious. Imprecision: serious.**

References

91. Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. The Cochrane database of systematic reviews 2010;(4):CD006657 Pubmed Journal

4.1.3. Supplementary interventions

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Larviciding

Comparator: No larviciding

Summary

Four studies were included in the systematic review, of which only one was an RCT; the remaining three studies were non-randomized. Studies were undertaken in Gambia, Kenya, Sri Lanka and United Republic of Tanzania.

Larviciding applied to mosquito aquatic habitats exceeding 1km^2 in area:
It is unknown whether larviciding has an effect on malaria incidence compared to no larviciding
(Odds ratio: 1.97; 95% CI (1.39–2.81); one study; very low certainty evidence)
It is unknown whether larviciding has an effect on parasite prevalence compared to no larviciding
(Odds ratio: 1.49; 95% CI (0.45–4.93); one study; very low certainty evidence)

Larviciding applied to mosquito aquatic habitats less than 1km^2 in area:
Larviciding probably reduces malaria incidence compared to no larviciding
(Rate ratio: 0.20; 95% CI (0.16–0.25); one study; moderate certainty evidence)
Larviciding may reduce parasite prevalence compared to no larviciding
(Odds ratio: 0.72; 95% CI (0.58–0.89); two studies; low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** No larviciding	**Intervention** Larviciding	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria incidence of habitats >1km2	Odds ratio 1.97 (CI 95% 1.39 — 2.81) Based on data from 1,793 participants in 1 studies. (Observational (non-randomized))	230 per 1000 Difference:	370 per 1000 **140 more per 1000** (CI 95% 70 more — 230 more)	Very low Due to serious inconsistency, Due to serious imprecision [1]	The evidence is very uncertain about the effect of larviciding on malaria incidence in areas where mosquito aquatic habitats are more than 1 km² compared to no larviciding.
Parasite prevalence of habitats >1km2	Odds ratio 1.49 (CI 95% 0.45 — 4.93) Based on data from 3,574 participants in 1 studies. (Observational (non-randomized))	140 per 1000 Difference:	190 per 1000 **50 more per 1000** (CI 95% 70 fewer — 300 more)	Very low Due to serious inconsistency, Due to very serious imprecision [2]	The evidence is very uncertain about the effect of larviciding on parasite prevalence in areas where mosquito aquatic habitats are more than 1 km² compared to no larviciding.
Malaria incidence of habitats <1km2	Relative risk 0.2 (CI 95% 0.16 — 0.25) Based on data from 4,649 participants in 1 studies. (Randomized controlled)	230 per 1000 Difference:	50 per 1000 **180 fewer per 1000** (CI 95% 190 fewer — 170 fewer)	Moderate Due to serious imprecision [3]	Larviciding probably decreases malaria incidence in areas where mosquito aquatic habitats are less than 1 km² compared to no larviciding.
Parasite prevalence of habitats <1km2	Odds ratio 0.72 (CI 95% 0.58 — 0.89) (Observational (non-randomized))	120 per 1000 Difference:	90 per 1000 **30 fewer per 1000** (CI 95% 50 fewer — 10 fewer)	Low	Larviciding may reduce parasite prevalence in areas where mosquito aquatic habitats are less than 1 km² compared to no larviciding

1. **Inconsistency: serious. Imprecision: serious.**
2. **Inconsistency: serious. Imprecision: very serious.**
3. **Imprecision: serious.**

References

106. Choi L, Majambere S, Wilson AL. Larviciding to prevent malaria transmission. The Cochrane database of systematic reviews 2019;(8):CD012736 Pubmed Journal Website

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Larval habitat manipulation (water management using spillways across streams)

Comparator: No larval habitat manipulation

Summary

The systematic review identified one study from the Philippines that investigated the impact of habitat manipulation by controlling the release of water from spillways (overflow channels) across streams to flush downstream areas with water against malaria. It is unknown whether larval habitat manipulation has an effect on malaria parasite prevalence compared to no larval habitat manipulation (relative risk: 0.01; 95% CI: 0.0–0.16; one study; very low-certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** No larval habitat manipulation	**Intervention** Larval habitat manipulation	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria parasite prevalence in children aged 2 -10 years	Relative risk 0.01 (CI 95% 0 — 0.16) Based on data from 866 participants in 1 studies. (Observational (non-randomized))	86 per 1000 Difference:	0 per 1000 **86 fewer per 1000** (CI 95% 86 fewer — 72 fewer)	Very low Due to very serious risk of bias, due to very serious imprecision [1]	The evidence is very uncertain about the effect of using spillways across streams to manipulate larval habitats on malaria parasite prevalence compared to no larval habitat manipulation.

1. **Risk of Bias: very serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Larval habitat manipulation (water management using floodgates on a dam across a stream) and annual IRS

Comparator: Annual IRS

Summary

The systematic review identified one study from India that investigated the impact of habitat manipulation by controlling the release of water using floodgates on dams in areas with IRS. It is unknown whether larval habitat manipulation combined with IRS has an effect on malaria clinical incidence compared to IRS alone (odds ratios or relative risks could not be calculated because the numbers of participants in each arm or at follow-up were not reported; one study; very low-certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** IRS	**Intervention** Larval habitat manipulation and IRS	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinical malaria incidence	Based on data from participants in 1 studies. (Observational (non-randomized))	The study did not report the number of participants in either arm. At baseline, the mean annual incidence rates were 1304 cases per 1000 children in control villages versus 786 per 1000 children in intervention villages. Following dam construction, a decline in malaria incidence was seen each year in the intervention villages (1000, 636.4, 181.8 and 181.8 per 1000 children), compared to increases in malaria incidence during the corresponding periods in the control villages.		Very low Due to serious risk of bias, due to very serious imprecision [1]	The evidence is very uncertain about the effect of using floodgates on a dam to manipulate larval habitats on clinical malaria incidence compared to no larval habitat manipulation in areas with IRS.

Outcome Timeframe	**Study results and measurements**	**Comparator** IRS	**Intervention** Larval habitat manipulation and IRS	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria parasite prevalence (all ages)	Based on data from participants in 1 studies. (Observational (non-randomized))	At baseline there were 271 participants in the intervention group and 299 in the comparator group. The parasite prevalence in intervention villages and control villages during the pre-construction year were 17.6% and 18.9%, respectively. However, in subsequent years after construction of the dam, there was gradual and significant decline in parasite rate (P < 0.01) in intervention villages. (Data on numbers of participants at follow-up not provided)		Very low Due to serious risk of bias, due to very serious imprecision [2]	The evidence is very uncertain about the effect of using flushing through floodgates on a dam to manipulate larval habitats on malaria parasite prevalence compared to no flushing in areas with IRS.

1, 2. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Larvivorous fish

Comparator: no larvivorous fish

Summary

Fifteen studies were included in the systematic review. Studies were undertaken in Comoros, Ethiopia, India (three studies), Indonesia, Kenya, Republic of Korea (two studies), Sri Lanka (two studies), Sudan, and Tajikistan (two studies).

Treated aquatic habitats included wells, domestic water containers, fishponds and pools (seven studies); river bed pools below dams (two studies); rice field plots (four studies); and canals (two studies).

No studies reported on clinical malaria, EIR or adult vector densities; 12 studies reported on density of immature stages; and five studies reported on the number of aquatic habitats positive for immature stages of the vector species.

The studies were not suitable for a pooled analysis.
It is unknown whether larvivorous fish reduce the density of immature vector stages compared to no larvivorous fish (unpooled data; 12 studies; very low certainty evidence)
Larvivorous fish may reduce the number of larval sites positive for immature vector stages compared to no larvivorous fish (unpooled data; five studies; low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** no larvivorous fish	**Intervention** Larvivorous fish	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinical malaria (incidence)					No studies
Entomological inoculation rate					No studies

Outcome Timeframe	**Study results and measurements**	**Comparator** no larvivorous fish	**Intervention** Larvivorous fish	**Certainty of the evidence** (Quality of evidence)	**Summary**
Density of adult malaria vectors					No studies
Density of immature stages of vectors in aquatic habitats (Quasi-experimental studies)	Based on data from participants in 12 studies. (Observational (non-randomized))	Not pooled. Variable effects reported.		Very low Due to serious inconsistency [1]	The evidence is very uncertain about the effect of larvivorous fish on the density of immature anopheline mosquitoes in water bodies compared to no fish.
Larval sites positive for immature stages of the vectors (Quasi-experimental studies)	Based on data from participants in 5 studies. (Observational (non-randomized))	Not pooled. Positive effects reported		Low Downgraded by two: the included studies were non-randomized controlled trials	Larvivorous fish may reduce the number of larval sites positive for immature anopheline mosquitoes compared to no fish.

1. **Inconsistency: serious.**

References

107. Walshe DP, Garner P, Adeel AA, Pyke GH, Burkot TR. Larvivorous fish for preventing malaria transmission. The Cochrane database of systematic reviews 2017;(12):CD008090 Pubmed Journal Website

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Topical repellent

Comparator: Placebo or no topical repellent

Summary

The systematic review included eight studies, of which six were included in the meta-analysis (five cRCTs and one RCT) and two were reported narratively. Studies were carried out in South America, South-East Asia and Africa.

Topical repellents may have little or no protective effect in terms of *P. falciparum* infection incidence in study participants when followed up for a mean of six months from the time of provision of repellents (rate ratio: 0.76; 95% CI: 0.56–1.02; three studies; low-certainty evidence) and malaria case incidence when followed up for a mean of 12 months (rate ratio: 0.66; 95% CI:

0.32–1.36; one study; low-certainty evidence). When *P. falciparum* infection and clinical case incidence were combined, however, this indicated that topical repellents may slightly reduce the incidence of these outcomes (rate ratio: 0.74; 95% CI: 0.56–0.98; four studies; low certainty evidence.

Topical repellents may or may slightly reduce *P. falciparum* prevalence (odds ratio: 0.81; 95% CI: 0.67–0.97; four studies; low-certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or no topical repellent	**Intervention** Topical repellent	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria infection incidence follow-up: mean 6 months	Rate ratio 0.76 (CI 95% 0.56 — 1.02) Based on data from 12,813 participants in 3 studies.	37 per 1000 Difference:	28 per 1000 **9 fewer per 1000** (CI 95% 16 fewer — 1 more)	Low Due to serious indirectness, Due to serious risk of bias [1]	Topical repellents may result in little to no difference in P. falciparum infection incidence compared to no topical repellents.
Malaria case incidence follow-up: mean 12 months	Rate ratio 0.66 (CI 95% 0.32 — 1.36) Based on data from 48,838 participants in 1 studies.	22 per 1000 Difference:	15 per 1000 **7 fewer per 1000** (CI 95% 15 fewer — 8 more)	Low Due to serious risk of bias, Due to serious imprecision [2]	Topical repellents may result in little to no difference in P. falciparum clinical case incidence compared to no topical repellents.
Malaria case and infection incidence together follow-up: mean 13 months	Relative risk 74 (CI 95% 0.56 — 0.98) Based on data from 61,651 participants in 4 studies.	24 per 1000 Difference:	18 per 1000 **6 fewer per 1000** (CI 95% 10 fewer — 0 fewer)	Low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [3]	Topical repellents may slightly reduce P. falciparum infection and clinical case incidence compared to no topical repellents when both outcomes are pooled.
Malaria prevalence	Relative risk 0.81 (CI 95% 0.67 — 0.97) Based on data from 55,366 participants in 4 studies.	13 per 1000 Difference:	11 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 0 fewer)	Low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [4]	Topical repellents may slightly reduce P. falciparum prevalence.

1. **Risk of Bias: serious.** Downgraded 1 level due to risk of bias associated with the procedures used to randomize participants, conceal allocation, and imbalances in the allocation groups. **Indirectness: serious.** Downgraded 1 level due to indirectness associated with the inclusion of only pregnant women in one study.
2. **Risk of Bias: serious.** Downgraded 1 level due to risk of bias associated with imbalances in the allocation groups and the lack of placebo in controls. **Imprecision: serious.** Downgraded 1 level due to imprecision as 95% CIS include a relevant reduction in malaria incidence and no effect.
3. **Risk of Bias: serious.** Downgraded 1 level due to risk of bias associated with procedures used to conceal allocation, imbalances in the allocation groups, and a large proportion of losses to follow-up (16.6%) in one study. . **Indirectness: serious.** Downgraded 1 level due to indirectness associated with the inclusion of only pregnant women in one study. **Imprecision: serious.**
4. **Risk of Bias: serious.** Downgraded 1 level due to risk of bias associated with the step-wedged design and the lack of placebo in the control group of two studies, issues in the procedures used to blind participants, and imbalances in allocation groups. **Indirectness: serious.** Downgraded 1 level due to indirectness associated with the inclusion of only pregnant women in one

study. **Imprecision: serious.**

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Insecticide-treated clothing

Comparator: placebo or untreated clothing

Summary

Two RCTs were included in the systematic review. Studies were conducted in specific populations in Colombia (military personnel) and Pakistan (Afghan refugees).

Insecticide-treated clothing may have a protective effect against clinical malaria caused by *P. falciparum* (Risk ratio: 0.49; 95% CI (0.29–0.83); two studies; low certainty evidence).

Insecticide-treated clothing may have a protective effect against clinical malaria caused by *P. vivax* (Risk ratio: 0.64; 95% CI (0.40–1.01); two studies; low certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** placebo or untreated clothing	**Intervention** Insecticide-treated clothing	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinical malaria (P. falciparum)	Relative risk 0.49 (CI 95% 0.29 — 0.83) Based on data from 997 participants in 2 studies.	35 per 1000 Difference:	17 per 1000 **18 fewer per 1000** (CI 95% 25 fewer — 6 fewer)	Low Due to serious risk of bias, Due to serious imprecision [1]	Insecticide-treating clothing may reduce P. falciparum clinical malaria compared to no insecticide-treated clothing.
Clinical malaria (P. vivax)	Relative risk 0.64 (CI 95% 0.4 — 1.01) Based on data from 997 participants in 2 studies.	116 per 1000 Difference:	74 per 1000 **42 fewer per 1000** (CI 95% 69 fewer — 1 more)	Low Due to serious risk of bias, Due to serious imprecision [2]	Insecticide-treating clothing may reduce P. vivax clinical malaria compared to no insecticide-treated clothing.

1, 2. **Risk of Bias: serious. Imprecision: serious.**

References

100. Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ. Mosquito repellents for malaria prevention. The Cochrane database of systematic reviews 2018;(2):CD011595 Pubmed Journal Website

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Spatial/airborne repellents

Comparator: placebo or no malaria prevention intervention

Summary

Two RCTs were included in the systematic review. Studies were conducted in China and Indonesia. It is unknown whether spatial repellents protect against malaria parasitaemia (Risk ratio: 0.24; 95% CI (0.03–1.72); two studies; very low certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** placebo or no malaria prevention intervention	**Intervention** Spatial/airborne repellents	**Certainty of the evidence** (Quality of evidence)	**Summary**
Parasitaemia (all species)	Relative risk 0.24 (CI 95% 0.03 — 1.72) Based on data from 6,683 participants in 2 studies.	10 per 1000 Difference:	2 per 1000 **8 fewer per 1000** (CI 95% 10 fewer — 8 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency [1]	The evidence is very uncertain about the effect of spatial repellents on malaria parasitaemia compared to no spatial repellents.

1. **Risk of Bias: serious. Inconsistency: serious. Imprecision: serious.**

References

100. Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ. Mosquito repellents for malaria prevention. The Cochrane database of systematic reviews 2018;(2):CD011595 Pubmed Journal Website

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Space spraying

Comparator: no space spraying

Summary

The review included a single interrupted time series study from India that reported the monthly incidence of malaria over a four-year period, with at least one year prior and at least two years post-intervention.

It is not known if space spraying causes a step change in malaria incidence (1.00, 95% CI 0.51 to 1.92, 1 study, very low-certainty evidence).

It is not known if space spraying causes a change in the slope of malaria incidence over time (risk ratio 0.85, 95% CI 0.79 to 0.91, 1 study, very low-certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** no space spraying	**Intervention** Space spraying	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria cases per month (Instant effect)	Relative risk 1 (CI 95% 0.51 — 1.92) Based on data from participants in 1 studies. (Observational (non-	6 per 1000 Difference:	6 per 1000 **0 more per 1000** (CI 95% 3 fewer	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious	The evidence is very uncertain about the effect of space spraying on monthly malaria cases compared to no space spraying.

Outcome Timeframe	Study results and measurements	Comparator no space spraying	Intervention Space spraying	Certainty of the evidence (Quality of evidence)	Summary
	randomized))		— 6 more)	imprecision [1]	
Malaria cases per month (Effect after 12 months follow-up)	Relative risk 0.85 (CI 95% 0.79 — 0.91) Based on data from participants in 1 studies. (Observational (non-randomized))	6 per 1000 Difference:	1 per 1000 **5 fewer per 1000** (CI 95% 6 fewer — 4 fewer)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [2]	The evidence is very uncertain about the effect of space spraying on monthly malaria cases after 12 months compared to no space spraying.

1, 2. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**

References

108. Pryce J, Choi L, Richardson M, Malone D. Insecticide space spraying for preventing malaria transmission. The Cochrane database of systematic reviews 2018;(11):CD012689 Pubmed Journal Website

Clinical question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Screening of windows, ceilings, doors and eaves with untreated material

Comparator: No house screening

Summary

Two cRCTs met the inclusion criteria and were included in the meta-analysis. One trial in Ethiopia assessed screening of windows and doors. Another trial in Gambia assessed full screening (screening of eaves, doors and windows), as well as screening of ceilings only.

Screening may reduce clinical malaria incidence caused by *Plasmodium falciparum* (rate ratio 0.38, 95% CI 0.18 to 0.82; 1 trial, low-certainty evidence; Ethiopian study).

Screening may have a small effect on malaria parasite prevalence, (RR 0.84, 95% CI 0.60 to 1.17; 1 trial; low-certainty evidence).

Screening probably reduces anaemia (RR 0.61, 95% CI 0.42, 0.89; 705 participants; 1 trial, moderate-certainty evidence).

Screening may reduce the entomological inoculation rate (EIR). In the trial in Gambia, there was a mean difference in EIR between the control houses and treatment houses ranging from 0.45 to 1.50 (CIs ranged from -0.46 to 2.41; low-certainty evidence), the trial in Ethiopia reported a mean difference in EIR of 4.57, favouring screening (95% CI 3.81 to 5.33; low-certainty evidence).

Outcome Timeframe	Study results and measurements	Comparator No screening	Intervention Screening	Certainty of the evidence (Quality of evidence)	Summary
Clinical malaria incidence caused by P. falciparum	Relative risk 0.38 (CI 95% 0.18 — 0.82) Based on data from participants in 1 studies.	91 per 1000	35 per 1000	Low Due to serious risk of bias, Due to	Screening of houses may reduce clinical P. falciparum malaria incidence compared to no

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening	**Intervention** Screening	**Certainty of the evidence** (Quality of evidence)	**Summary**
	(Randomized controlled) Follow up: 6 months.	Difference:	**56 fewer per 1000** (CI 95% 75 fewer — 21 fewer)	serious imprecision [1]	screening.
Malaria parasite prevalence	Relative risk 0.84 (CI 95% 0.6 — 1.17) Based on data from 713 participants in 1 studies. [2] (Randomized controlled) Follow up: 1 year.	234 per 1000 Difference:	197 per 1000 **37 fewer per 1000** (CI 95% 94 fewer — 40 more)	Low Due to serious imprecision [3]	Screening of houses may result in little to no effect on malaria parasite prevalence compared to no screening.
Anaemia (haemoglobin conc <80g/L) prevalence	Relative risk 0.61 (CI 95% 0.42 — 0.89) Based on data from 705 participants in 1 studies. [4] (Randomized controlled) Follow up: 1 year.	211 per 1000 Difference:	128 per 1000 **82 fewer per 1000** (CI 95% 122 fewer — 23 fewer)	Moderate Due to serious imprecision [5]	Screening of houses probably reduces anaemia prevalence compared to no house screening.
Entomological Inoculation Rate (EIR)	Based on data from participants in 2 studies. (Randomized controlled) Follow up: range 6 months to 2 years.	In one study, the mean difference in EIR between the control houses and treatment houses ranged from 0.45 to 1.50 (CIs ranged from -0.46 to 2.41), depending on the study year and treatment arm; in a second study, there was a mean difference in EIR of 4.57 (95% CI 3.81 to 5.33).		Low Due to very serious imprecision [6]	Screening of houses may reduce EIR compared to no house screening.

1. **Risk of Bias: serious. Imprecision: serious.**
2, 4. with included studies: Kirby 2009.
3, 5. **Imprecision: serious.**
6. **Imprecision: very serious.** the CIs around the mean estimates are very wide..

4.1.4. Research needs

4.2. Preventive chemotherapies

4.2.1. Intermittent preventive treatment of malaria in pregnancy (IPTp)

Clinical question/ PICO

Population: Pregnant women
Intervention: Therapeutic course of SP
Comparator: No medicine

Outcome Timeframe	**Study results and measurements**	**Comparator** No medicine	**Intervention** Therapeutic course of SP	**Certainty of the evidence** (Quality of evidence)	**Summary**
Low birthweight, per dose of SP (low prevalence – 2.5%) 9 Critical	Relative risk 0.75 (CI 95% 0.71 — 0.78) Based on data from 80,519 participants in 98 studies. (Observational (non-randomized))	25 per 1000 Difference:	19 per 1000 **6 fewer per 1000** (CI 95% 7 fewer — 5 fewer)	Low Upgraded due to clear dose-response gradient, Due to serious publication bias [1]	Therapeutic courses of SP may improve low birthweight in low-burden areas.
Low birthweight, per dose of SP (high prevalence – 56.7%) 9 Critical	Relative risk 0.75 (CI 95% 0.71 — 0.78) Based on data from 80,519 participants in 98 studies. (Observational (non-randomized))	567 per 1000 Difference:	425 per 1000 **142 fewer per 1000** (CI 95% 164 fewer — 125 fewer)	Low Upgraded due to clear dose-response gradient, Due to serious publication bias [2]	Therapeutic courses of SP may result in a large improvement in low birthweight in high-burden areas.
Maternal anaemia, per dose of SP 8 Critical	Relative risk 0.9 (CI 95% 0.87 — 0.93) Based on data from participants in 53 studies. (Observational (non-randomized))	108 per 1000 Difference:	97 per 1000 **11 fewer per 1000** (CI 95% 14 fewer — 8 fewer)	Low Upgraded due to clear dose-response gradient, Due to serious publication bias [3]	Therapeutic courses of SP may decrease maternal anaemia.
Maternal malaria infection at delivery, per dose of SP 7 Critical	Relative risk 0.8 (CI 95% 0.75 — 0.85) Based on data from participants in 72 studies. (Observational (non-randomized))	20 per 1000 Difference:	16 per 1000 **4 fewer per 1000** (CI 95% 5 fewer — 3 fewer)	Moderate Upgraded due to clear dose-response gradient [4]	Therapeutic courses of SP probably decrease maternal malaria infection at delivery.
Placental malaria infection 6 Important	Relative risk 0.78 (CI 95% 0.74 — 0.84) Based on data from participants in 76 studies. (Observational (non-randomized))	9 per 1000 Difference:	7 per 1000 **2 fewer per 1000** (CI 95% 2 fewer — 1 fewer)	Moderate Upgraded due to clear dose-response gradient [5]	Therapeutic courses of SP probably decrease placental malaria infection.
Preterm delivery, per dose of SP 6 Important	Relative risk 0.76 (CI 95% 0.71 — 0.81) Based on data from participants in 59 studies. (Observational (non-randomized))	16 per 1000 Difference:	12 per 1000 **4 fewer per 1000** (CI 95% 5 fewer — 3 fewer)	Very low Due to serious publication bias, Due to serious inconsistency [6]	We are uncertain whether therapeutic courses of SP improve or worsen preterm delivery.
Stillbirths and/or abortions 6 Important	Relative risk 0.68 (CI 95% 0.59 — 0.78) Based on data from 0 participants in 46 studies. (Observational (non-randomized))	10 per 1000 Difference:	7 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 2 fewer)	Very low Due to serious inconsistency, Due to serious indirectness [7]	We are uncertain whether therapeutic courses of SP improve or worsen stillbirths and/or abortions.

Outcome Timeframe	**Study results and measurements**	**Comparator** No medicine	**Intervention** Therapeutic course of SP	**Certainty of the evidence** (Quality of evidence)	**Summary**
Maternal deaths 5 Important	Relative risk 1.17 (CI 95% 0.49 — 2.8) Based on data from 8,755 participants in 6 studies. (Randomized controlled)	3 per 1000 Difference:	4 per 1000 **1 more per 1000** (CI 95% 2 fewer — 5 more)	Low Very few events, Wide CIs include both no effect and appreciable risk [8]	Therapeutic courses of SP may result in little to no difference in maternal deaths.
Mean birthweight, per dose of SP 5 Important	Based on data from participants in 82 studies. (Observational (non-randomized))	Difference:	**MD 57 higher** (CI 95% 44 higher — 69 higher)	Moderate Upgraded due to clear dose-response gradient [9]	Therapeutic courses of SP probably improve mean birthweight.
Maternal haemoglobin, per dose of SP 4 Important	Based on data from participants in 46 studies. (Observational (non-randomized))	Difference:	**MD 0.19 higher** (CI 95% 0.15 higher — 0.22 higher)	Low Upgraded due to clear dose-response gradient [10]	Therapeutic courses of SP may improve maternal haemoglobin.
Maternal serious adverse events 6 Important	Based on data from participants in 8 studies. (Randomized controlled)	The pooled prevalence of serious adverse events among IPTp-SP recipients was 3.84% (95% CI 2.20-5.88).		Low Due to very serious risk of bias (no events reported in comparison arm) [11]	Therapeutic courses of SP may increase maternal serious adverse events.
Maternal adverse events, IPTp-SP vs placebo or case management	Based on data from 8,122 participants in 16 studies. (Randomized controlled)	The pooled prevalence of adverse events was 14.3% (95% CI 4.9-27.5%)		Moderate Due to serious imprecision [12]	Therapeutic courses of SP probably increase maternal adverse events compared to placebo or case management.

1, 2, 3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: serious.** Due to participation bias (women who did not attend ANC are likely to be different from those receiving three doses of IPTp). **Upgrade: clear dose-response gradient.**
4, 5, 9, 10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious. Upgrade: clear dose-response gradient.**
6. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I-squared 77.0%.. **Indirectness: no serious. Imprecision: no serious. Publication bias: serious.** Due to participation bias (women who did not attend ANC are likely to be different from those receiving three doses of IPTp).
7. **Inconsistency: serious.** Small numbers. The magnitude of statistical heterogeneity was high, with I-squared 79%. **Indirectness: serious.** Low numbers contributing to outcome. Distinction is not always made between these outcomes in participating studies. **Imprecision: no serious. Publication bias: no serious.**
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few events, Wide CIs include both no effect and appreciable risk. **Publication bias: no serious.**
11. **Risk of Bias: very serious.** No events reported in comparison arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Very few events. **Publication bias: no serious.**
12. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI crosses the null. **Publication bias: no serious.**

4.2.2. Perennial malaria chemoprevention (PMC) - formerly intermittent preventive treatment of malaria in infants (IPTi)

Clinical question/ PICO

Population: Children up to 24 months living in malaria-endemic areas

Intervention: PMC

Comparator: No intervention, or alternative medicines

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention, or alternative medicines	**Intervention** PMC	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinical malaria: all antimalarials, various regimens 9 Critical	Rate ratio 0.7 (CI 95% 0.62 — 0.8) Based on data from 10,602 participants in 10 studies. (Randomized controlled) Follow up: 9-36 months of age.	Difference:	**220 fewer per 1000** (CI 95% 280 fewer — 150 fewer)	Moderate Due to serious imprecision [1]	PMC probably reduces incidence of clinical malaria.
Clinical malaria: SP (various dosing regimens) [2] 9 Critical	Rate ratio 0.78 (CI 95% 0.69 — 0.88) Based on data from 8,774 participants in 8 studies. (Randomized controlled) Follow up: 9-36 months of age.	Difference:	**160 fewer per 1000** 230 fewer — 90 fewer	Moderate Due to serious imprecision [3]	PMC with SP probably reduces incidence of clinical malaria.
Clinical malaria: AS-AQ (at 10, 14 weeks and 9 months) 9 Critical	Rate ratio 0.75 (CI 95% 0.61 — 0.94) Based on data from 547 participants in 1 studies. (Randomized controlled) Follow up: 24 months of age.	Difference:	**330 fewer per 1000** (CI 95% 520 fewer — 120 fewer)	Moderate Due to serious imprecision [4]	PMC with AS-AQ probably reduces incidence of clinical malaria.
Clinical malaria: DHAP (monthly doses from 6–24 months of age) 9 Critical	Rate ratio 0.42 (CI 95% 0.33 — 0.54) Based on data from 147 participants in 1 studies. (Randomized controlled) Follow up: 36 months of age.	Difference:	**3,720 fewer per 1000** (CI 95% 430 fewer — 325 fewer)	Moderate Due to serious imprecision [5]	PMC with DHAP probably reduces incidence of clinical malaria.
Clinical malaria: SP+AS (at 10, 14 weeks and 9 months) 9 Critical	Rate ratio 0.78 (CI 95% 0.62 — 0.97) Based on data from 508 participants in 1 studies. (Randomized controlled) Follow up: up to 24 months of age.	Difference:	**290 fewer per 1000** (CI 95% 510 fewer — 40 fewer)	High	PMC with SP+AS reduces incidence of clinical malaria.
Severe malaria incidence: SP (various dosing regimens)	Rate ratio 0.92 (CI 95% 0.47 — 1.81) Based on data from 1,347 participants in 2 studies. (Randomized controlled)	Difference:	**1 fewer per 1000** (CI 95% 9 fewer — 11 more)	Low Due to serious inconsistency, Due to serious imprecision [6]	PMC with SP may reduce severe malaria incidence.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention, or alternative medicines	**Intervention** PMC	**Certainty of the evidence** (Quality of evidence)	**Summary**
8 Critical					
Severe malaria incidence: DHAP (monthly doses from 6–24 months of age) [7] 8 Critical	Rate ratio 1.29 (CI 95% 0.28 — 5.98) Based on data from 147 participants in 1 studies. (Randomized controlled)	Difference:	**8 more per 1000** (CI 95% 21 fewer — 144 more)	Low Due to very serious imprecision [8]	PMC with DHAP may increase severe malaria incidence.
Anaemia incidence: AS-AQ (at 10, 14 weeks and 9 months) 7 Critical	Rate ratio 0.77 (CI 95% 0.53 — 1.12) Based on data from 684 participants in 1 studies. (Randomized controlled)	Difference:	**70 fewer per 1000** 140 fewer — 40 more	Moderate Due to serious imprecision [9]	PMC with AS-AQ probably reduces anaemia incidence.
Anaemia incidence: SP+AS (at 10, 14 weeks and 9 months) 7 Critical	Rate ratio 0.72 (CI 95% 0.49 — 1.07) Based on data from 676 participants in 1 studies. (Randomized controlled)	Difference:	**80 fewer per 1000** (CI 95% 150 fewer — 20 more)	Moderate Due to serious imprecision [10]	PMC with SP+AS probably reduces anaemia incidence.
Anaemia incidence: SP (various dosing regimens) 7 Critical	Rate ratio 0.82 (CI 95% 0.68 — 0.98) Based on data from 7,438 participants in 6 studies. (Randomized controlled)	Difference:	**6 fewer per 1000** (CI 95% 100 fewer — 10 fewer)	Moderate Due to serious inconsistency [11]	PMC with SP probably reduces anaemia incidence.
Anaemia incidence: MQ (at 10, 14 weeks and 9 months) 7 Critical	Rate ratio 1.06 (CI 95% 0.78 — 1.44) Based on data from 480 participants in 1 studies. (Randomized controlled)	Difference:	**20 fewer per 1000** (CI 95% 60 fewer — 130 more)	Moderate Due to serious imprecision [12]	PMC with MQ probably increases anaemia incidence.
All-cause mortality: SP (various dosing regimens) 5 Important	Relative risk 0.93 (CI 95% 0.74 — 1.15) Based on data from 14,588 participants in 9 studies. (Randomized controlled)	23 per 1000 Difference:	21 per 1000 **2 fewer per 1000** (CI 95% 6 fewer — 3 more)	Moderate Due to serious inconsistency [13]	PMC with SP probably reduces all-cause mortality slightly.
All-cause mortality: AS-AQ	Relative risk 1.21 (CI 95% 0.58 — 2.55)	36	44	Moderate Due to serious	PMC with AS-AQ probably increases all-cause

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention, or alternative medicines	**Intervention** PMC	**Certainty of the evidence** (Quality of evidence)	**Summary**
(at 10, 14 weeks and 9 months) 5 Important	Based on data from 684 participants in 1 studies. (Randomized controlled)	per 1000 Difference:	per 1000 **8 more per 1000** (CI 95% 15 fewer — 56 more)	imprecision [14]	mortality slightly.
All-cause mortality: DHAP (monthly doses from 6–24 months of age) 5 Important	Relative risk 0.33 (CI 95% 0.01 — 8.08) Based on data from 196 participants in 1 studies. (Randomized controlled)	10 per 1000 Difference:	3 per 1000 **7 fewer per 1000** (CI 95% 10 fewer — 71 more)	Low Due to very serious imprecision [15]	PMC with DHAP may reduce all-cause mortality slightly.
All-cause mortality: SP+AS (at 10, 14 weeks and 9 months) 5 Important	Relative risk 0.83 (CI 95% 0.36 — 1.89) Based on data from 676 participants in 1 studies. (Randomized controlled)	36 per 1000 Difference:	30 per 1000 **6 fewer per 1000** (CI 95% 23 fewer — 32 more)	Moderate Due to serious imprecision [16]	PMC with SP+AS probably reduces all-cause mortality slightly.
Adverse events: DHAP (monthly doses from 6–24 months of age) 4 Important	Relative risk 0.58 (CI 95% 0.46 — 0.73) Based on data from 980 participants in 1 studies. (Randomized controlled)	227 per 1000 Difference:	132 per 1000 **95 fewer per 1000** (CI 95% 122 fewer — 61 fewer)	Moderate Due to serious imprecision [17]	PMC with DHAP probably reduces adverse events slightly.

1, 3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The overall meta-analysis was underpowered to detect a difference or to prove equivalence. **Publication bias: no serious.**
2. Per 1000 person years
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small population, wide CIs around effect estimate. **Publication bias: no serious.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Very few infants contributed to this analysis. Only data from one study. **Publication bias: no serious.**
6. **Inconsistency: serious.** There was considerable variation in the size of effect. The direction of the effect was not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** The trials were underpowered to detect a difference or to prove equivalence. Wide CIs including a null effect.. **Publication bias: no serious.**
7. DHAP given monthly for 18 months
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few infants contributed to this analysis. Only data from one study. Wide CIs. **Publication bias: no serious.**
9. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Only data from one study. **Publication bias: no serious.**
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. Only data from one study. **Publication bias: no serious.**
11. **Inconsistency: serious.** Unexplained statistical heterogeneity observed in this meta-analysis (I-squared: 67%.). **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
12. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
13. **Inconsistency: serious.** Wide variance of point estimates observed among the nine trials in this meta-analysis. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
14, 16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CIs include potential for important harm and benefit. **Publication bias: no serious.**

15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Wide CIs. Only data from one study. **Publication bias: no serious.**
17. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Very few infants contributed to this analysis. **Publication bias: no serious.**

4.2.3. Seasonal malaria chemoprevention (SMC)

Clinical question/ PICO

Population: Children aged ≤10 years in areas of seasonal transmission
Intervention: Full treatment doses of antimalarial medicines monthly during the malaria transmission season
Comparator: No intervention, or alternative medicines

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinical malaria: children <5 years (various regimens) Per 100 person-years 7 Critical	Rate ratio 0.27 (CI 95% 0.25 — 0.29) Based on data from participants in 8 studies. (Randomized controlled)	Difference:	**315 fewer per 1000** (CI 95% 335 fewer — 212 fewer)	Moderate Due to serious inconsistency [1]	SMC probably reduces clinical malaria incidence in children <5 years.
Clinical malaria: children <5 years, 3–4 cycles, SP+AQ 7 Critical	Rate ratio 0.28 (CI 95% 0.26 — 0.31) Based on data from participants in 4 studies. (Randomized controlled)	Difference:	**338 fewer per 1000** (CI 95% 374 fewer — 314 fewer)	Moderate Due to serious inconsistency [2]	3–4 cycles of SMC with SP+AQ probably reduces clinical malaria incidence in children <5 years.
Clinical malaria: children <5 years, 5–6 cycles, SP+AQ 7 Critical	Rate ratio 0.22 (CI 95% 0.18 — 0.25) Based on data from participants in 2 studies. (Randomized controlled)	Difference:	**205 fewer per 1000** (CI 95% 233 fewer — 168 fewer)	Moderate Due to serious inconsistency [3]	5–6 cycles of SMC with SP+AQ probably reduces clinical malaria incidence in children <5 years.
Clinical malaria: children <5 years, 5–6 cycles, AS-AQ 7 Critical	Rate ratio 0.31 (CI 95% 0.26 — 0.37) Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**122 fewer per 1000** (CI 95% 146 fewer — 103 fewer)	High	5–6 cycles of SMC with AS-AQ reduces clinical malaria incidence in children <5 years.
Clinical malaria: children <5	Rate ratio 0.14 (CI 95% 0.1 — 0.2)	Difference:	**315 fewer per**	High	3–4 cycles of SMC with SP+AS reduces clinical

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the evidence** (Quality of evidence)	**Summary**
years, 3–4 cycles, SP+AS 7 Critical	Based on data from participants in 1 studies. (Randomized controlled)		**1000** (CI 95% 450 fewer — 225 fewer)		malaria incidence in children <5 years.
Clinical malaria incidence: children ≥5 years (various regimens) 7 Critical	Rate ratio 0.27 (CI 95% 0.25 — 0.3) Based on data from participants in 3 studies. (Randomized controlled)	Difference:	**170 fewer per 1000** (CI 95% 189 fewer — 158 fewer)	Low Due to serious risk of bias, Due to serious inconsistency [4]	SMC may reduce clinical malaria incidence in children ≥ 5 years.
Clinical malaria: children 5–9 years, 3–4 cycles, SP+AQ 7 Critical	Rate ratio 0.39 (CI 95% 0.35 — 0.44) Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**2 fewer per 1000** (CI 95% 3 fewer — 2 fewer)	Moderate Due to serious risk of bias [5]	3–4 cycles of SMC with SP+AQ probably reduces clinical malaria incidence in children 5–9 years.
Clinical malaria: children 5–9 years, 5–6 cycles, SP+AQ 7 Critical	Rate ratio 0.17 (CI 95% 0.15 — 0.2) Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**248 fewer per 1000** (CI 95% 292 fewer — 219 fewer)	High	5–6 cycles of SMC with SP+AQ reduces clinical malaria incidence in children 5–9 years.
Clinical malaria: children <10 years, 3–4 cycles, SP+AQ 7 Critical	Rate ratio 0.4 (CI 95% 0.35 — 0.45) Based on data from participants in 2 studies. (Randomized controlled)	Difference:	**53 fewer per 1000** (CI 95% 60 fewer — 46 fewer)	Moderate Due to serious risk of bias [6]	3–4 cycles of SMC with SP+AQ probably reduces clinical malaria incidence in children <10 years.
Clinical malaria: children <10 years, 5–6 cycles, SP+AQ 7 Critical	Rate ratio 0.17 (CI 95% 0.15 — 0.2) Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**262 fewer per 1000** (CI 95% 308 fewer — 231 fewer)	Moderate Due to serious risk of bias [7]	5–6 cycles of SMC with SP+AQ probably reduces clinical malaria incidence in children <10 years.
Clinical malaria: children 6–15 years, 3–4 cycles, AS-AQ 7 Critical	Rate ratio 0.15 (CI 95% 0.11 — 0.21) Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**64 fewer per 1000** (CI 95% 89 fewer — 47 fewer)	Low Due to very serious risk of bias [8]	3–4 cycles of SMC with AS-AQ may reduce clinical malaria incidence in children 6–15 years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the evidence** (Quality of evidence)	**Summary**
Incidence of severe malaria, children <5 years, SP+AQ, 3–4 cycles 9 Critical	Rate ratio 0.57 (CI 95% 0.37 — 0.89) Based on data from 2,000 participants in 3 studies. (Randomized controlled)	Difference:	**14 fewer per 1000** (CI 95% 22 fewer — 9 fewer)	High	3–4 cycles of SMC with SP+AQ decreases incidence of severe malaria in children <5 years.
Incidence of severe malaria, children 5–9 years, SP+AQ, 3–4 cycles 9 Critical	Rate ratio 0.44 (CI 95% 0.23 — 0.84) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**4 fewer per 1000** (CI 95% 8 fewer — 2 fewer)	Moderate Due to serious risk of bias [9]	3–4 cycles of SMC with SP+AQ probably decreases incidence of severe malaria in children 5–9 years.
Incidence of severe malaria, children <10 years 9 Critical	Rate ratio 0.53 (CI 95% 0.37 — 0.76) Based on data from 2,000 participants in 4 studies. (Randomized controlled)	Difference:	**11 fewer per 1000** (CI 95% 16 fewer — 8 fewer)	High	SMC decreases incidence of severe malaria in children <10 years.
Incidence of all-cause hospitalization, children <5 years, SP+AQ moderate transmission, 3–4 cycles 8 Critical	Rate ratio 1.38 (CI 95% 0.71 — 2.67) Based on data from 2,000 participants in 2 studies. (Randomized controlled)	Difference:	**8 more per 1000** (CI 95% 4 fewer — 86 more)	Moderate Due to serious imprecision [10]	3-4 cycles of SMC with SP+AQ probably increases incidence of all-cause hospitalization in children <5 years in moderate transmission settings.
Incidence of all-cause hospitalization, children <5 years, SP+AQ, high transmission, 3–4 cycles 8 Critical	Rate ratio 0.54 (CI 95% 0.31 — 0.94) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**50 fewer per 1000** (CI 95% 87 fewer — 29 fewer)	High	3-4 cycles of SMC with SP+AQ reduces incidence of all-cause hospitalization in children <5 years in high transmission settings.
Incidence of all-cause hospitalization, children <5 years, AS-AQ, 5–6 cycles	Rate ratio 0.42 (CI 95% 0.2 — 0.87) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**23 fewer per 1000** (CI 95% 48 fewer — 11 fewer)	High	5–6 cycles of SMC with AS-AQ reduces incidence of all-cause hospitalization in children <5 years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the evidence** (Quality of evidence)	**Summary**
8 Critical					
All-cause mortality, children <5 years (various regimens) 6 Important	Rate ratio 0.89 (CI 95% 0.68 — 1.17) Based on data from 2,000 participants in 6 studies. (Randomized controlled)	Difference:	**8 fewer per 1000** (CI 95% 10 fewer — 6 fewer)	Low Due to serious inconsistency, Due to serious imprecision [11]	SMC may reduce all-cause mortality in children <5 years.
All-cause mortality, children <5 years, SP+AQ, 3–4 cycles 6 Important	Rate ratio 0.86 (CI 95% 0.64 — 1.16) Based on data from 2,000 participants in 4 studies. (Randomized controlled)	Difference:	**7 fewer per 1000** (CI 95% 10 fewer — 5 fewer)	Low Due to serious inconsistency, Due to serious imprecision [12]	3–4 cycles of SMC with SP+AQ may reduce all-cause mortality in children <5 years.
All-cause mortality, children <5 years, SP+AQ, 5–6 cycles 6 Important	Rate ratio 1.06 (CI 95% 0.47 — 2.4) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**2 fewer per 1000** (CI 95% 1 fewer — 5 more)	Very low Due to serious imprecision, Due to very serious risk of bias [13]	We are uncertain about the effect of 5–6 cycles of SMC with SP+AQ on all-cause mortality in children <5 years.
All-cause mortality, children <5 years, AS-AQ, 5–6 cycles 6 Important	Rate ratio 1.04 (CI 95% 0.39 — 2.77) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**18 fewer per 1000** (CI 95% 7 fewer — 9 more)	Moderate Due to serious imprecision [14]	5–6 cycles of SMC with AS-AQ probably has little or no difference on all-cause mortality in children <5 years.
All-cause mortality, children 5–9 years, SP+AQ, 3–4 cycles 6 Important	Rate ratio 0.97 (CI 95% 0.6 — 1.57) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**5 fewer per 1000** (CI 95% 4 fewer — 2 more)	Low Due to serious risk of bias, Due to serious imprecision [15]	3–4 cycles of SMC with SP+AQ may have little or no difference on all-cause mortality in children 5–9 years.
All-cause mortality, children 5–9 years, SP+AQ, 5–6 cycles 6 Important	Rate ratio 1.82 (CI 95% 0.16 — 20.24) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**0 fewer per 1000** (CI 95% 0 fewer — 4 more)	Very low Due to serious imprecision, Due to very serious risk of bias [16]	We are uncertain whether 5–6 cycles of SMC with SP+AQ increases or decreases all-cause mortality in children 5–9 years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the evidence** (Quality of evidence)	**Summary**
Parasite prevalence, children <5 years (various regimens) 4 Important	Relative risk 0.38 (CI 95% 0.34 — 0.43) Based on data from 200 participants in 9 studies. (Randomized controlled)	221 per 1000 Difference:	84 per 1000 **137 fewer per 1000** (CI 95% 146 fewer — 126 fewer)	Moderate Due to serious inconsistency [17]	SMC probably reduces parasite prevalence in children <5 years.
Parasite prevalence, children <5 years, SP+AQ, 3–4 cycles 4 Important	Relative risk 0.28 (CI 95% 0.24 — 0.32) Based on data from 200 participants in 4 studies. (Randomized controlled)	159 per 1000 Difference:	45 per 1000 **114 fewer per 1000** (CI 95% 121 fewer — 108 fewer)	High	3–4 cycles of SMC with SP+AQ reduces parasite prevalence in children <5 years.
Parasite prevalence, children <5 years, SP+AQ, 5–6 cycles 4 Important	Relative risk 0.55 (CI 95% 0.43 — 0.7) Based on data from 200 participants in 2 studies. (Randomized controlled)	192 per 1000 Difference:	106 per 1000 **86 fewer per 1000** (CI 95% 109 fewer — 58 fewer)	Moderate Due to serious inconsistency [18]	5–6 cycles of SMC with SP+AQ probably reduces parasite prevalence in children <5 years.
Parasite prevalence, children <5 years, AS-AQ, 3–4 cycles 4 Important	Relative risk 0.67 (CI 95% 0.53 — 0.85) Based on data from 200 participants in 1 studies. (Randomized controlled)	412 per 1000 Difference:	276 per 1000 **136 fewer per 1000** (CI 95% 194 fewer — 62 fewer)	Moderate Due to serious risk of bias [19]	3–4 cycles of SMC with AS-AQ probably reduces parasite prevalence in children <5 years.
Parasite prevalence, children <5 years, SP+AS, 3–4 cycles 4 Important	Relative risk 0.32 (CI 95% 0.15 — 0.67) Based on data from 200 participants in 1 studies. (Randomized controlled)	370 per 1000 Difference:	118 per 1000 **252 fewer per 1000** (CI 95% 314 fewer — 122 fewer)	Low Due to very serious imprecision [20]	3–4 cycles of SMC with SP+AS may reduce parasite prevalence in children <5 years.
Parasite prevalence, children <5 years, AS-AQ, 5–6 cycles 4 Important	Relative risk 0.24 (CI 95% 0.16 — 0.36) Based on data from 200 participants in 1 studies. (Randomized controlled)	196 per 1000 Difference:	47 per 1000 **149 fewer per 1000** (CI 95% 165 fewer — 125 fewer)	High	5–6 cycles of SMC with AS-AQ reduces parasite prevalence in children <5 years.
Parasite prevalence, children 5–9	Relative risk 0.23 (CI 95% 0.11 — 0.48) Based on data from 200	250 per 1000	57 per 1000	High	5–6 cycles of SMC with SP+AQ reduces parasite prevalence in children 5–9

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the evidence** (Quality of evidence)	**Summary**
years, SP+AQ, 5–6 cycles 4 Important	participants in 1 studies. (Randomized controlled)	Difference:	**193 fewer per 1000** (CI 95% 223 fewer — 130 fewer)		years.
Parasite prevalence, children <10 years, SP+AQ, 3–6 cycles 4 Important	Relative risk 0.28 (CI 95% 0.17 — 0.44) Based on data from 200 participants in 2 studies. (Randomized controlled)	84 per 1000 Difference:	24 per 1000 **60 fewer per 1000** 70 fewer — 47 fewer	High	SMC with SP+AQ reduces parasite prevalence of malaria in children <10 years.
Parasite prevalence, children <10 years, SP+AQ, 3–4 cycles 4 Important	Relative risk 0.29 (CI 95% 0.14 — 0.61) Based on data from 200 participants in 1 studies. (Randomized controlled)	19 per 1000 Difference:	6 per 1000 **13 fewer per 1000** (CI 95% 16 fewer — 7 fewer)	High	3–4 cycles of SMC with SP+AQ reduces parasite prevalence in children <10 years.
Parasite prevalence, children <10 years, SP+AQ, 5–6 cycles 4 Important	Relative risk 0.27 (CI 95% 0.15 — 0.48) Based on data from 200 participants in 1 studies. (Randomized controlled)	215 per 1000 Difference:	58 per 1000 **157 fewer per 1000** (CI 95% 183 fewer — 112 fewer)	High	5–6 cycles of SMC with SP+AQ reduces parasite prevalence in children <10 years.
Any anaemia, children <5 years 2 Not Important	Relative risk 0.84 (CI 95% 0.8 — 0.88) Based on data from 200 participants in 6 studies. (Randomized controlled)	524 per 1000 Difference:	440 per 1000 **84 fewer per 1000** (CI 95% 105 fewer — 63 fewer)	Moderate Due to serious inconsistency [21]	SMC probably reduces any anaemia in children <5 years.
Anaemia prevalence: SP+AQ 2 Not Important	Relative risk 0.47 (CI 95% 0.35 — 0.63) (Randomized controlled)	Difference:	**26 fewer per 1000** (CI 95% 32 fewer — 18 fewer)	High	SMC with SP+AQ reduces anaemia prevalence.
Any anaemia, children <5 years, SP+AQ, 3–4 cycles 2 Not Important	Relative risk 0.77 (CI 95% 0.72 — 0.83) Based on data from 200 participants in 3 studies. (Randomized controlled)	494 per 1000 Difference:	380 per 1000 **114 fewer per 1000** (CI 95% 138 fewer — 84 fewer)	Moderate Due to serious inconsistency [22]	3–4 cycles of SMC with SP+AQ probably decreases any anaemia in children <5 years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the evidence** (Quality of evidence)	**Summary**
Any anaemia, children <5 years, SP+AQ, 5–6 cycles 2 Not Important	Relative risk 0.88 (CI 95% 0.82 — 0.95) Based on data from 200 participants in 2 studies. (Randomized controlled)	598 per 1000 Difference:	526 per 1000 **72 fewer per 1000** (CI 95% 108 fewer — 30 fewer)	High	5–6 cycles of SMC with SP+AQ reduces any anaemia in children <5 years.
Any anaemia, children <5 years, AS-AQ, 3–4 cycles 2 Not Important	Relative risk 0.98 (CI 95% 0.85 — 1.13) Based on data from 200 participants in 1 studies. (Randomized controlled)	463 per 1000 Difference:	454 per 1000 **9 fewer per 1000** (CI 95% 69 fewer — 60 more)	Very low Due to serious imprecision [23]	We are uncertain whether 3–4 cycles of SMC with AS-AQ increases or decreases any anaemia in children <5 years.
Any anaemia, children 5–9 years, SP+AQ, 5–6 cycles 2 Not Important	Relative risk 0.7 (CI 95% 0.52 — 0.95) Based on data from 200 participants in 1 studies. (Randomized controlled)	475 per 1000 Difference:	332 per 1000 **143 fewer per 1000** (CI 95% 228 fewer — 24 fewer)	High	5–6 cycles of SMC with SP+AQ reduces any anaemia in children 5–9 years.
Moderate anaemia in children <5 years (various regimens) 2 Not Important	Relative risk 0.82 (CI 95% 0.73 — 0.93) Based on data from 200 participants in 6 studies. (Randomized controlled)	100 per 1000 Difference:	82 per 1000 **18 fewer per 1000** (CI 95% 27 fewer — 7 fewer)	Moderate Due to serious inconsistency [24]	SMC probably reduces moderate anaemia in children <5 years slightly.
Moderate anaemia in children <5 years, SP+AQ, 3–4 cycles, moderate to high transmission 2 Not Important	Relative risk 0.47 (CI 95% 0.35 — 0.63) Based on data from 200 participants in 2 studies. (Randomized controlled)	48 per 1000 Difference:	22 per 1000 **26 fewer per 1000** (CI 95% 32 fewer — 18 fewer)	High	3–4 cycles of SMC with SP+AQ decreases moderate anaemia in children <5 years, in moderate to high transmission areas.
Moderate anaemia in children <5 years, SP+AQ, 3–4 cycles, low transmission 2 Not Important	Relative risk 0.93 (CI 95% 0.81 — 1.07) Based on data from 200 participants in 2 studies. (Randomized controlled)	184 per 1000 Difference:	171 per 1000 **13 fewer per 1000** (CI 95% 35 fewer — 13 more)	High	3–4 cycles of SMC with SP+AQ reduces moderate anaemia in children <5 years, in low transmission areas.
Moderate anaemia in	Relative risk 0.91 (CI 95% 0.64 — 1.3) Based on data from 200	102 per 1000	93 per 1000	High	5–6 cycles of SMC with AS-AQ reduces moderate anaemia in children <5

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the evidence** (Quality of evidence)	**Summary**
children <5 years, AS-AQ, 5–6 cycles 2 Not Important	participants in 1 studies. (Randomized controlled)	Difference:	**9 fewer per 1000** (CI 95% 37 fewer — 31 more)		years.
Adverse events, children up to 15 years, various regimens, 3–4 cycles, active surveillance 5 Important	Relative risk 1.4 (CI 95% 1.31 — 1.51) Based on data from 18,042 participants in 4 studies. (Randomized controlled)	114 per 1000 Difference:	160 per 1000 **46 more per 1000** (CI 95% 35 more — 58 more)	High	SMC increases adverse events in children up to 15 years.

1, 2. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I-squared > 50%.. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3, 17, 18, 21, 22, 24. **Inconsistency: serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
4. **Risk of Bias: serious.** Randomization was imbalanced. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I-squared: > 50%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** Imbalanced randomization. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6, 7. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
8. **Risk of Bias: very serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
9. **Risk of Bias: serious.** Outcome evaluated by health system staff aware of study arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
11. **Inconsistency: serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: serious.** Wide range of effect sizes. **Publication bias: no serious.**
12. **Inconsistency: serious.** Wide range of effect sizes. **Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
13. **Risk of Bias: very serious.** Extra method of finding deaths in intervention arm. Selective outcome reporting. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
14. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. Only data from one study. **Publication bias: no serious.**
15. **Risk of Bias: serious.** Outcome evaluated by health system staff aware of study arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
16. **Risk of Bias: very serious.** Extra method of finding deaths in intervention arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
19. **Risk of Bias: serious.** High loss to follow-up, much higher in control arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide CIs. Only data from one study. **Publication bias: no serious.**
23. **Risk of Bias: very serious.** High loss to follow-up, much higher in control arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**

4.2.4. Intermittent preventive treatment of malaria in school-aged children (IPTsc)

Clinical question/ PICO

Population: School-aged children
Intervention: Therapeutic course of an antimalarial medicine
Comparator: No intervention

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention	**Intervention** Therapeutic course of an antimalarial medicine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinical malaria during follow-up (6 to 103 weeks) 8 Critical	Relative risk 0.5 (CI 95% 0.36 — 0.6) Based on data from 1,815 participants in 4 studies. (Randomized controlled)	226 per 1000 Difference:	113 per 1000 **113 fewer per 1000** (CI 95% 145 fewer — 90 fewer)	Low Due to serious risk of bias, Due to serious inconsistency [1]	Therapeutic courses of an antimalarial medicine may decrease clinical malaria during follow-up.
Anaemia 8 Critical	Relative risk 0.85 (CI 95% 0.77 — 0.92) Based on data from 14,940 participants in 11 studies. (Randomized controlled)	279 per 1000 Difference:	237 per 1000 **42 fewer per 1000** (CI 95% 64 fewer — 22 fewer)	Low Due to serious risk of bias, Due to serious inconsistency [2]	Therapeutic courses of an antimalarial medicine may decrease anaemia.
Parasite prevalence	Relative risk 0.46 (CI 95% 0.4 — 0.53) Based on data from 15,658 participants in 11 studies. (Randomized controlled)	349 per 1000 Difference:	160 per 1000 **189 fewer per 1000** (CI 95% 209 fewer — 164 fewer)	Low Due to serious risk of bias, Due to serious inconsistency [3]	Therapeutic courses of an antimalarial medicine may decrease parasite prevalence.

1, 2, 3. **Risk of Bias: serious.** Participants and personnel giving the treatments were not blinded. **Inconsistency: serious.** Unexplained between-study heterogeneity . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

4.2.5. Post-discharge malaria chemoprevention (PDMC)

Clinical question/ PICO

Population: Post-discharge children hospitalized with severe anaemia
Intervention: Therapeutic courses of an antimalarial medicine
Comparator: Placebo or no intervention

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or no intervention	**Intervention** Therapeutic courses of an antimalarial medicine	**Certainty of the evidence** (Quality of evidence)	**Summary**
All-cause	Relative risk 0.23	12	3	High	Therapeutic courses of an

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or no intervention	**Intervention** Therapeutic courses of an antimalarial medicine	**Certainty of the evidence** (Quality of evidence)	**Summary**
mortality (intervention period) 9 Critical	(CI 95% 0.08 — 0.7) Based on data from 3,356 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 14 weeks.	per 1000 Difference:	per 1000 **9 fewer per 1000** (CI 95% 11 fewer — 4 fewer)		antimalarial medicine decrease all-cause mortality in the intervention period.
All-cause mortality (post-intervention period) 9 Critical	Relative risk 1.61 (CI 95% 0.81 — 3.19) Based on data from 3,352 participants in 2 studies. (Randomized controlled) Follow up: 15 weeks to 26 weeks.	8 per 1000 Difference:	13 per 1000 **5 more per 1000** (CI 95% 2 fewer — 18 more)	Moderate Due to serious imprecision [1]	Therapeutic courses of an antimalarial medicine probably result in little to no difference in all-cause mortality in the post-intervention period.
All-cause mortality (intervention plus post-intervention period) 8 Critical	Relative risk 0.77 (CI 95% 0.47 — 1.28) Based on data from 3,387 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 26 weeks.	21 per 1000 Difference:	16 per 1000 **5 fewer per 1000** (CI 95% 11 fewer — 6 more)	Moderate Due to serious imprecision [2]	Therapeutic courses of an antimalarial medicine probably reduce all-cause mortality. However, the effect varies and it is possible that it makes little to no difference for all-cause mortality.
All-cause re-admission (intervention period) 9 Critical	Relative risk 0.42 (CI 95% 0.34 — 0.52) Based on data from 682 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 14 weeks.	833 per 1000 Difference:	350 per 1000 **483 fewer per 1000** (CI 95% 550 fewer — 400 fewer)	Moderate Due to serious inconsistency [3]	Therapeutic courses of an antimalarial medicine probably decrease all-cause re-admission in the intervention period.
All-cause re-admission (post-intervention period) 9 Critical	Hazard ratio 1.04 (CI 95% 0.83 — 1.3) Based on data from 558 participants in 2 studies. (Randomized controlled) Follow up: 15 weeks to 26 weeks.	632 per 1000 Difference:	646 per 1000 **14 more per 1000** (CI 95% 68 fewer — 95 more)	Moderate Due to serious imprecision [4]	Therapeutic courses of an antimalarial medicine probably result in little to no difference in all-cause re-admission in the post-intervention period.
Severe anaemia re-admission (intervention period) 8 Critical	Hazard ratio 0.38 (CI 95% 0.26 — 0.56) Based on data from 5,481 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 14 weeks.	44 per 1000 Difference:	17 per 1000 **27 fewer per 1000** (CI 95% 32 fewer — 19 fewer)	Moderate Due to serious inconsistency [5]	Therapeutic courses of an antimalarial medicine probably decrease severe anaemia re-admission in the intervention period.
Severe anaemia re-admission (post-intervention period) 8 Critical	Hazard ratio 0.74 (CI 95% 0.52 — 1.05) Based on data from 558 participants in 2 studies. (Randomized controlled) Follow up: 15 weeks to 26 weeks.	289 per 1000 Difference:	223 per 1000 **66 fewer per 1000** (CI 95% 126 fewer — 12 more)	Moderate Due to serious imprecision [6]	Therapeutic courses of an antimalarial medicine probably decrease severe anaemia re-admission in the post-intervention period.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or no intervention	**Intervention** Therapeutic courses of an antimalarial medicine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Severe malaria re-admission (intervention period) 8 Critical	Hazard ratio 0.32 (CI 95% 0.22 — 0.48) Based on data from 470 participants in 2 studies. (Randomized controlled) Follow up: 2 weeks to 14 weeks.	851 per 1000 Difference:	456 per 1000 **395 fewer per 1000** (CI 95% 509 fewer — 252 fewer)	Moderate Due to serious inconsistency [7]	Therapeutic courses of an antimalarial medicine probably decrease severe malaria re-admission in the intervention period
Severe malaria re-admission (post-intervention period) 8 Critical	Hazard ratio 1.06 (CI 95% 0.81 — 1.39) Based on data from 558 participants in 2 studies. (Randomized controlled) Follow up: 15 weeks to 26 weeks.	368 per 1000 Difference:	385 per 1000 **17 more per 1000** (CI 95% 58 fewer — 104 more)	Moderate Due to serious imprecision [8]	Therapeutic courses of an antimalarial medicine probably result in little to no difference in severe malaria re-admission in the post-intervention period.
Clinical malaria (intervention period) 6 Important	Hazard ratio 0.43 (CI 95% 0.36 — 0.5) Based on data from 3,356 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 14 weeks.	372 per 1000 Difference:	181 per 1000 **191 fewer per 1000** (CI 95% 218 fewer — 164 fewer)	Moderate Due to serious inconsistency [9]	Therapeutic courses of an antimalarial medicine probably decrease clinical malaria (intervention period).
Clinical malaria (post-intervention period) 6 Important	Hazard ratio 0.96 (CI 95% 0.83 — 1.11) Based on data from 3,325 participants in 3 studies. (Randomized controlled) Follow up: 15 weeks to 26 weeks.	241 per 1000 Difference:	233 per 1000 **8 fewer per 1000** (CI 95% 36 fewer — 23 more)	Moderate Due to serious imprecision [10]	Therapeutic courses of an antimalarial medicine probably result in little to no difference in clinical malaria (post-intervention period).
Clinical malaria (intervention plus post-intervention period) 6 Important	Hazard ratio 0.64 (CI 95% 0.58 — 0.72) Based on data from 3,387 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 26 weeks.	607 per 1000 Difference:	450 per 1000 **157 fewer per 1000** (CI 95% 189 fewer — 117 fewer)	Moderate Due to serious inconsistency [11]	Therapeutic courses of an antimalarial medicine probably decrease clinical malaria (intervention plus post-intervention period).
Drug-related adverse events (safety) 8 Critical	Based on data from 0 participants in 3 studies. (Randomized controlled)	Monthly SP was well tolerated. Minor symptoms recorded during the 30 days after the administration of each treatment were similar in the SP and placebo groups. The proportion of participants who vomited DHAP at least once within 60 minutes after drug intake was higher (12.4%) compared to placebo (3.8%), but no participant stopped the study medicine. DHAP was associated with an 18.6ms (95% CI: 15.6–21.8) increase in the QTc interval (Fridericia correction) after the third dose of each course (n = 33, all asymptomatic). All events of QTc (Fridericia's method for rate correction) prolongation were asymptomatic. None of the children in the DHAP group had		Moderate Due to serious indirectness [12]	Therapeutic courses of an antimalarial medicine probably result in little to no difference in the risk of drug-related adverse events (safety). Most adverse events are minor.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or no intervention	**Intervention** Therapeutic courses of an antimalarial medicine	**Certainty of the evidence** (Quality of evidence)	**Summary**
		QTc values of more than 500 ms.			

1, 2, 4, 6, 8, 10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The range of effect includes the null. **Publication bias: no serious.**
3. **Inconsistency: serious.** Considerable heterogeneity with I-squared = 87%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. **Inconsistency: serious.** Substantial heterogeneity with I-squared = 69%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. **Inconsistency: serious.** Considerable heterogeneity with I-squared = 93%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
9, 11. **Inconsistency: serious.** Substantial heterogeneity with I-squared = 71%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
12. **Inconsistency: no serious. Indirectness: serious.** ECG monitoring was conducted in a nested cardiac monitoring study involving 33 children receiving DHAP (one study). **Imprecision: no serious. Publication bias: no serious.**

4.2.6. Mass drug administration (MDA)

4.2.6.1. MDA for burden reduction

Clinical question/ PICO

Population: Adults and children residing in a delimited geographical area
Intervention: MDA
Comparator: No MDA, routine service

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinical malaria incidence: RCT, Pf, mod/high transmission 1–3 months post-MDA 9 Critical	Rate ratio 0.41 (CI 95% 0.04 — 4.42) Based on data from 144,422 participants in 1 studies. (Randomized controlled)	Difference:	**1 fewer per 1000** (CI 95% 2 fewer — 8 more)	Low Due to very serious imprecision [1]	MDA may decrease clinical malaria incidence in delimited moderate to high malaria transmission areas 1–3 months post-MDA.
Clinical malaria incidence: RCT, Pf, low/very low transmission 1–3 months post-MDA 9 Critical	Rate ratio 0.58 (CI 95% 0.12 — 2.73) Based on data from 130,651 participants in 2 studies. (Randomized controlled)	Difference:	**20 fewer per 1000** (CI 95% 50 fewer — 90 more)	Low Due to very serious imprecision [2]	MDA may decrease clinical malaria incidence in delimited low to very low malaria transmission areas 1–3 months post-MDA.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the evidence** (Quality of evidence)	**Summary**
Clinical malaria incidence: RCT, Pf, low/very low transmission 4–12 months post-MDA 9 Critical	Rate ratio 0.47 (CI 95% 0.21 — 1.03) Based on data from 26,576 participants in 3 studies. (Randomized controlled)	Difference:	**5 fewer per 1000** (CI 95% 7 fewer — 0 fewer)	Very low Due to serious risk of bias, Due to serious imprecision [3]	We are uncertain whether MDA increases or decreases clinical malaria incidence in delimited low to very low transmission areas 4–12 months post-MDA.
Clinical malaria incidence: RCT, Pf, low/very low transmission 12–24 months post-MDA 9 Critical	Rate ratio 0.77 (CI 95% 0.2 — 3.03) Based on data from 23,251 participants in 1 studies. (Randomized controlled)	Difference:	**4 fewer per 1000** (CI 95% 14 fewer — 34 more)	Low Due to very serious imprecision [4]	MDA may decrease clinical malaria incidence in delimited low to very low malaria transmission areas 12–24 months post-MDA.
Clinical malaria incidence: RCT, Pv 4–12 months post-MDA 9 Critical	Rate ratio 1.38 (CI 95% 0.97 — 1.95) Based on data from 3,325 participants in 2 studies. (Randomized controlled)	Difference:	**16 fewer per 1000** (CI 95% 39 fewer — 1 fewer)	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [5]	We are uncertain whether MDA increases or decreases P. vivax clinical malaria incidence 4–12 months post-MDA.
Clinical malaria incidence: non-RCT, Pv <1 month post-MDA 9 Critical	Rate ratio 0.23 (CI 95% 0.21 — 0.25) Based on data from 62,744 participants in 2 studies. (Observational (non-randomized))	Difference:	**36 fewer per 1000** (CI 95% 39 fewer — 33 fewer)	Very low Due to very serious risk of bias [6]	We are uncertain whether MDA increases or decreases P. vivax clinical malaria incidence <1 month post-MDA.
Clinical malaria incidence: non-RCT, Pv 1–3 months post-MDA 9 Critical	Rate ratio 0.29 (CI 95% 0.26 — 0.31) Based on data from 62,744 participants in 2 studies. (Observational (non-randomized))	Difference:	**45 fewer per 1000** (CI 95% 48 fewer — 41 fewer)	Very low Due to serious inconsistency [7]	We are uncertain whether MDA increases or decreases P. vivax clinical malaria incidence 1–3 months post-MDA.
Clinical malaria incidence: non-RCT, Pv 4–12 months post-MDA 9 Critical	Rate ratio 0.72 (CI 95% 0.68 — 0.76) Based on data from 11,300 participants in 1 studies. (Observational (non-randomized))	Difference:	**44 fewer per 1000** (CI 95% 50 fewer — 37 fewer)	Very low Due to very serious risk of bias [8]	We are uncertain whether MDA increases or decreases P. vivax clinical malaria incidence 4–12 months post-MDA.
Clinical malaria	Rate ratio 0.04			Very low	We are uncertain whether

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the evidence** (Quality of evidence)	**Summary**
incidence: non-RCT, Pv 12–24 months post-MDA 9 Critical	(CI 95% 0.02 — 0.07) Based on data from 11,300 participants in 1 studies. (Observational (non-randomized))	Difference:	**150 fewer per 1000** (CI 95% 153 fewer — 145 fewer)	Due to very serious risk of bias [9]	MDA increases or decreases P. vivax clinical malaria incidence 12–24 months post-MDA.
All-cause mortality: all ages, non-RCT, Pf, mod/high transmission <1 month post-MDA 7 Critical	Relative risk 0.68 (CI 95% 0.57 — 0.81) Based on data from 7,541,000 participants in 1 studies. (Observational (non-randomized))	81 per 1 million Difference:	55 per 1 million **26 fewer per 1 million** (CI 95% 35 fewer — 15 fewer)	Very low Due to serious risk of bias [10]	We are uncertain whether MDA increases or decreases all-cause mortality in all ages <1 month post-MDA.
All-cause mortality: <5 years, non-RCT, Pf, mod/high transmission <1 month post-MDA 7 Critical	Relative risk 0.34 (CI 95% 0.25 — 0.47) Based on data from 1,353,070 participants in 1 studies. (Observational (non-randomized))	250 per 1 million Difference:	85 per 1 million **165 fewer per 1 million** (CI 95% 187 fewer — 132 fewer)	Very low Due to serious risk of bias [11]	We are uncertain whether MDA increases or decreases all-cause mortality in children <5 years <1 month post-MDA.
All-cause mortality: all ages, non-RCT, Pf, mod/high transmission 1–3 months post-MDA 7 Critical	Odds ratio 1.77 (CI 95% 1.54 — 2.04) Based on data from 11,419,200 participants in 1 studies. (Observational (non-randomized))	51 per 1 million Difference:	87 per 1 million **36 more per 1 million** (CI 95% 25 more — 48 more)	Very low Due to serious risk of bias [12]	We are uncertain whether MDA increases or decreases all-cause mortality in all ages 1–3 months post-MDA.
All-cause mortality: <5 years, non-RCT, Pf, mod/high transmission 1–3 months post-MDA 7 Critical	Odds ratio 1.13 (CI 95% 0.87 — 1.46) Based on data from 2,008,720 participants in 1 studies. (Observational (non-randomized))	106 per 1 million Difference:	118 per 1 million **12 more per 1 million** (CI 95% 12 fewer — 42 more)	Very low Due to serious risk of bias, Due to serious imprecision [13]	We are uncertain whether MDA increases or decreases all-cause mortality in children <5 years 1–3 months post-MDA.
Parasite prevalence: non-RCT, Pf, mod/high transmission 4–12 months post-	Relative risk 0.6 (CI 95% 0.55 — 0.67) Based on data from 3,154 participants in 1 studies. (Observational (non-randomized))	418 per 1000 Difference:	251 per 1000 **167 fewer per 1000** (CI 95% 188	Very low Due to serious risk of bias [14]	We are uncertain whether MDA increases or decreases P. falciparum parasite prevalence in moderate to high transmission areas 4–12 months post-MDA.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the evidence** (Quality of evidence)	**Summary**
MDA 6 Important			fewer — 138 fewer)		
Parasite incidence: RCT, Pf, mod/high transmission 1–3 months post-MDA 3 Not Important	Rate ratio 0.61 (CI 95% 0.4 — 0.92) Based on data from 820 participants in 1 studies. (Randomized controlled)	57 per 1000 Difference:	35 per 1000 **22 fewer per 1000** (CI 95% 20 fewer — 205 more)	Moderate Due to serious risk of bias [15]	MDA probably reduces the incidence of P. falciparum in moderate to high transmission areas 1–3 months post-MDA.
Parasite incidence: RCT, Pf, mod/high transmission 4–12 months post-MDA 3 Not Important	Rate ratio 0.91 (CI 95% 0.55 — 1.5) Based on data from 518 participants in 1 studies. (Randomized controlled)	108 per 1000 Difference:	98 per 1000 **10 fewer per 1000** (CI 95% 53 fewer — 270 more)	Very low Due to serious risk of bias, Due to serious imprecision [16]	We are uncertain whether MDA increases or decreases the incidence of P. falciparum in moderate to high transmission areas 4–12 months post-MDA.
Parasite incidence: RCT, Pf, low/very low transmission 1–3 months post-MDA 3 Not Important	Rate ratio 0.37 (CI 95% 0.21 — 0.66) Based on data from 812 participants in 1 studies. (Randomized controlled)	12 per 1000 Difference:	5 per 1000 **7 fewer per 1000** (CI 95% 20 fewer — 205 more)	Moderate Due to serious risk of bias [17]	MDA probably reduces the incidence of P. falciparum in low to very low transmission areas 1– 3 months post-MDA.
Parasite prevalence: RCT, Pf, mod/ high transmission 1–3 months post-MDA 6 Important	Relative risk 1.76 (CI 95% 0.58 — 5.36) Based on data from 786 participants in 1 studies. (Randomized controlled)	47 per 1000 Difference:	83 per 1000 **36 more per 1000** (CI 95% 20 fewer — 205 more)	Low Due to very serious imprecision [18]	MDA may increase P. falciparum parasite prevalence slightly in moderate to high transmission areas 1–3 months post-MDA.
Parasite prevalence: RCT, Pf, mod/ high transmission 4–12 months post-MDA 6 Important	Relative risk 1.18 (CI 95% 0.89 — 1.56) Based on data from 1,497 participants in 1 studies. (Randomized controlled)	483 per 1000 Difference:	570 per 1000 **87 more per 1000** (CI 95% 53 fewer — 270 more)	Low Due to very serious imprecision [19]	MDA may increase P. falciparum parasite prevalence slightly in moderate to high transmission areas 4–12 months post-MDA.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the evidence** (Quality of evidence)	**Summary**
Parasite prevalence: non-RCT, Pf, mod/ high transmission 1–3 months post-MDA 6 Important	Relative risk 0.85 (CI 95% 0.78 — 0.93) Based on data from 1,000 participants in 1 studies. (Observational (non-randomized))	723 per 1000 Difference:	615 per 1000 **108 fewer per 1000** (CI 95% 159 fewer — 51 fewer)	Very low Due to serious risk of bias [20]	We are uncertain whether MDA increases or decreases P. falciparum parasite prevalence in moderate to high transmission areas 1–3 months post-MDA.
Parasite prevalence: non-RCT, Pf, mod/ high transmission 12–24 months post-MDA 6 Important	Relative risk 0.77 (CI 95% 0.7 — 0.84) Based on data from 3,261 participants in 1 studies. (Observational (non-randomized))	431 per 1000 Difference:	332 per 1000 **99 fewer per 1000** (CI 95% 129 fewer — 69 fewer)	Low	MDA may decrease P. falciparum parasite prevalence in moderate to high transmission areas 12–24 months post-MDA.
Parasite prevalence: RCT, Pf, low/ very low transmission 12–24 months post-MDA 6 Important	Relative risk 0.34 (CI 95% 0.06 — 1.97) Based on data from 1,390 participants in 1 studies. (Randomized controlled)	32 per 1000 Difference:	11 per 1000 **21 fewer per 1000** (CI 95% 30 fewer — 31 more)	Very low Due to serious risk of bias, Due to serious indirectness [21]	We are uncertain whether MDA increases or decreases P. falciparum parasite prevalence in low to very low transmission areas 12–24 months post-MDA.
Parasite prevalence: RCT, Pf, low/ very low transmission <1 month post-MDA 6 Important	Relative risk 0.12 (CI 95% 0.03 — 0.52) Based on data from 718 participants in 2 studies. (Randomized controlled)	35 per 1000 Difference:	4 per 1000 **31 fewer per 1000** (CI 95% 34 fewer — 17 fewer)	Moderate Due to serious risk of bias [22]	MDA probably decreases P. falciparum parasite prevalence in low to very low transmission areas <1 month post-MDA.
Parasite prevalence: RCT, Pf, low/ very low transmission 1–3 months post-MDA 6 Important	Relative risk 0.25 (CI 95% 0.15 — 0.41) Based on data from 6,511 participants in 8 studies. (Randomized controlled)	24 per 1000 Difference:	6 per 1000 **18 fewer per 1000** (CI 95% 20 fewer — 14 fewer)	Moderate Due to serious risk of bias [23]	MDA probably decreases P. falciparum parasite prevalence in low to very low transmission areas 1–3 months post-MDA.
Parasite prevalence: RCT, Pv	Relative risk 0.18 (CI 95% 0.08 — 0.4) Based on data from 234 participants in 1 studies.	272 per 1000	49 per 1000	Moderate Due to serious risk of bias [24]	MDA probably decreases P. vivax parasite prevalence <1 month post-MDA.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the evidence** (Quality of evidence)	**Summary**
<1 month post-MDA 6 Important	(Randomized controlled)	Difference:	**223 fewer per 1000** (CI 95% 250 fewer — 163 fewer)		
Parasite prevalence: RCT, Pf, low/ very low transmission 4–12 months post-MDA 6 Important	Relative risk 0.82 (CI 95% 0.56 — 1.22) Based on data from 5,102 participants in 6 studies. (Randomized controlled)	19 per 1000 Difference:	16 per 1000 **3 fewer per 1000** (CI 95% 8 fewer — 4 more)	Low Due to serious risk of bias, Due to serious inconsistency [25]	MDA may decrease P. falciparum parasite prevalence in low to very low transmission areas 4–12 months post-MDA.
Parasite prevalence: RCT, Pv 1–3 months post-MDA	Relative risk 0.15 (CI 95% 0.1 — 0.24) Based on data from 2,672 participants in 5 studies. (Randomized controlled)	133 per 1000 Difference:	20 per 1000 **113 fewer per 1000** (CI 95% 119 fewer — 101 fewer)	Low Due to serious risk of bias, Due to serious inconsistency [26]	MDA may decrease P. vivax parasite prevalence 1–3 months post-MDA.
Parasite prevalence: RCT, Pv 4-12 months post-MDA 6 Important	Relative risk 1.01 (CI 95% 0.87 — 1.18) Based on data from 6,255 participants in 5 studies. (Randomized controlled)	96 per 1000 Difference:	97 per 1000 **1 more per 1000** (CI 95% 12 fewer — 17 more)	Low Due to serious risk of bias, Due to serious inconsistency [27]	MDA may have little or no effect on P. vivax parasite prevalence 4–12 months post-MDA.
Parasite prevalence: RCT, Pv 12–24 months post-MDA 6 Important	Relative risk 0.81 (CI 95% 0.44 — 1.48) Based on data from 243 participants in 1 studies. (Randomized controlled)	175 per 1000 Difference:	142 per 1000 **33 fewer per 1000** (CI 95% 98 fewer — 84 more)	Low Due to serious risk of bias, Due to serious imprecision [28]	MDA may have little or no effect on P. vivax parasite prevalence 12–24 months post-MDA.
Parasite prevalence: non-RCT, Pv <1 month post-MDA 6 Important	Relative risk 0.32 (CI 95% 0.12 — 0.87) Based on data from 449 participants in 1 studies. (Observational (non-randomized))	71 per 1000 Difference:	23 per 1000 **48 fewer per 1000** (CI 95% 62 fewer — 9 fewer)	Very low Due to serious risk of bias [29]	We are uncertain whether MDA increases or decreases P. vivax parasite prevalence <1 month post-MDA.
Parasite prevalence: non-RCT, Pv 1–3 months post-	Relative risk 0.18 (CI 95% 0.1 — 0.33) Based on data from 1,024 participants in 2	231 per 1000 Difference:	42 per 1000 **189 fewer per**	Very low Due to very serious risk of bias [30]	We are uncertain whether MDA increases or decreases P. vivax parasite prevalence 1–3 months post-MDA.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the evidence** (Quality of evidence)	**Summary**
MDA 6 Important	studies. (Observational (non-randomized))		**1000** (CI 95% 208 fewer — 155 fewer)		
Parasite prevalence: non-RCT, Pv 4–12 months post-MDA 6 Important	Relative risk 0.34 (CI 95% 0.15 — 0.78) Based on data from 939 participants in 1 studies. (Observational (non-randomized))	71 per 1000 Difference:	24 per 1000 **47 fewer per 1000** (CI 95% 60 fewer — 16 fewer)	Very low Due to very serious risk of bias [31]	We are uncertain whether MDA increases or decreases P. vivax parasite prevalence 4–12 months post-MDA.
Serious adverse events: Pf, low/ very low transmission 0–3 months post-MDA 5 Important	Odds ratio 3.61 (CI 95% 0.43 — 30.03) Based on data from 6,911 participants in 1 studies. (Randomized controlled)	385 per 1 million Difference:	693 per 1 million **308 more per 1 million** (CI 95% 173 fewer — 564 more)	Moderate Due to serious imprecision [32]	MDA probably increases serious adverse events 0–3 months post-MDA.
Serious adverse events: RCT, Pf, low/very low transmission 4–12 months post-MDA 5 Important	Odds ratio 1.47 (CI 95% 0.68 — 3.2) Based on data from 6,911 participants in 1 studies. (Randomized controlled)	3,466 per 1 million Difference:	1,938 per 1 million **1,528 fewer per 1 million** (CI 95% 25,065 fewer — 2,180 fewer)	Moderate Due to serious imprecision [33]	MDA probably increases serious adverse events 4–12 months post-MDA.
Adverse events: RCT, Pf, mod/ high transmission 1–3 months post-MDA 5 Important	Odds ratio 3.25 (CI 95% 0.68 — 15.53) Based on data from 90 participants in 1 studies. (Randomized controlled)	133 per 1000 Difference:	333 per 1000 **200 more per 1000** (CI 95% 39 fewer — 571 more)	Very low [34]	We are uncertain whether MDA increases or decreases adverse events 1–3 months post-MDA.
Adverse event (vomiting): SP+AS +/-PQ, RCT, Pf, low/ very low transmission 4 Important	Odds ratio 0.54 (CI 95% 0.19 — 1.54) Based on data from 703 participants in 1 studies. (Randomized controlled)	43 per 1000 Difference:	24 per 1000 **19 fewer per 1000** (CI 95% 35 fewer — 22 more)	Moderate Due to serious imprecision [35]	MDA with SP+AS +/-PQ probably increases vomiting.
Difference in haemoglobin between day 1	High better Based on data from 680 participants in 1 studies.	Difference:	**MD 0.53 higher** (CI 95% 0.27 higher — 0.79	High	MDA improves difference in haemoglobin levels between day 1 and day 7 post-MDA treatment.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the evidence** (Quality of evidence)	**Summary**
and day 7, Pf, low/very low transmission 4 Important	(Randomized controlled)		higher)		
Pf: Adverse events in low/ very low transmission settings, cRCTs	Based on data from participants in 5 studies. (Randomized controlled)	SAE: Morris_2018 reported no SAEs, Shekalaghe_2011 reported two SAEs: a serious skin reaction and severe anaemia, Eisele_2020 reported four SAEs, of which three were deemed unrelated to drug ingestion, and McLean_2021 reported six SAEs (three deaths [all deemed unrelated to the drug], one stillbirth, one miscarriage, and one episode of severe dehydration secondary to vomiting and diarrhoea). AE: Morris_2018 used both active and passive detection of AEs; 298 individuals reported a total of 414 events out of 2411 doses of DHAP + single low dose primaquine; the most commonly reported AEs were nausea and vomiting (33.1% of all reports), dizziness, headache, and fatigue (23.5%), and stomach pain and diarrhoea (18.9%). von Seidlein_2019 reported that “1535 of 8112 (19%) MDA participants recalled 2577 AEs, of which 911 (35%) were considered related to the antimalarials; 592 (23%) of the 2577 AEs were dizziness, 199 (8%) nausea, 96 (4%) vomiting, and 39 (2%) itching, and 1653 (64%) participants reported a range of other minor complaints. There were no cases of severe haemolysis.” Among 336821 courses of DHAP, Eisele_2020 reported 687 AEs. The most common AE reported was gastrointestinal disturbances (diarrhoea, vomiting, abdominal pain, and nausea) at 48.6%; dizziness 19.8%; headache 16.0%, and general body weakness at 11.4%. McLean_2021 reported 151 AEs out of a total of 10677 doses. The majority of these (120) were mild, and dizziness and rash or itching were most commonly reported. Only 18 AEs were assessed as probably related to the medicine.		Low 36	
Drug resistance: PfKelch13 mutations among those who received MDA	Based on data from participants in 1 studies. (Randomized controlled)	269 patients with P. falciparum were identified at baseline, of which 221 completed at least one round of MDA and had parasites sequenced for PfKelch13 at baseline and one month post-MDA. At baseline, 10/221 were positive for PfKelch13 (4.5%) and one month post-MDA, there was one infection out of 14 (7%) remaining P. falciparum infections that showed the PfKelch13 genotype.		Very low Due to serious risk of bias [37]	

1, 2, 4, 18, 19. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
3. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: very serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
5. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I-squared >50%.. **Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
6, 8, 9. **Risk of Bias: very serious.** High or unclear risk of bias in included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: very serious.** High or unclear risk of bias in included studies. **Inconsistency: serious.** The CIs of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
10, 11, 12, 22. **Risk of Bias: serious.** High or unclear risk of bias in included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
13, 28. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
14, 20, 23, 24, 29. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
15, 17. **Risk of Bias: serious.**
16. **Risk of Bias: serious. Imprecision: serious.**
21. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: serious.** McLean had contact-tracing for neighbours in the 50 km surrounding positive cases in the intervention, but not for the control arm; this effect measures the combined intervention.. **Imprecision: very serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
25. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: serious.** Completely non-overlapping CIs. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
26. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: serious.** I-squared > 50%. Completely non-overlapping CIs. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
27. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
30, 31. **Risk of Bias: very serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
32, 33, 35. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect. **Publication bias: no serious.**
34. **Inconsistency: very serious.** Rates of events in both arms are much higher than in other studies; unclear how questions were asked.. **Indirectness: no serious. Imprecision: very serious.** Wide CIs that include both no effect and substantial effect. **Publication bias: no serious.**
36. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Although an RCT, outcome was collected in the MDA arm only, not in the control group. **Publication bias: no serious.**
37. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Although an RCT, data on adverse events, severe adverse events and drug resistance markers were only collected in the MDA arm, thus there is no control. **Publication bias: no serious.**

4.2.6.2. MDA for burden reduction in emergency settings

Clinical question/ PICO

Population: All ages during emergencies or periods of health service disruption
Intervention: MDA
Comparator: No MDA, routine service

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the evidence** (Quality of evidence)	**Summary**
All-cause mortality: 3 rounds, <1 month post-MDA, all ages [1] 7 Critical	Relative risk 0.68 (CI 95% 0.57 — 0.81) Based on data from 7,541,000 participants in 1 studies. (Observational (non-randomized))	81 per 1 million Difference:	55 per 1 million **26 fewer per 1 million** (CI 95% 35 fewer — 15 fewer)	Very low Due to serious risk of bias [2]	We are uncertain about the effect of MDA on all-cause mortality in all ages <1 month post-MDA.
All-cause mortality: 3 rounds, <1 month post-MDA, <5 years [3] 7 Critical	Relative risk 0.34 (CI 95% 0.25 — 0.47) Based on data from 1,353,070 participants in 1 studies. (Observational (non-randomized))	250 per 1 million Difference:	85 per 1 million **165 fewer per 1 million** (CI 95% 187 fewer — 132 fewer)	Very low Due to serious risk of bias [4]	We are uncertain about the effect of MDA on all-cause mortality in children <5 years <1 month post-MDA.
All-cause mortality: 3 rounds, 1–3 months post-MDA, all ages [5] 7 Critical	Odds ratio 1.77 (CI 95% 1.54 — 2.04) Based on data from 11,419,200 participants in 1 studies. (Observational (non-randomized))	51 per 1 million Difference:	87 per 1 million **36 more per 1 million** (CI 95% 25 more — 48 more)	Very low Due to serious risk of bias, Due to serious imprecision [6]	We are uncertain about the effect of MDA on all-cause mortality in all ages 1–3 months post-MDA.
All-cause mortality: 3 rounds, 1–3 months post-MDA, <5 years [7] 7 Critical	Odds ratio 1.13 (CI 95% 0.87 — 1.46) Based on data from 2,008,720 participants in 1 studies. (Observational (non-randomized))	106 per 1 million Difference:	118 per 1 million **12 more per 1 million** (CI 95% 12 fewer — 42 more)	Very low Due to serious risk of bias and serious imprecision [8]	We are uncertain about the effect of MDA on all-cause mortality in children <5 years 1–3 months post-MDA.
All cause hospitalization 0–1 months post-MDA 7 Critical	Based on data from participants in 1 studies. (Observational (non-randomized))	The number of all-cause hospital admissions decreased by between 5% and 21% during the four weeks after the first round of MDA, and by between 8% and 19% during the four weeks after the second round of MDA. Observed statistically significant changes at only one of eight time-points. Data on sample population sizes and from non-MDA control areas were not available, so absolute effects could not be calculated.		Very low Due to serious risk of bias and serious imprecision [9]	We are uncertain whether MDA increases or decreases all-cause hospitalization 0–1 months post-MDA.
Severe malaria hospitalization 0–1 months post-MDA 7 Critical	Based on data from participants in 1 studies. (Observational (non-randomized))	Change in the number of hospital admissions secondary to severe malaria ranged from a decrease of 31% to an increase of 8% during the four weeks after the first round of MDA, and by a 19% decrease to an 8% increase during the four weeks after the second round of MDA. Observed statistically significant changes at three		Very low Due to serious risk of bias and serious imprecision [10]	We are uncertain whether MDA increases or decreases severe malaria hospitalization 0–1 months post-MDA.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the evidence** (Quality of evidence)	**Summary**
		of eight time-points. Data on sample population sizes and from non-MDA control areas were not available, so absolute effects could not be calculated.			
Parasitologically confirmed malaria 0–1 months post-MDA 7 Critical	Based on data from participants in 1 studies. (Observational (non-randomized))	Point estimates of changes in parasitologically-confirmed malaria cases at health facilities decreased by between 35% and 62% during the four weeks after the first round of MDA, and by between 26% and 58% during the four weeks after the second round of MDA. All change estimates represented a statistically significant change from baseline. However, reductions in the number of parasitologically confirmed cases were also observed at all time points in no-MDA control areas during this time. 95% confidence intervals of the estimated changes in both MDA and non-MDA groups overlapped at all but two time points immediately after the first round of MDA. Data on sample population sizes were not available, so calculation of absolute effect was not possible.		Very low Due to serious risk of bias [11]	We are uncertain about the effect of MDA on parasitologically confirmed malaria 0–1 months post-MDA.

1, 3, 5, 7. Rounds 1-2 with AS-AQ, round 3 with AS-PYR
2. **Risk of Bias: very serious.** Unclear risk of bias in exposure measurement and control for confounding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
4. **Risk of Bias: serious.** Unclear risk of bias in exposure measurement and control for confounding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: serious.** Unclear risk of bias in exposure measurement and control for confounding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
8, 9, 10. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
11. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

4.2.6.3. MDA to reduce transmission of *P. falciparum* in very low to low transmission settings

Clinical question/ PICO

Population: Adults and children in delimited geographical area with very low to low transmission of P. falciparum
Intervention: Mass drug administration (MDA)
Comparator: no MDA

Summary

The systematic review identified eight cRCTs in very low to low transmission settings of six countries (Cambodia, Lao People's Democratic Republic, Myanmar, United Republic of Tanzania, Viet Nam and Zambia) assessing the impact of MDA on *P. falciparum* prevalence or incidence compared to no MDA (Schneider *et al* unpublished evidence). Two studies used DP alone; five studies used DP plus single low-dose primaquine; and one study used sulfadoxine-pyrimethamine/ artesunate (SP+AS) plus a single dose of primaquine at 0.75 mg/kg. Most (5) studies conducted three rounds of MDA within one year; one study conducted four rounds of MDA over 15 months; one study conducted two rounds and one study conducted one round of MDA over a one-year period.

Meta-analyses of the results showed reductions in prevalence and incidence of *P. falciparum* infection, but not clinical disease, 1–3 months after the last round of MDA. Multiple studies evaluated these outcomes at longer time periods but either no impact was found or the evidence was of very low certainty. Adverse events were often not measured in both arms, which complicated interpretation of the findings, but reported rates of adverse events or serious adverse events were low. Markers of artemisinin resistance were measured in only one study, which found no evidence of increases in drug-resistant parasites.

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the evidence** (Quality of evidence)	**Summary**
1-3 months - Incidence of clinical malaria	Rate ratio 0.58 (CI 95% 0.12 — 2.73) Based on data from 130,651 participants in 2 studies. (Randomized controlled)	6 per 1000	4 per 1000	Low Due to very serious imprecision [1]	MDA may result in little to no difference in the incidence of P. falciparum clinical malaria between 1-3 months
1-3 months - Prevalence	Relative risk 0.25 (CI 95% 0.15 — 0.41) Based on data from 6,511 participants in 8 studies. (Randomized controlled)	24 per 1000 Difference:	6 per 1000 **18 fewer per 1000** (CI 95% 20 fewer — 14 fewer)	Moderate Due to serious risk of bias [2]	MDA probably reduces P. falciparum prevalence between 1-3 months
4-12 months - Prevalence	Relative risk 0.82 (CI 95% 0.56 — 1.22) Based on data from 5,102 participants in 6 studies. (Randomized controlled)	19 per 1000 Difference:	16 per 1000 **3 fewer per 1000** (CI 95% 8 fewer — 4 more)	Low Due to serious risk of bias, and serious inconsistency [3]	MDA may result in little to no difference in P. falciparum prevalence between 4-12 months
1-3 months - Incidence of parasitaemia	Rate ratio 0.37 (CI 95% 0.21 — 0.66) Based on data from 811 participants in 1 studies. (Randomized controlled)	12 per 1000	5 per 1000	Moderate Due to serious risk of bias [4]	MDA probably reduces the incidence of P. falciparum parasitaemia between 1-3 months
4-12 months - Incidence of clinical malaria	Rate ratio 0.47 (CI 95% 0.21 — 1.03) Based on data from 26,576 participants in 4 studies. (Randomized controlled)	11 per 1000	5 per 1000	Very low Due to serious risk of bias, and serious imprecision [5]	The evidence is very uncertain about the effect of MDA on the incidence of P. falciparum clinical malaria between 4-12 months

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the evidence** (Quality of evidence)	**Summary**
1-3 months - Adverse events	Relative risk 3.25 (CI 95% 0.68 — 15.53) Based on data from 90 participants in 1 studies. (Randomized controlled)	133 per 1000 Difference:	433 per 1000 **300 more per 1000** (CI 95% 43 fewer — 1,000 more)	Very low Due to serious indirectness [6]	The evidence is very uncertain about the effect of MDA on adverse events between 1-3 months
12-24 months - Prevalence	Relative risk 0.34 (CI 95% 0.06 — 1.97) Based on data from 1,390 participants in 1 studies. (Randomized controlled)	32 per 1000 Difference:	11 per 1000 **21 fewer per 1000** (CI 95% 30 fewer — 31 more)	Very low Due to serious risk of bias, and serious indirectness [7]	The evidence is very uncertain about the effect of MDA on the prevalence of P. falciparum clinical malaria between 12-24 months
12-24 months - Incidence of clinical malaria	Rate ratio 0.77 (CI 95% 0.2 — 3.03) Based on data from 23,251 participants in 1 studies. (Randomized controlled)	17 per 1000	13 per 1000	Low Due to very serious imprecision [8]	MDA may reduce the incidence of P. falciparum clinical malaria between 12-24 months
4-12 months - Serious adverse events	Odds ratio 1.47 (CI 95% 0.68 — 3.2) Based on data from 6,911 participants in 1 studies. (Randomized controlled)	3 per 1000 Difference:	5 per 1000 **2 more per 1000** (CI 95% 1 fewer — 8 more)	Low Due to very serious imprecision [9]	MDA may have little to no effect on serious adverse events between 4-12 months
0-3 months - Serious Adverse Events	Odds ratio 3.61 (CI 95% 0.43 — 30.03) Based on data from 6,911 participants in 1 studies. (Randomized controlled)	0 per 1000 Difference:	1 per 1000 **1 more per 1000** (CI 95% 0 more — 11 more)	Moderate Due to serious imprecision [10]	MDA probably results in little to no difference in serious adverse events between 0-3 months
Pf - Vomiting among people receiving SP+AS with or without PQ vs Placebo - Low/Very Low - cRCTs	Odds ratio 0.54 (CI 95% 0.19 — 1.54) Based on data from 703 participants in 1 studies. (Randomized controlled)	43 per 1000 Difference:	24 per 1000 **19 fewer per 1000** (CI 95% 35 fewer — 22 more)	Moderate Due to serious imprecision [11]	MDA probably does not increase vomiting among people receiving SP+AS with or without PQ vs Placebo
SAEs among people who received MDA	Based on data from 353,143 participants in 4 studies. (Randomized controlled)		0.03 per 1000	[12]	

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the evidence** (Quality of evidence)	**Summary**
1-3 months - Drug resistance markers (PfKelch13) among people who were Pf positive	Relative risk 0.82 (CI 95% 0.45 — 1.51) Based on data from 63 participants in 1 studies. (Randomized controlled)	608 per 1000 Difference:	498 per 1000 **109 fewer per 1000** (CI 95% 334 fewer — 310 more)	Very low Due to serious risk of bias [13]	The evidence is very uncertain about the effect of MDA on artemisinin resistance markers (PfKelch13) among P. falciparum infections between 1-3 months
1-3 months - Drug resistance markers (PfKelch13) among all samples	Relative risk 0.13 (CI 95% 0.05 — 0.3) Based on data from 1,232 participants in 1 studies. (Randomized controlled)	64 per 1000 Difference:	8 per 1000 **56 fewer per 1000** (CI 95% 61 fewer — 45 fewer)	Low Due to serious risk of bias, and serious imprecision [14]	MDA may reduce the proportion of drug resistance markers (PfKelch13) among all samples between 1-3 months
4-12 months - Drug resistance markers (PfKelch13) among people who were Pf positive	Relative risk 1.16 (CI 95% 0.83 — 1.61) Based on data from 75 participants in 1 studies. (Randomized controlled)	610 per 1000 Difference:	707 per 1000 **98 more per 1000** (CI 95% 104 fewer — 372 more)	Very low Due to serious risk of bias [15]	The evidence is very uncertain about the effect of MDA on artemisinin resistance markers (PfKelch13) among P. falciparum infections between 4-12 months
4-12 months - Drug resistance markers (PfKelch13) among all samples	Relative risk 0.49 (CI 95% 0.28 — 0.85) Based on data from 2,595 participants in 1 studies. (Randomized controlled)	29 per 1000 Difference:	14 per 1000 **15 fewer per 1000** (CI 95% 21 fewer — 4 fewer)	Low Due to serious risk of bias, and serious imprecision [16]	MDA may reduce the proportion of drug resistance markers (PfKelch13) among all samples between 4-12 months
12-24 months - Drug resistance markers (PfKelch13) among people who were Pf positive	Relative risk 1.07 (CI 95% 0.82 — 1.4) Based on data from 78 participants in 1 studies. (Randomized controlled)	714 per 1000 Difference:	764 per 1000 **50 more per 1000** (CI 95% 129 fewer — 286 more)	Very low Due to serious risk of bias [17]	The evidence is very uncertain about the effect of MDA on artemisinin resistance markers (PfKelch13) among P. falciparum infections between 12-24 months
12-24 months - Drug resistance markers (PfKelch13) among all	Relative risk 0.66 (CI 95% 0.4 — 1.11) Based on data from 2,990 participants in 1 studies. (Randomized	25 per 1000 Difference:	17 per 1000 **8 fewer per 1000**	Low Due to serious risk of bias, and serious imprecision [18]	MDA may result in little to no reduction in drug resistance markers (PfKelch13) among all samples between 12-24

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the evidence** (Quality of evidence)	**Summary**
samples	controlled)		(CI 95% 15 fewer — 3 more)		months

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Substantial variability in point estimates including both appreciable risk and appreciable benefit.. **Publication bias: no serious.**
2, 4. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: serious.** Completely non-overlapping confidence intervals. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: very serious.** I-squared 72%. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
6. **Inconsistency: no serious. Indirectness: serious.** Self-reported symptoms, serious indirectness. **Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
7. **Risk of Bias: serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: serious.** McLean had contact tracing for neighbors in 50 km surrounding positive cases in the intervention but not control arm; this effect measures the combined intervention.. **Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
8, 9. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
10, 11. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
12. **Risk of Bias: very serious.** Although an RCT, data on AEs, SAEs and drug resistance markers was only collected in the MDA arm, thus there is no control. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Unable to calculate effect measure as there is no comparison group. **Publication bias: no serious.**
13, 15, 17. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk; Small event numbers, does not meet Optimal Information Size. **Publication bias: no serious.**
14, 16, 18. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small event numbers, does not meet Optimal Information Size. **Publication bias: no serious.**

4.2.6.4. MDA to reduce transmission of *P. falciparum* in moderate to high transmission settings

Clinical question/ PICO

Population: Adults and children in a delimited geographic area with moderate to high transmission of P. falciparum
Intervention: Mass drug administration (MDA)
Comparator: no MDA

Summary

The systematic review identified two cRCTs and two NRSs in moderate to high transmission settings in four countries (Burkina Faso, Gambia, Nigeria and Zambia) assessing the impact of MDA on *P. falciparum* compared to no MDA (Schneider *et al* *unpublished evidence*). The cRCTs and NRSs were analysed and GRADEd separately.

Among the cRCTs, one study conducted four rounds of MDA with DP alone over 15 months and the other conducted one round with SP+AS. Among the NRSs, one study provided nine rounds of sulfadoxine-pyrimethamine every 10 weeks over 18 months and the other provided either chloroquine or amodiaquine in combination with single low dose primaquine every 14 days for either eight or 15 rounds.

Meta-analyses of the results from the cRCTs showed little to no effect of MDA on *P. falciparum* prevalence or incidence or the incidence of clinical malaria across all time points with low- to moderate-certainty. The results from the NRSs were more likely to show a slight impact of MDA on *P. falciparum* prevalence at 4 – 12 and 12 – 24 months, with low-certainty evidence. Only one cRCT measured adverse events in a subset of both study arms and found a small increase in adverse events in the MDA arm but the certainty of the evidence was very low. None of the studies measured markers of drug resistance.

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the evidence** (Quality of evidence)	**Summary**
1-3 months - Prevalence	Relative risk 1.76 (CI 95% 0.58 — 5.36) Based on data from 786 participants in 1 studies. (Randomized controlled)	50 per 1000 Difference:	88 per 1000 **38 more per 1000** (CI 95% 21 fewer — 219 more)	Low Due to very serious imprecision [1]	MDA may result in little to no difference in P. falciparum prevalence between 1-3 months
1-3 months - Prevalence (NRS)	Relative risk 0.85 (CI 95% 0.78 — 0.93) Based on data from 1,000 participants in 1 studies. (Observational (non-randomized))	723 per 1000 Difference:	614 per 1000 **108 fewer per 1000** (CI 95% 159 fewer — 51 fewer)	Very low Due to serious risk of bias [2]	The evidence is very uncertain about the effect of MDA on P. falciparum prevalence between 1-3 months
1-3 months - Incidence of parasitaemia	Rate ratio 0.61 (CI 95% 0.4 — 0.92) Based on data from 820 participants in 1 studies. (Randomized controlled)	57 per 1000	35 per 1000	Moderate Due to serious imprecision [3]	MDA probably reduces the incidence of P. falciparum parasitaemia between 1-3 months
1-3 months - Incidence of clinical malaria	Rate ratio 0.41 (CI 95% 0.04 — 4.42) Based on data from 144,422 participants in 1 studies. (Randomized controlled)	2 per 1000	1 per 1000	Low Due to very serious imprecision [4]	MDA may result in little to no difference in the incidence of P. falciparum clinical malaria between 1-3 months
4-12 months - Prevalence	Relative risk 1.18 (CI 95% 0.89 — 1.56) Based on data from 1,497 participants in 1 studies. (Randomized controlled)	483 per 1000 Difference:	570 per 1000 **87 more per 1000** (CI 95% 53 fewer — 271 more)	Low Due to very serious imprecision [5]	MDA may result in little to no difference in P. falciparum prevalence between 4-12 months
4- 12 months - Prevalence (NRS)	Relative risk 0.6 (CI 95% 0.55 — 0.67) Based on data from	418 per 1000	251 per 1000	Low	MDA may reduce the prevalence of P. falciparum between 4-12

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the evidence** (Quality of evidence)	**Summary**
	3,154 participants in 1 studies. (Observational (non-randomized))	Difference:	**167 fewer per 1000** (CI 95% 188 fewer — 138 fewer)		months
4-12 months - Incidence of parasitaemia	Rate ratio 0.91 (CI 95% 0.55 — 1.5) Based on data from 517 participants in 1 studies. (Randomized controlled)	108 per 1000	98 per 1000	Very low Due to serious risk of bias [6]	The evidence is very uncertain about the effect of MDA on the incidence of P. falciparum parasitaemia between 4-12 months
12-24 months - Prevalence (NRS)	Relative risk 0.77 (CI 95% 0.7 — 0.84) Based on data from 3,261 participants in 1 studies. (Observational (non-randomized))	431 per 1000 Difference:	332 per 1000 **99 fewer per 1000** (CI 95% 129 fewer — 69 fewer)	Low	MDA may reduce P. falciparum prevalence between 12-24 months
Adverse events	Odds ratio 3.25 (CI 95% 0.68 — 15.53) Based on data from 90 participants in 1 studies. (Randomized controlled)	133 per 1000 Difference:	333 per 1000 **200 more per 1000** (CI 95% 39 fewer — 572 more)	Very low Due to very serious inconsistency [7]	The evidence is very uncertain about the effect of MDA on adverse events
AEs among people who received MDA	Based on data from 336,821 participants in 1 studies. (Randomized controlled)		2 per 1000	[8]	The evidence is very uncertain about the effect of MDA on adverse events
SAEs among people who received MDA	Based on data from 336,821 participants in 1 studies. (Randomized controlled)		0.01 per 1000	[9]	The evidence is very uncertain about the effect of MDA on adverse events

1, 4, 5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
2. **Risk of Bias: serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** GDG determined that the lower confidence bound (5 fewer per 1000) was not an important reduction and concluded that the finding was imprecise.. **Publication bias: no serious.**
6. **Risk of Bias: serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**

7. **Inconsistency: very serious.** Rates of events in both arms are much higher than in other studies; unclear how questions were asked.. **Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
8, 9. **Risk of Bias: very serious.** Although an RCT, outcome was collected in MDA arm only, not in control group. **Inconsistency: no serious. Indirectness: no serious. Publication bias: no serious.**

4.2.6.5. MDA to reduce transmission of *P. vivax*

Clinical question/ PICO

Population: Adults and children in a delimited geographical area with transmission of P. vivax
Intervention: Mass drug administration (MDA)
Comparator: no MDA

Summary

The systematic review identified five cRCTs and seven NRSs in eight countries (Cambodia, India, Kenya, Lao People's Democratic Republic, Myanmar, Panama, Solomon Islands, Venezuela [Bolivarian Republic of] and Viet Nam) assessing the impact of MDA on *P. vivax* transmission to no MDA (Schneider *et al* *unpublished evidence*). All of the cRCTs used DP and four of the studies also administered single low-dose primaquine, but none of the cRCTs used sufficient dosage of an 8-aminoquinoline to achieve radical cure of *P. vivax* hypnozoites[1]. One study provided a single round of MDA while the other four conducted three rounds of MDA. Among the NRSs, only one study reported radical cure of *P. vivax*. There was more variability in the design of MDA among the NRSs with respect to drug regimens and number of rounds, ranging from a single round to 24 weekly rounds.

The meta-analysis of the data from cRCTs showed MDA may reduce *P. vivax* prevalence 1–3 months after the last round of MDA but there was no impact of MDA on prevalence of *P. vivax* at later time periods. The certainty of evidence obtained from the NRSs was very low across all time periods and outcomes. Data from a cRCT that did not provide an 8-aminoquinoline medicine found that MDA probably did not increase the rate of severe adverse events within 0 – 3 months.

[1] The systematic review considered the following as the minimum adult dosage of 8-aminoquinoline medicines to achieve radical cure: 210 mg of primaquine over eight weeks; 1.25 g of plasmochin over 14 days. One study that contributed to the adverse events outcome (Comer 1971) considered its primaquine adult dosage regimen (40 mg of primaquine every two weeks for two years) to be radical cure, but as the total dose for an eight-week period (i.e. 160 mg) was less than 210 mg, the systematic review did not consider this to be radical cure.

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the evidence** (Quality of evidence)	**Summary**
1-3 months - Prevalence - NRS	Relative risk 0.18 (CI 95% 0.1 — 0.33) Based on data from 1,024 participants in 2 studies. (Observational (non-randomized))	231 per 1000 Difference:	42 per 1000 **189 fewer per 1000** (CI 95% 208 fewer — 155 fewer)	Very low Due to serious risk of bias, Due to serious inconsistency [1]	The evidence is very uncertain about the effect of MDA on P. vivax prevalence between 1-3 months
1-3 months - Prevalence	Relative risk 0.15 (CI 95% 0.1 — 0.24) Based on data from 2,672 participants in 5	133 per 1000	20 per 1000	Low Due to serious risk of bias, Due to serious	MDA may reduce P. vivax prevalence between 1-3 months

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the evidence** (Quality of evidence)	**Summary**
	studies. (Randomized controlled)	Difference:	**113 fewer per 1000** (CI 95% 119 fewer — 101 fewer)	inconsistency [2]	
1-3 months - Incidence of parasitaemia - NRS (low risk)	Rate ratio 0.37 (CI 95% 0.32 — 0.43) Based on data from 226,390 participants in 2 studies. (Observational (non-randomized))	5 per 1000 Difference:	2 per 1000 **3 fewer per 1000** (CI 95% 3 fewer — 3 fewer)	Very low Due to very serious risk of bias [3]	
1-3 months - Incidence of parasitaemia - NRS (high risk)	Rate ratio 0.37 (CI 95% 0.32 — 0.43) Based on data from 226,390 participants in 2 studies. (Observational (non-randomized))	180 per 1000 Difference:	67 per 1000 **113 fewer per 1000** (CI 95% 103 fewer — 122 fewer)	Very low Due to very serious risk of bias [4]	
1-3 months - Incidence of clinical malaria - NRS (low risk)	Rate ratio 0.29 (CI 95% 0.26 — 0.31) Based on data from 62,744 participants in 2 studies. (Observational (non-randomized))	22 per 1000	6 per 1000	Very low Due to serious inconsistency [5]	The evidence is very uncertain about the effect of MDA on the incidence of P. vivax clinical malaria between 1-3 months
1-3 months - Incidence of clinical malaria - NRS (high risk)	Rate ratio 0.29 (CI 95% 0.26 — 0.31) Based on data from 62,744 participants in 2 studies. (Observational (non-randomized))	156 per 1000 Difference:	45 per 1000 **111 fewer per 1000** 108 fewer — 115 fewer	Very low Due to serious inconsistency [6]	The evidence is very uncertain about the effect of MDA on the incidence of P. vivax clinical malaria between 1-3 months
4-12 months - Prevalence	Relative risk 1.01 (CI 95% 0.87 — 1.18) Based on data from 6,255 participants in 5 studies. (Randomized controlled)	96 per 1000 Difference:	97 per 1000 **1 more per 1000** (CI 95% 12 fewer — 17 more)	Low Due to serious risk of bias, Due to serious inconsistency [7]	MDA may result in little to no difference in P. vivax prevalence between 4-12 months
4-12 months - Prevalence - NRS	Relative risk 0.34 (CI 95% 0.15 — 0.78) Based on data from 939 participants in 1 studies. (Observational (non-randomized))	71 per 1000 Difference:	24 per 1000 **47 fewer per 1000** (CI 95% 60 fewer — 16 fewer)	Very low Due to very serious risk of bias [8]	The evidence is very uncertain about the effect of MDA on the prevalence of P. vivax between 4-12 months

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the evidence** (Quality of evidence)	**Summary**
4-12 months - Incidence of parasitaemia- NRS	Rate ratio 0.15 (CI 95% 0.07 — 0.34) Based on data from 223,990 participants in 1 studies. (Observational (non-randomized))	5 per 1000	1 per 1000	Very low Due to very serious risk of bias [9]	The evidence is very uncertain about the effect of MDA on the incidence of P. vivax parasitaemia between 4-12 months
4-12 months - Incidence of clinical malaria	Rate ratio 1.38 (CI 95% 0.97 — 1.95) Based on data from 3,325 participants in 1 studies. (Randomized controlled)	41 per 1000	57 per 1000	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [10]	The evidence is very uncertain about the effect of MDA on the incidence of P. vivax clinical malaria between 4-12 months
4-12 months - Incidence of clinical malaria - NRS	Rate ratio 0.72 (CI 95% 0.68 — 0.76) Based on data from 11,300 participants in 1 studies. (Observational (non-randomized))	156 per 1000	112 per 1000	Very low Due to very serious risk of bias [11]	The evidence is very uncertain about the effect of MDA on P. vivax clinical malaria between 4-12 months
12-24 months - Prevalence	Relative risk 0.81 (CI 95% 0.44 — 1.48) Based on data from 243 participants in 1 studies. (Randomized controlled)	175 per 1000 Difference:	142 per 1000 **33 fewer per 1000** (CI 95% 98 fewer — 84 more)	Low Due to serious risk of bias, Due to serious imprecision [12]	MDA may result in little to no difference in P. vivax prevalence between 12-24 months
12-24 months - Incidence of clinical malaria - NRS	Rate ratio 0.04 (CI 95% 0.02 — 0.07) Based on data from 11,300 participants in 1 studies. (Observational (non-randomized))	156 per 1000	6 per 1000	Very low Due to very serious risk of bias [13]	The evidence is very uncertain about the effect of MDA on the incidence of P. vivax clinical malaria between 12-24 months
0-3 Months - serious adverse events	Odds ratio 3.61 (CI 95% 0.43 — 30.03) Based on data from 6,911 participants in 1 studies. (Randomized controlled)	0.38 per 1000	1.39 per 1000	Moderate Due to serious imprecision [14]	MDA probably results in little to no difference in serious adverse events within 0-3 months
4-12 months - serious adverse events	Odds ratio 1.47 (CI 95% 0.68 — 3.2) Based on data from 6,911 participants in 1 studies. (Randomized controlled)	3 per 1000 Difference:	5 per 1000 **2 more per 1000** (CI 95% 1 fewer — 8 more)	Moderate Due to serious imprecision [15]	MDA probably results in little to no difference in serious adverse events between 4-12 months

1. **Risk of Bias: serious.** High risk of bias in all included studies. **Inconsistency: serious.** Completely non-overlapping confidence intervals. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

2. **Risk of Bias: serious.** High or unclear risk of bias in some/ all studies. **Inconsistency: serious.** Completely non-overlapping confidence intervals; I-squared 84%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3, 4. **Risk of Bias: very serious.** High risk of bias in all included studies.
5, 6. **Risk of Bias: very serious.** High risk of bias in all included studies. **Inconsistency: serious.** Completely non-overlapping confidence intervals. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: serious.** High or unclear risk of bias in some/ all studies. **Inconsistency: serious.** I-squared 74%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
8, 9, 11, 13. **Risk of Bias: very serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
10. **Risk of Bias: serious.** High or unclear risk of bias in some/ all studies. **Inconsistency: serious.** I-squared 52%. **Indirectness: no serious. Imprecision: serious.** Wide confidence interval; include both null effect and appreciable risk/ benefit. **Publication bias: no serious.**
12. **Risk of Bias: serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence interval; include both null effect and appreciable risk/ benefit. **Publication bias: no serious.**
14, 15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence interval; include both null effect and appreciable risk/ benefit. **Publication bias: no serious.**

4.2.6.6. Mass relapse prevention (MRP) to reduce transmission of *P. vivax*

Clinical question/ PICO

Population: Adults and children in a delimited geographical area with transmission of P. vivax
Intervention: Mass relapse prevention
Comparator: No MRP

Summary

The systematic review identified two NRSs that provided data on MRP for *P. vivax* (Shah *et al* unpublished evidence). Studies were conducted in the Democratic People's Republic of Korea in 2002 and in the Republic of Azerbaijan in 1970–1971. Both studies provided primaquine for 14 days at 0.25 mg/kg per day, administered in a single round prior to the peak transmission season. Both studies reported decreases in the incidence of *P. vivax* 1–3 months after the start of the intervention but the risk of bias in the studies was considered very serious. Both studies found a decrease in the incidence of *P. vivax* 4–12 months after the intervention and one study reported a decrease in the prevalence of *P. vivax* during that time period but the risk of bias in the studies was considered very serious. Information on adverse events was obtained from the intervention group in one study: no cases of severe haemolysis were reported, and side-effects were reported from less than 4% of 400 000 people. However, the overall certainty of the evidence was GRADEd as very low due to potential biases resulting from the study designs.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MRP	**Intervention** Mass relapse prevention	**Certainty of the evidence** (Quality of evidence)	**Summary**
1-3 months - Incidence of P. vivax infection - NRS	Rate ratio 0.08 (CI 95% 0.07 — 0.08) Based on data from 218,308 participants in 2 studies. (Observational (non-randomized))	111 per 1000	9 per 1000	Very low Due to very serious risk of bias [1]	The evidence is very uncertain about the effect of MRP on the incidence of P. vivax infection between 1-3 months

Outcome Timeframe	Study results and measurements	Comparator No MRP	Intervention Mass relapse prevention	Certainty of the evidence (Quality of evidence)	Summary
4-12 months - Prevalence - NRS	Relative risk 0.07 (CI 95% 0.01 — 0.57) Based on data from 6,710 participants in 1 studies. (Observational (non-randomized))	4 per 1000	0 per 1000	Very low Due to risk of bias. [2]	The evidence is very uncertain about the effect of MRP on the prevalence of P. vivax infection between 4-12 months
4-12 months - Incidence of P. vivax infection - NRS	Rate ratio 0.2 (CI 95% 0.18 — 0.22) Based on data from 416,617 participants in 2 studies. (Observational (non-randomized))	13 per 1000 Difference:	3 per 1000 **10 fewer per 1000** (CI 95% 11 fewer — 10 fewer)	Very low Due to very serious risk of bias [3]	The evidence is very uncertain about the effect of MRP on the incidence of P. vivax infection between 4-12 months
Adverse events	Based on data from 333,946 participants in 1 studies. (Observational (non-randomized))		40 per 1000	Very low Due to serious risk of bias, and very serious indirectness [4]	The evidence is very uncertain about the effect of MRP on adverse events

1, 3. **Risk of Bias: very serious.** Downgraded by 2 due to risk of bias. Many risk of bias domains judged as high risk or not enough information to determine. High risk of bias due to confounding in both studies included for this outcome. **Inconsistency: no serious.** Not downgraded for inconsistency. Both studies provided the same direction and a similar magnitude (qualitatively) of effect. **Indirectness: no serious.** Not downgraded for indirectness since evidence was judged to be sufficiently direct for the domains of population, intervention, comparator, direct comparison, and outcome. **Imprecision: no serious.** Not downgraded for imprecision since lower and upper confidence limits indicate the same direction of effect.
2. **Risk of Bias: serious.** Downgraded by 1 due to risk of bias. Quasi-experimental study design with a control group, but allocation was not done at random and no baseline data were provided to assess potential confounders. **Inconsistency: no serious.** Not downgraded for inconsistency due to single study result. **Indirectness: no serious.** Not downgraded for indirectness since evidence was judged to be sufficiently direct for the domains of population, intervention, comparator, direct comparison, and outcome. **Imprecision: no serious.** Not downgraded for imprecision since lower and upper confidence limits indicate the same direction of effect.
4. **Risk of Bias: serious.** Downgraded by 1 due to risk of bias. Quasi-experimental study design with a control group, but allocation was not done at random and no baseline data were provided to assess potential confounders. **Inconsistency: no serious.** Not downgraded for inconsistency due to single study result. **Indirectness: very serious.** Downgraded by 2 due to indirectness. Side effects were not measured or reported in the control group, so evidence is only provided in the intervention population. **Imprecision: no serious.** Not downgraded for imprecision since this criteria is not applicable for this outcome (no effect measure presented). **Upgrade: large magnitude of effect.**

4.3. Vaccines

Clinical question/ PICO

Population: Children ≥5 months of age living in areas with endemic malaria transmission

Intervention: A minimum of four doses of malaria vaccine (given as a three-dose initial series; first dose should be provided from around 5 months of age) with a minimum interval of four weeks between doses

Comparator: Malaria interventions currently in place without malaria vaccination

Summary

Systematic review summary

Six studies form the basis of these recommendations: five were individual randomized controlled trials (RCTs) and one was an open-label extension study of an included RCT. One RCT was a multicentre study evaluating three or four doses of the RTS,S/AS01 malaria vaccine compared to no malaria vaccination. One RCT evaluated the seasonal administration of RTS,S/AS01 malaria vaccine alone compared to SMC alone, and also compared a combination of malaria vaccine and SMC to either the malaria vaccine alone or SMC alone. One RCT was a single-site Phase 2b study evaluating the seasonal administration of the R21/Matrix-M malaria vaccine compared to no malaria vaccine in setting with highly seasonal malaria transmission where SMC was standard of care. One RCT was a multi-centre study evaluating age-based or seasonal vaccination of 4-doses of R21/Matrix-M compared to no malaria vaccination. One RCT was an open-label Phase 2b study evaluating the efficacy of RTS,S/AS01 as a full, fractional and delayed dose regimen. Based on WHO regions, all five studies were conducted in Africa, specifically: Burkina Faso (five studies), Gabon, Ghana (two studies), Kenya (four studies), Malawi, Mali (two studies), Mozambique, and the United Republic of Tanzania (two studies).

In addition, data from the observational evaluation during 46 months of pilot implementation in Ghana, Malawi, and Kenya were considered by SAGE/MPAG and included in the evidence summary.

The RCTs showed that RTS,S/AS01 reduces clinical malaria episodes, hospital admissions with a positive malaria test, hospitalization with severe malaria, all-cause hospital admissions, severe malaria anaemia and the need for blood transfusions. Compared to SMC, RTS,S/AS01 is non-inferior in reducing clinical malaria and severe malaria anaemia and may be superior in reducing hospitalization with severe malaria. The combination of RTS,S/AS01 and SMC is probably better than SMC alone in reducing all-cause mortality and clinical malaria, and may reduce the need for blood transfusions and all-cause hospital admissions. The pilot programme showed that delivery of RTS,S/AS01 through routine systems probably reduces hospital admissions with severe malaria.

The RCTs evaluating RTS,S/AS01 had too few cases to determine an association between the vaccine and meningitis, but the pilot study showed that RTS,S/AS01 introduction was probably not associated with an increase in hospital admissions with meningitis. There was uncertainty whether RTS,S/AS01 was associated with an increase in cerebral malaria in the RCTs, but the pilot programme showed that vaccine introduction was probably not associated with an increase in hospital admission with cerebral malaria. One RCT found that vaccination with RTS,S/AS01 may be associated with an increase in deaths in girls, but the other found no evidence that the effect of RTS,S/AS01 (alone or in combination with SMC) on mortality differed between girls and boys compared to SMC alone. The pilot programme found that the effect of the RTS,S/AS01 vaccine introduction on all-cause mortality probably did not differ between girls and boys.

The RCTs evaluating R21/Matrix-M showed that the vaccine reduces clinical malaria episodes using both age-based and seasonal vaccination approaches. Due to small sample size and too few events in the R21/Matrix-M RCTs, it was not possible to determine an association between vaccination and severe malaria, malaria hospital admissions or all-cause mortality. There was little to no difference between the R21/Matrix-M arm and the control arm in the number of blood transfusions and all-cause hospital admissions. Meningitis and cerebral malaria were included as adverse events of special interest (AESIs); both AESIs were uncommon and there was no imbalance between R21/Matrix-M and control arms.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
Protective efficacy (%) against clinical malaria; 4 doses RTS,S/AS01 vs control (age-based vaccination, low to high transmission) [1] Phase 3 randomized trial 2009–2014 9 Critical	36.3 (CI 95% 31.8 — 40.5) Based on data from 5,950 participants in 1 studies. [2] (Randomized controlled) Follow up: month 0 to study end (median 48 months).	Difference:	**1,774 fewer per 1000** (CI 95% 1,387 fewer — 2,186 fewer)	High	RTS,S/AS01 vaccination reduces clinical malaria episodes
Protective efficacy (%) against	39 (CI 95% 23 — 51)	1,172	715	Moderate Due to imprecision	RTS,S/AS01 vaccination probably reduces clinical

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
clinical malaria; 4 doses of RTS,S/ AS01 vs. control (age-based vaccination, high transmission) [3] Phase 2b randomized trial 2017–2018 9 Critical	Based on data from 591 participants in 1 studies. [4] (Randomized controlled) Follow up: month 0 to month 20.	per 1000 Difference:	per 1000 **457 fewer per 1000** (CI 95% 598 fewer — 270 fewer)	- confidence interval crosses threshold for a worthwhile effect [5]	malaria episodes
Protective efficacy (%) against clinical malaria; 3 doses of R21/ Matrix-M vs. control (age-based vaccination, low to moderate transmission) [6] Phase 3 randomized trial 2021–ongoing 9 Critical	66 (CI 95% 56 — 73) Based on data from 1,885 participants in 1 studies. [7] (Randomized controlled) Follow up: 12 months post dose 3.	446 per 1000 Difference:	171 per 1000 **272 fewer per 1000** (CI 95% 299 fewer — 236 fewer)	Moderate Due to indirectness - lack of data in high perennial transmission settings.	R21/Matrix-M vaccination probably reduces clinical malaria episodes
Protective efficacy (hazard ratio) against clinical malaria ; RTS,S/ AS01 alone vs. SMC alone (seasonal vaccination) [8] Phase 3b randomized trial 2017–2020 9 Critical	Hazard ratio 0.92 (CI 99% 0.84 — 1.01) Based on data from 3,953 participants in 1 studies. [9] (Randomized controlled) Follow up: 3 years.	305 per 1000 Difference:	278 per 1000 **21 fewer per 1000** (CI 95% 47 fewer — 10 fewer)	High	RTS,S/AS01 vaccination is non-inferior to SMC in reducing clinical malaria.
Protective efficacy (%) against clinical malaria; RTS,S/AS01 + SMC combination vs. SMC alone (seasonal vaccination) [10] Phase 3b randomized trial 2017–2020 9 Critical	62.8 (CI 95% 58.4 — 66.8) Based on data from 3,932 participants in 1 studies. [11] (Randomized controlled) Follow up: 3 years.	305 per 1000 Difference:	113 per 1000 **191 fewer per 1000** (CI 95% 204 fewer — 178 fewer)	High	The combination of RTS,S/ AS01 vaccination with SMC is superior to SMC alone in reducing clinical malaria.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
Protective efficacy (%) against clinical malaria; 3 doses R21/Matrix-M vs. control (seasonal vaccination) [12] Phase 2b randomized trial 2019–2021 9 Critical	77 (CI 95% 67 — 84) Based on data from 293 participants in 1 studies. [13] (Randomized controlled) Follow up: 12 months post dose 3.	720 per 1000 Difference:	267 per 1000 **555 fewer per 1000** (CI 95% 606 fewer — 483 fewer)	High	R21/Matrix-M vaccination reduces clinical malaria cases.
Protective efficacy (%) against clinical malaria; 4 doses R21/Matrix-M vs. control (seasonal vaccination) [14] Phase 3 randomized trial 2021–ongoing 9 Critical	73 (CI 95% 69 — 76) Based on data from 2,182 participants in 1 studies. [15] (Randomized controlled) Follow up: 18 months post dose 3.	1,264 per 1000 Difference:	350 per 1000 **936 fewer per 1000** (CI 95% 961 fewer — 885 fewer)	High	R21/Matrix-M vaccination reduces clinical malaria cases.
Protective efficacy (%) against severe malaria; 4 doses of RTS,S/AS01 vs. control (age-based vaccination, low to high transmission) [16] Phase 3 randomized trial 2009–2014 6 Important	32.2 (CI 95% 13.7 — 46.9) Based on data from 5,950 participants in 1 studies. [17] (Randomized controlled) Follow up: month 0 to study end (median 48 months).	Difference:	**19 fewer per 1000** (CI 95% 4 fewer — 35 fewer)	High [18]	RTS,S/AS01 vaccination reduces severe malaria.
Protective efficacy (%) against severe malaria; 3 doses of R21/Matrix-M vs. control (age-based vaccination, low to moderate transmission) [19] Phase 3 randomized trial; 2021-ongoing 6 Important	38 (CI 95% -176 — 86) Based on data from 1,885 participants in 1 studies. [20] (Randomized controlled) Follow up: 12 months post dose 3.	3.81 per 1000 Difference:	3.3 per 1000 **0 fewer per 1000** (CI 95% 3 fewer — 12 more)	Low Due to serious imprecision [21]	Too few events and small sample size to determine an association between R21/Matrix-M vaccination and severe malaria from this study.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
Ratio of ratios: incidence ratio of hospital admissions with severe malaria in age-eligible and age-ineligible children in RTS,S/AS01 implementing vs. comparison areas (age-based vaccination) [22] Pilot implementation study 2019–2023 6 Important	0.78 (CI 95% 0.64 — 0.97) Based on data from 58,114 participants in 1 studies. [23] Follow up: month 0 to month 46.			Moderate Due to serious imprecision [24]	RTS,S/AS01 vaccine introduction is probably associated with a reduction in incidence of hospital admissions with severe malaria.
Protective efficacy (%) against hospitalization due to severe malaria; RTS,S/AS01 alone vs. SMC alone (seasonal vaccination) [25] Phase 3b randomized trial 2017–2020 6 Important	-0.4 (CI 95% -60.2 — 37.1) Based on data from 3,953 participants in 1 studies. [26] (Randomized controlled) Follow up: 3 years.	6.8 per 1000 Difference:	6.7 per 1000 **0.1 fewer per 1000** (CI 95% 2 fewer — 2.4 more)	Low Due to very serious imprecision [27]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing hospitalization with severe malaria.
Protective efficacy (%) against hospitalization due to severe malaria; RTS,S/AS01 + SMC combination vs. SMC alone (seasonal vaccination) [28] Phase 3b randomized trial 2017–2020 6 Important	70.5 (CI 95% 41.9 — 85) Based on data from 3,932 participants in 1 studies. [29] (Randomized controlled) Follow up: 3 years.	6.8 per 1000 Difference:	2 per 1000 **4.8 fewer per 1000** (CI 95% 3.2 fewer — 5.7 fewer)	Moderate Due to serious imprecision [30]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in reducing hospitalization with severe malaria.
Protective efficacy (%) against severe malaria; 3 doses of R21/Matrix-M vs. control (seasonal vaccination) [31] Phase 3 randomized trial	58 (CI 95% -37 — 87) Based on data from 2,182 participants in 1 studies. [32] (Randomized controlled) Follow up: 18 months post dose 3.	10 per 1000 Difference:	5 per 1000 **5 fewer per 1000** (CI 95% 8 fewer — 3 more)	Low Due to serious imprecision [33]	Too few events and small sample size to determine an association between R21/Matrix-M vaccination and severe malaria from this study.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
2021-ongoing 6 Important					
Protective efficacy (%) against severe malaria anemia; 4 doses RTS,S/AS01 vs. control (age-based vaccination, low to high transmission) [34] Phase 3 randomized trial 2009–2014 6 Important	47.8 (CI 95% 11.6 — 69.9) Based on data from 5,950 participants in 1 studies. [35] (Randomized controlled) Follow up: month 0 to end of study (median 48 months).	Difference:	**11 fewer per 1000** (CI 95% 1 fewer — 24 fewer)	Moderate Due to serious imprecision [36]	RTS,S/AS01 vaccination probably reduces severe malaria anaemia.
Protective efficacy (%) against severe malaria anemia; RTS,S/AS01 alone vs. SMC alone (seasonal vaccination) [37] Phase 3b randomized trial 2017–2020 6 Important	18.4 (CI 95% -39.3 — 52.2) Based on data from 3,953 participants in 1 studies. [38] (Randomized controlled) Follow up: 3 years.	5.69 per 1000 Difference:	4.52 per 1000 **1.17 fewer per 1000** (CI 95% 2.64 fewer — 0.99 more)	Low Due to very serious imprecision [39]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing severe malaria anaemia.
Protective efficacy (%) against severe malaria anemia; RTS,S/AS01 + SMC combination vs. SMC alone (seasonal vaccination) [40] Phase 3b randomized trial 2017–2020 6 Important	67.9 (CI 95% 34.1 — 84.3) Based on data from 3,932 participants in 1 studies. [41] (Randomized controlled) Follow up: 3 years.	5.69 per 1000 Difference:	1.82 per 1000 **3.87 fewer per 1000** (CI 95% 2.32 fewer — 4.71 fewer)	Moderate Due to serious imprecision [42]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in reducing severe malaria anaemia.
Protective efficacy (%) against blood transfusions; 4 doses RTS,S/AS01 vs. control (age-based vaccination, low to high	28.5 (CI 95% 3.5 — 47.2) Based on data from 5,950 participants in 1 studies. [44] (Randomized controlled) Follow up: month 0 to end of study (median 48 months).	Difference:	**15 fewer** (CI 95% 1 fewer — 31 fewer)	Moderate Due to serious imprecision [45]	RTS,S/AS01 vaccination probably reduces the need for blood transfusions.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
transmission) [43] Phase 3 randomized trial 2009–2014 6 Important					
Protective efficacy (%) against blood transfusions; 4 doses of R21/ Matrix-M vs. control (age-based vaccination, low to moderate transmission) [46] Phase 3 randomized trial 2021-ongoing 6 Important	61 (CI 95% -7 — 86) Based on data from 1,751 participants in 1 studies. [47] (Randomized controlled) Follow up: 18 months post dose 3.	7.8 per 1000 Difference:	3.5 per 1000 **4.3 fewer per 1000** (CI 95% 7 fewer — 1 more)	Moderate Due to imprecision	There is probably little or no difference between R21/ Matrix-M vaccination and control in reducing the number of blood transfusions.
Protective efficacy (%) against blood transfusions; RTS,S/AS01 alone vs. SMC alone (seasonal vaccination) [48] Phase 3b randomized trial 2017–2020 6 Important	8.27 (CI 95% -67.6 — 49.8) Based on data from 3,953 participants in 1 studies. [49] (Randomized controlled) Follow up: 3 years.	4.22 per 1000 Difference:	3.79 per 1000 **0.43 fewer per 1000** (CI 95% 1.75 fewer — 1.6 more)	Low Due to very serious imprecision [50]	There may be little or no difference between RTS,S/ AS01 vaccination and SMC in reducing the need for blood transfusions.
Protective efficacy (%) against blood transfusions; RTS,S/AS01 + SMC combination vs. SMC alone (seasonal vaccination) [51] Phase 3b randomized trial 2017–2020 6 Important	65.4 (CI 95% 22.9 — 84.5) Based on data from 3,932 participants in 1 studies. [52] (Randomized controlled) Follow up: 3 years.	4.22 per 1000 Difference:	1.45 per 1000 **2.77 fewer per 1000** (CI 95% 1.32 fewer — 3.49 fewer)	Low Due to very serious imprecision [53]	The combination of RTS,S/ AS01 vaccination with SMC may be superior to SMC alone in reducing the need for blood transfusions.
Protective efficacy (%) against blood transfusions; 3 doses of R21/ Matrix-M vs. control (seasonal	20 (CI 95% -242 — 81) Based on data from 2,182 participants in 1 studies. [55] (Randomized controlled) Follow up: 18 months post dose 3.	5.5 per 1000 Difference:	3.9 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 7 more)	Moderate Due to imprecision	There is probably little or no difference between R21/ Matrix-M vaccination and control in reducing the number of blood transfusions.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
vaccination) [54] Phase 3 randomized trial 2021-ongoing 6 Important					
Protective efficacy (%) against all-cause hospital admissions; 4 doses RTS,S/AS01 vs. control (age-based vaccination, low to high transmission) [56] Phase 3 randomized trial 2009–2014 6 Important	16.5 (CI 95% 7.2 — 24.9) Based on data from 5,950 participants in 1 studies. [57] (Randomized controlled) Follow up: month 0 to end of study (median of 48 months).	259 per 1000 Difference:	216 per 1000 **59 fewer per 1000** (CI 95% 18 fewer — 103 fewer)	High [58]	RTS,S/AS01 vaccination reduces all-cause hospital admissions.
Ratio of ratios: incidence ratio of all-cause hospital admissions in age-eligible and age-ineligible children in RTS,S/AS01 implementing vs. comparison areas (age-based vaccination) [59] Pilot implementation study 2019–2023 6 Important	0.92 (CI 95% 0.81 — 1.05) Based on data from 58,114 participants in 1 studies. [60] Follow up: month 0 to month 46.			Moderate Due to serious imprecision. [61]	RTS,S/AS01 vaccine introduction probably has little or no difference on all-cause hospital admissions.
Protective efficacy (%) against all-cause hospitalizations; 3 doses of R21/Matrix-M vs. control (age-based vaccination, low to moderate transmission) [62] Phase 3 randomized trial 2021-ongoing 6 Important	11 (CI 95% -67 — 52) Based on data from 1,751 participants in 1 studies. [63] (Randomized controlled) Follow up: 18 months post dose 3.	19.5 per 1000 Difference:	19.2 per 1000 **0 fewer per 1000** (CI 95% 8 fewer — 12 more)	Moderate Due to imprecision	There is probably little or no difference between R21/Matrix-M vaccination and control in reducing the number of all-cause hospitalizations.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
Protective efficacy (%) against all-cause hospital admissions; RTS,S/AS01 alone vs. SMC alone (seasonal vaccination) [64] Phase 3b randomized trial 2017–2020 6 Important	-22.3 (CI 95% -74.4 — 14.3) Based on data from 3,953 participants in 1 studies. [65] (Randomized controlled) Follow up: 3 years.	11 per 1000 Difference:	13.2 per 1000 **2.2 more per 1000** (CI 95% 0.5 fewer — 5.6 more)	Low Due to very serious imprecision [66]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing all-cause hospital admissions.
Protective efficacy (%) against all-cause hospital admissions; RTS,S/AS01 + SMC combination vs. SMC alone (seasonal vaccination) [67] Phase 3b randomized trial 2017–2020 6 Important	18.7 (CI 95% -19.4 — 44.7) Based on data from 3,932 participants in 1 studies. [68] (Randomized controlled) Follow up: 3 years.	11 per 1000 Difference:	8.9 per 1000 **2.1 fewer per 1000** (CI 95% 4.28 fewer — 0.8 more)	Low Due to very serious imprecision [69]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in reducing all-cause hospital admissions.
Protective efficacy (%) against all-cause hospitalizations; 4 doses of R21/Matrix-M vs. control (seasonal vaccination) [70] Phase 3 randomized trial 2021-ongoing 6 Important	26 (CI 95% -43 — 62) Based on data from 2,182 participants in 1 studies. [71] (Randomized controlled) Follow up: 18 months post dose 3.	16.4 per 1000 Difference:	13.6 per 1000 **3 fewer per 1000** (CI 95% 9 fewer — 8 more)	Moderate Due to imprecision	There is probably little or no difference between R21/Matrix-M vaccination and control in reducing the number of all-cause hospitalizations.
Ratio of ratios: incidence ratio of admissions with a positive malaria test in age-eligible and age-ineligible children in RTS,S/AS01 implementing vs. comparison areas (age-based vaccination) [72] Pilot implementation study 2019–2023	0.83 (CI 95% 0.73 — 0.95) Based on data from 58,114 participants in 1 studies. [73] Follow up: month 0 to month 46.			High [74]	RTS,S/AS01 vaccine introduction is associated with reduced hospital admissions with a positive malaria test.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
6 Important					
Protective efficacy (%) against malaria hospitalizations; 3 doses of R21/ Matrix-M vs. control (age-based vaccination, low to moderate transmission) [75] Phase 3 randomized trial 2021-ongoing 6 Important	23 (CI 95% -224 — 82) Based on data from 1,885 participants in 1 studies. [76] (Randomized controlled) Follow up: 12 months post dose 3.	5 per 1000 Difference:	5.5 per 1000 **0 fewer per 1000** (CI 95% 3 fewer — 3 more)	Low Due to serious imprecision [77]	Too few events and small sample size to determine an association between R21/Matrix-M vaccination and malaria hospital admissions from this study.
Protective efficacy (%) against malaria hospitalizations; 4 doses of R21/ Matrix-M vs. control (seasonal vaccination) [78] Phase 3 randomized trial 2021-ongoing 6 Important	58 (CI 95% -37 — 87) Based on data from 2,182 participants in 1 studies. [79] (Randomized controlled) Follow up: 18 months post dose 3.	10 per 1000 Difference:	5 per 1000 **5 fewer per 1000** (CI 95% 8 fewer — 3 more)	Low Due to serious imprecision [80]	Too few events and small sample size to determine an association between R21/Matrix-M vaccination and malaria hospital admissions from this study.
Incidence rate ratio against all-cause mortality; 3 or 4 doses RTS,S/AS01 vs. control (age-based vaccination, low to high transmission) [81] Phase 3 randomized trial 2009–2014 6 Important	Rate ratio 1.21 (CI 95% 0.86 — 1.72) Based on data from 8,922 participants in 1 studies. [82] (Randomized controlled) Follow up: month 0 to end of study (median of 48 months).	15 per 1000 Difference:	18.83 per 1000 **3 more per 1000** (CI 95% 2 fewer — 11 more)	Low Due to very serious imprecision [83]	There were too few deaths to determine the impact of RTS,S/AS01 vaccination on all-cause mortality.
Protective efficacy (%) against all-cause mortality; 3 doses of R21/ Matrix-M vs. control (age-	Based on data from 2,451 participants in 1 studies. [85] (Randomized controlled) Follow up: 14 months post dose 1.	1.23 per 1000	3.05 per 1000	Low Due to serious imprecision [86]	Too few events to determine an association between R21/Matrix-M vaccination and all-cause mortality from this study.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
based vaccination, low to moderate transmission) [84] Phase 3 randomized trial 2021-ongoing 6 Important					
Ratio of ratios: incidence ratio of all-cause mortality in age-eligible and age-ineligible children in RTS,S/AS01 implementing vs. comparison areas (age-based vaccination) [87] Pilot implementation study 2019-2023 6 Important	0.87 (CI 95% 0.77 — 0.97) Based on data from 58,114 participants in 1 studies. [88] Follow up: month 0 to month 46.				RTS,S/AS01 vaccine introduction probably reduces all-cause mortality.
Protective efficacy (%) against all-cause mortality; RTS,S/AS01 alone vs. SMC alone (seasonal vaccination) [89] Phase 3b randomized trial 2017–2020 6 Important	12.1 (CI 95% -55.7 — 50.4) Based on data from 3,953 participants in 1 studies. [90] (Randomized controlled) Follow up: 3 years.	4.59 per 1000 Difference:	3.97 per 1000 **0.62 fewer per 1000** (CI 95% 1.97 fewer — 1.45 more)	Low Due to very serious imprecision [91]	There may be little or no difference between the impact of RTS,S/AS01 vaccination and SMC administration on all-cause mortality.
Protective efficacy (%) against all-cause mortality; RTS,S/AS01 + SMC combination vs. SMC alone (seasonal vaccination) [92] Phase 3b randomized trial 2017–2020 6 Important	52.3 (CI 95% 4.99 — 76) Based on data from 3,932 participants in 1 studies. [93] (Randomized controlled) Follow up: 3 years.	4.59 per 1000 Difference:	2.18 per 1000 **2.41 fewer per 1000** (CI 95% 0.75 fewer — 3.35 fewer)	Moderate Due to serious imprecision [94]	The combination of RTS,S/AS01 vaccination and SMC is probably associated with a reduction in all-cause mortality.
Protective efficacy (%) against all-cause mortality; 3	Based on data from 2,424	2.47 per 1000	4.34 per 1000	Low Due to serious imprecision [97]	Too few events to determine an association between R21/Matrix-M

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
doses of R21/ Matrix-M vs. control (seasonal vaccination) [95] Phase 3 randomized trial 2021-ongoing 6 Important	participants in 1 studies. [96] (Randomized controlled) Follow up: 20 months post dose 1.				vaccination on all-cause mortality from this study.
Protective efficacy (%) all-cause mortality; 3 doses R21/Matrix-M vs. control (seasonal vaccination) [98] Phase 2b randomized trial 2019–2021 6 Important	Based on data from 293 participants in 1 studies. [99] (Randomized controlled) Follow up: 12 months post dose 3.			Low Due to serious imprecision [100]	Due to zero events and small sample size, cannot determine an association between R21/Matrix-M vaccination and all-cause mortality from this study.
Serious adverse events; RTS,S/ AS01 vs. control [101] Phase 3 randomized trial 2009–2014 9 Critical	Rate ratio 0.88 (CI 95% 0.81 — 0.95) Based on data from 8,922 participants in 1 studies. [102] (Randomized controlled) Follow up: month 0 to study end (median 48 months).	264 per 1000 Difference:	232 per 1000 **32 fewer per 1000** (CI 95% 50 fewer — 13 fewer)	Moderate Due to imprecision	RTS,S/AS01 vaccination probably reduces the risk of serious adverse events compared with control
Serious adverse events; RTS,S/ AS01 vs. control [103] Phase 2b randomized trial 2017–2018 9 Critical	Rate ratio 0.76 (CI 95% 0.52 — 1.13) Based on data from 591 participants in 1 studies. [104] (Randomized controlled) Follow up: month 0 to month 20.	167 per 1000 Difference:	128 per 1000 **40 fewer per 1000** (CI 95% 80 fewer — 22 more)	Low Due to serious imprecision [105]	Too few events and small sample size to determine an association between RTS,S/AS01 vaccination and serious adverse events from this study.
Serious adverse events; RTS,S/ AS01 alone vs. SMC alone [106] Phase 3b randomized trial 2017–2020 9 Critical	Based on data from 3,953 participants in 1 studies. [107] (Randomized controlled) Follow up: 3 years.	0 per 1000	1.5 per 1000	Low Due to serious imprecision; zero events in the control group. [108]	Due to zero events in the control group, cannot determine an association between RTS,S/AS01 vaccination and serious adverse events from this study.
Serious adverse events; RTS,S/ AS01 + SMC	Based on data from 3,932	0 per 1000	1 per 1000	Low Due to serious imprecision; zero	Due to zero events in the control group, cannot determine an association

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
combination vs. SMC alone [109] Phase 3b randomized trial 2017–2020 9 Critical	participants in 1 studies. [110] (Randomized controlled) Follow up: 3 years.			events in the control group. [111]	between RTS,S/AS01 vaccination and serious adverse events from this study.
Serious adverse events; R21/ Matrix-M vs. control [112] Phase 2b randomized trial 2019–2021 9 Critical	Rate ratio 4.29 (CI 95% 0.48 — 37.88) Based on data from 290 participants in 1 studies. [113] (Randomized controlled) Follow up: 12 months post dose 3.	7 per 1000 Difference:	29 per 1000 **22 more per 1000** (CI 95% 3 fewer — 246 more)	Low Due to serious imprecision [114]	Too few events and small sample size to determine an association between R21/Matrix-M vaccination and serious adverse events from this study.
Serious adverse events; R21/ Matrix-M vs. control [115] Phase 3 randomized trial 2021-ongoing 9 Critical	Rate ratio 1.07 (CI 95% 0.74 — 1.55) Based on data from 4,878 participants in 1 studies. [116] (Randomized controlled) Follow up: April 2021 to 31 March 2023.	25 per 1000 Difference:	27 per 1000 **2 more per 1000** (CI 95% 7 fewer — 14 more)	Moderate Due to imprecision	There is probably no difference in serious adverse events between R21/Matrix-M vaccination and control.
Febrile convulsions (within 28 days of vaccination); RTS,S/AS01 vs. control [117] Phase 3 randomized trial 2009–2014 6 Important	Rate ratio 0.97 (CI 95% 0.78 — 1.2) Based on data from 5,950 participants in 1 studies. [118] (Randomized controlled) Follow up: month 0 to study end (median 48 months).	55 per 1000 Difference:	53 per 1000 **2 fewer per 1000** (CI 95% 12 fewer — 11 more)	Low Due to serious imprecision [119]	RTS,S/AS01 vaccination may result in little or no difference in febrile convulsions.
Febrile convulsions (within 28 days of vaccination); RTS,S/AS01 alone vs. SMC alone [120] Phase 3b randomized trial 2017–2020 6 Important	Based on data from 3,953 participants in 1 studies. [121] (Randomized controlled) Follow up: 3 years.	0 per 1000	1.5 per 1000	Low Due to serious imprecision; zero events in the control group [122]	RTS,S/AS01 vaccination may result in little or no difference in febrile convulsions compared with SMC.
Febrile convulsions		0	1	Low Due to serious	RTS,S/AS01 vaccination with SMC may result in

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
(within 28 days of vaccination); RTS,S/AS01 + SMC combination vs. SMC alone [123] Phase 3b randomized trial 2017–2020 6 Important	Based on data from 3,932 participants in 1 studies. [124] (Randomized controlled) Follow up: 3 years.	per 1000	per 1000	imprecision; zero events in the control group [125]	little or no difference in febrile convulsions compared with SMC alone.
Febrile convulsions (within 28 days of vaccination); R21/Matrix-M vs. control [126] Phase 2b randomized trial 2019–2021 6 Important	Based on data from 278 participants in 1 studies. [127] (Randomized controlled) Follow up: 12 months post dose 3.			Low Due to serious imprecision [128]	Due to zero events and small sample, cannot determine an association between R21/Matrix-M vaccination and febrile convulsions from this study.
Febrile convulsions (within 28 days of vaccination); R21/Matrix-M vs. control [129] Phase 3 randomized trial 2021-ongoing 6 Important	Rate ratio 4 (CI 95% 0.5 — 31.95) Based on data from 4,878 participants in 1 studies. [130] (Randomized controlled) Follow up: April 2021 - 31 March 2023.	0.6 per 1000 Difference:	2.5 per 1000 **2 more per 1000** (CI 95% 0 fewer — 19 more)	Moderate Due to imprecision	R21/Matrix-M probably results in an increased risk of febrile convulsions. In the vaccinated group, 5 events occurred in days 0-3 after vaccination, and 3 events occurred in days occurred in days 4-28.
Incidence rate ratio of meningitis; 3 or 4 doses RTS,S/AS01 vs. control [131] Post-hoc analysis of Phase 3 randomized trial 2009–2014 6 Important	Rate ratio 10.5 (CI 95% 1.41 — 78) Based on data from 8,922 participants in 1 studies. [132] (Randomized controlled) Follow up: month 0 to study end (median 48 months).	0.3 per 1000 Difference:	3.5 per 1000 **3 more per 1000** (CI 95% 0 fewer — 26 more)	Low Due to risk of bias and serious imprecision [133]	There were too few meningitis cases to determine an association with RTS,S/AS01 vaccination.
Incidence rate ratio of meningitis in RTS,S/AS01 alone vs. SMC alone vs. RTS,S/AS01 + SMC combination [134] Phase 3b randomized trial 2017–2020	Based on data from 6,861 participants in 1 studies. [135] (Randomized controlled) Follow up: 3 years.			Low Due to very serious imprecision [136]	There were no meningitis cases to determine an association with RTS,S/AS01 vaccination.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
6 Important					
Ratio of ratios: incidence ratio of hospital admission with meningitis in age-eligible and age-ineligible children in RTS,S/AS01 implementing vs. comparison areas (age-based vaccination) [137] Pilot implementation study 2019–2023 6 Important	0.98 (CI 95% 0.63 — 1.52) Based on data from 58,114 participants in 1 studies. [138] Follow up: month 0 to month 46.			Moderate Due to serious imprecision. [139]	There is probably no difference in meningitis with RTS,S/AS01 vaccination.
Incidence rate ratio of meningitis; R21/Matrix-M vs. control [140] Phase 3 randomized trial; 2021-ongoing 6 Important	Based on data from 4,878 participants in 1 studies. [141] (Randomized controlled) Follow up: April 2021 - 31 March 2023.	0 per 1000	0.6 per 1000	Low Due to serious imprecision; zero events in the control group. [142]	R21/Matrix-M may result in little to no difference in meningitis cases compared to control
Ratio of ratios: incidence ratio of hospital admission with cerebral malaria in age-eligible and age-ineligible children in RTS,S/AS01 implementing vs. comparison areas (age-based vaccination) [143] Pilot implementation study 2019–2023 6 Important	0.94 (CI 95% 0.63 — 1.39) Based on data from 58,114 participants in 1 studies. [144] Follow up: month 0 to month 46.			Moderate Due to serious inconsistency and serious imprecision. [145]	RTS,S/AS01 vaccination probably results in no difference in cerebral malaria.
Incidence rate ratio of possible cerebral malaria; 3 or 4 doses RTS,S/AS01 vs. control [146]	Rate ratio 2.15 (CI 95% 1.1 — 4.3) Based on data from 8,922 participants in 1 studies. [147] Follow up: month 0 to study end (median 48	3.4 per 1000 Difference:	7.2 per 1000 **4 more per 1000** (CI 95% 4 more — 1 more)	Very low Due to very serious risk of bias and serious imprecision [148]	Uncertainty whether RTS,S/AS01 vaccination is associated with an increase in cerebral malaria cases.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
Post-hoc analysis of Phase 3 randomized trial 2009–2014 6 Important	months).				
Incidence rate ratio of cerebral malaria; RTS,S/AS01 alone vs. SMC alone vs. RTS,S/AS01 + SMC combination [149] Phase 3b randomized study 2017–2020 6 Important	Based on data from 5,920 participants in 1 studies. [150] (Randomized controlled) Follow up: 3 years.			Low Due to very serious imprecision; very few events and 0 events in the control arm. [151]	The combination of RTS,S malaria vaccination with SMC may result in little or no difference in cerebral malaria compared with SMC alone.
Incidence rate ratio of cerebral malaria; RTS,S/AS01 vs. control [152] Phase 2b randomized trial 2017–2018 6 Important	Rate ratio 0.33 (CI 95% 0.01 — 8.04) Based on data from 591 participants in 1 studies. [153] (Randomized controlled) Follow up: month 0 to month 20.	3 per 1000 Difference:	0 per 1000 **2 fewer per 1000** (CI 95% 3 fewer — 24 more)	Low Due to serious imprecision; very few events and 0 events in the intervention arm [154]	RTS,S/AS01 vaccination may result in little or no difference in cerebral malaria.
Incidence rate ratio of cerebral malaria; R21/Matrix-M vs. control [155] Phase 3 randomized trial 2021-ongoing 6 Important	Rate ratio 0.5 (CI 95% 0.03 — 8) Based on data from 4,875 participants in 1 studies. [156] (Randomized controlled) Follow up: April 2021 - 31 March 2023.	0.6 per 1000 Difference:	0.3 per 1000 **0 more per 1000** (CI 95% 1 fewer — 4 more)	Low Due to serious imprecision; very few events [157]	Too few events to determine an association between R21/Matrix-M vaccination and cerebral malaria.
Female:male rate ratio of all-cause mortality; 3 or 4 doses RTS,S/AS01 vs. control [158] Post-hoc analysis of Phase 3 randomized trial 2009–2014 6 Important	1.5 (CI 95% 1.03 — 2.08) Based on data from 8,922 participants in 1 studies. [159] Follow up: month 0 to study end (median 48 months).			Low Due to very serious imprecision [160]	RTS,S/AS01 vaccination may be associated with a higher mortality in girls compared with boys.

Outcome Timeframe	**Study results and measurements**	**Comparator** No malaria vaccination	**Intervention** Malaria vaccination	**Certainty of the evidence** (Quality of evidence)	**Summary**
Female:male rate ratio of all-cause mortality; RTS,S/AS01 alone vs. SMC alone [161] Phase 3b randomized study 2017–2020 6 Important	Rate ratio 1.8 (CI 95% 0.56 — 5.79) Based on data from 3,953 participants in 1 studies. [162] (Randomized controlled) Follow up: 3 years.			Low Due to very serious imprecision [163]	RTS,S/AS01 vaccination may result in little to no difference in all-cause mortality between girls and boys.
Female:male rate ratio of all-cause mortality; RTS,S/AS01 + SMC combination vs SMC alone [164] Phase 3b randomized study 2017–2020 6 Important	Rate ratio 0.35 (CI 95% 0.06 — 1.98) Based on data from 3,932 participants in 1 studies. [165] (Randomized controlled) Follow up: 3 years.			Low Due to very serious imprecision [166]	RTS,S/AS01 vaccination may result in little to no difference in all-cause mortality between girls and boys.
Female:male rate ratio of all-cause mortality in age-eligible and age-ineligible children in RTS,S/AS01 implementing vs. comparison areas (age-based vaccination) [167] Pilot implementation study 2019–2023 6 Important	1.04 (CI 95% 0.93 — 1.15) Based on data from 15,444 participants in 1 studies. [168] Follow up: month 0 to month 46.				There is probably no difference in all-cause mortality between girls and boys.

1. [Impact outcome] Protective efficacy (%) against clinical malaria episodes (modified intention-to-treat analysis). Per-protocol analysis protective efficacy 39.0% (95% CI 34.3 to 43.3). Clinical malaria assessed with: illness in a child brought to a study facility with a measured temperature of 37.5°C and P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria. Severe malaria primary case definition: P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Co-existing illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration). 4-dose intervention group (R3R) received 3 doses of RTS,S/AS01 at months 0, 1, and 2 and a 4th dose at month 20. The control group (R3C) received the comparator vaccine (Rabies vaccine) at months 0, 1, 2, and 20. Low transmission trial sites included Kilifi, Kenya and Korogwe, Tanzania. Moderate transmission trial sites included Lambarene, Gabon; Bagamoyo, Tanzania; Lilongwe, Malawi; and Manhica, Mozambique. High transmission trial sites included Siaya, Kenya; Nanoro, Burkina Faso; Kintampo, Burkina Faso; Kombewa, Kenya and Agogo, Ghana.
2. [179]. The number of cases averted over time was calculated as the sum of 3-monthly differences in the estimated number of cases between the control and the RTS,S/AS01 groups (R3R and R3C combined up to the time of 4th dose and R3R and R3C separately after the 4th dose) and expressed per 1000 participants vaccinated. In children, 1774 cases of clinical malaria were averted per 1000

children (95% CI 1387–2186) in the R3R group and 1363 per 1000 children (995–1797) in the R3C group. The numbers of cases averted per 1000 young infants were 983 (95% CI 592–1337) in the R3R group and 558 (158–926) in the R3C group. Among the older children, in the 12 months following administration of the first three doses, protective efficacy against clinical (uncomplicated and severe) malaria was 51% (95% CI 47-55) (per protocol analysis).
3. [Impact outcome] Protective efficacy (%) against clinical malaria episodes (per protocol analysis) Clinical malaria assessed with: illness in a child brought to a study facility with a measured temperature of 37.5°C and P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria. Severe malaria primary case definition: P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Co-existing illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration). The overall study (in two sites Agogo, Ghana and Siaya, Kenya) included 1609 total participants with 4 dose groups - only group 1 is reported in this table. Group 1 [n=322]: RTS,S/AS01 – 3 standard 0.5 mL doses at months 0, 1 and 2, followed by standard dose at month 20 Group 2 [n=322]: RTS,S/AS01 – 3 standard 0.5 mL doses at months 0, 1 and 2, followed by standard doses at months 14, 26 and 38 Group 3 [n=322]: RTS,S/AS01 – 2 standard 0.5 mL doses at months 0 and 1, followed by fractional doses (0.1 mL) at months 2, 14, 26 and 38 Group 4 [n=322]: RTS,S/AS01 – 2 standard 0.5 mL doses at months 0 and 1, followed by fractional doses (0.1 mL) at months 7, 20 and 32; Group 5 [n=321]: Control received comparator vaccine (Rabies) at month 12
4. [192].
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Confidence interval crosses threshold for a worthwhile effect. **Publication bias: no serious.**
6. [Impact outcome] Protective efficacy (%) against clinical malaria episodes (per protocol analysis). Clinical malaria assessed with: illness in a child brought to a study facility with a measured temperature of 37.5°C and P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria. Severe malaria primary case definition: P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score 2 or lower (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Co-existing illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, sepsis (with positive blood culture), or gastroenteritis with severe dehydration). Laboratory tests and other examinations (chest x-ray, lumbar puncture, blood culture) to exclude co-morbidities were performed only if there was a clinical suspicion/diagnosis justifying additional investigations. Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S). Low to moderate transmission trial sites receiving age-based vaccination included Dande, Burkina Faso (moderate transmission); Bagamoyo, Tanzania (low transmission) and Kilifi, Kenya (moderate transmission).
7. [182]. Protective efficacy reported according to per protocol analysis, 12 months follow-up post dose 3. Absolute effects reported according to modified ITT analysis from month 0 to month 14. The R21 arm had 315 clinical malaria cases over 1840 total person-years at risk (PYAR) and the control arm had 406 cases over 911 PYAR.
8. [Impact outcome] Protective efficacy against clinical malaria episodes (modified intention-to-treat analysis). Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
9. [183]. The RTS,S vaccine alone group had 1,540 clinical malaria cases over 5535.7 total person-years at risk (PYAR) for an incidence rate of 278 cases (95% CI: 264.6 to 292.4) per 1000 PYAR. The SMC alone group had 1,661 cases over 5449.9 total PYAR for an incidence rate of 305 cases (95% CI: 290.5 to 319.8) per 1000 PYAR.
10. [Impact outcome] Protective efficacy (%) against clinical malaria episodes (modified intention-to-treat analysis) Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
11. [183]. The RTS,S + SMC combined group had 624 clinical malaria cases over 5508.0 total PYAR for an incidence rate of 113 cases (95% CI: 104.7 to 122.5) per 1000 PYAR. The SMC alone group has 1,661 cases over 5449.9 total PYAR for an incidence rate of 305 cases (95% CI: 290.5 to 319.8) per 1000 PYAR.
12. [Impact outcome] Protection efficacy (%) against clinical malaria (modified intention-to-treat analysis), defined as participants receiving at least one vaccine dose, with follow-up beginning from dose 3). Clinical malaria assessed with: illness in a child brought to a study facility with a measured temperature of 37.5°C and P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria. Severe malaria primary case definition: P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score 2

or lower (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Co-existing illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, sepsis (with positive blood culture), or gastroenteritis with severe dehydration). Laboratory tests and other examinations (chest x-ray, lumbar puncture, blood culture) to exclude co-morbidities were performed only if there was a clinical suspicion/diagnosis justifying additional investigations. The study included 450 total participants with three study arms. Only group 2 and 3 are used in this table. Group 1 [n=150]: 3 doses 5 µg R21 adjuvanted with 25 mcg Matrix-M at months 0, 1 and 3 (May – August, prior to the malaria season), with a fourth dose at month 12. Group 2 [n=150]: 3 doses 5 µg R21 adjuvanted with 50 mcg Matrix-M at months 0, 1 and 3 (May – August, prior to the malaria season), with a fourth dose at month 12. Group 3 [n=150]: control group received 3 doses Rabivax-S rabies vaccine at months 0, 1 and 3 (May – August, prior to the malaria season), with a fourth dose at month 12.

13. [199]. Absolute effect reported per 1000 children. The R21 ram had 39 clinical malaria cases in 146 children and the control arm had 106 cases in 147 children.

14. [Impact outcome] Protective efficacy (%) against clinical malaria episodes (per protocol analysis). Clinical malaria assessed with: illness in a child brought to a study facility with a measured temperature of 37.5°C and P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria. Severe malaria primary case definition: P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score 2 or lower (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Co-existing illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, sepsis (with positive blood culture), or gastroenteritis with severe dehydration). Laboratory tests and other examinations (chest x-ray, lumbar puncture, blood culture) to exclude co-morbidities were performed only if there was a clinical suspicion/diagnosis justifying additional investigations. Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S). Trial sites receiving seasonal vaccination included Bougouni, Mali (moderate transmission) and Nanoro, Burkina Faso (high transmission).

15. [182]. Protective efficacy reported according to per protocol analysis, 18 months follow-up post dose 3. Absolute effects reported according to modified ITT analysis from month 0 to month 20. The R21 arm had 932 clinical malaria cases over 2665 total person-years at risk (PYAR) and the control arm had 1688 cases over 1335 PYAR.

16. [Impact outcome] Protective efficacy (%) against severe malaria (modified intention-to-treat analysis). Severe malaria assessed with P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a co-existing illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of 2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Co-existing illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration). 4-dose intervention group (R3R) received 3 doses of RTS,S/AS01 at months 0, 1, and 2 and a 4th dose at month 20. The control group (R3C) received the comparator vaccine (Rabies vaccine) at months 0, 1, 2, and 20.

17. [179]. Protective efficacy according to per protocol analysis was 28.5% (95% CI 6.3 to 45.7). Among the older children, in the 12 months following administration of the first three doses, protective efficacy against severe malaria was 45% (95% CI 22-60) (per protocol analysis).

18, 58. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

19. [Impact outcome] Protective efficacy (%) against severe malaria (per protocol analysis). Severe malaria primary case definition: P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score 2 or lower (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Co-existing illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, sepsis (with positive blood culture), or gastroenteritis with severe dehydration). Laboratory tests and other examinations (chest x-ray, lumbar puncture, blood culture) to exclude co-morbidities were performed only if there was a clinical suspicion/diagnosis justifying additional investigations. Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S). Low to moderate transmission trial sites receiving age-based vaccination included Dande, Burkina Faso (moderate transmission); Bagamoyo, Tanzania (low transmission) and Kilifi, Kenya (moderate transmission).

20. [182]. Protective efficacy reported according to per protocol analysis, 12 months follow-up post dose 3. Absolute effects reported according to modified ITT analysis from month 0 to month 14. The R21 arm had 7 severe malaria cases over 1837.0 total person-years at risk (PYAR) and the control arm had 3 cases over 908.7 PYAR.

21, 33. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Certainty of evidence downgraded due to serious imprecision; too few events and small sample size. **Publication bias: no serious.**
22. [Impact outcome] Severe malaria assessed with P. falciparum infection with severe anaemia, or respiratory distress, or with impaired consciousness or convulsions but not meeting criteria for meningitis. Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries (Ghana, Kenya, and Malawi), there was a total of 58,114 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 12 July 2023. 14,461 were vaccine-eligible based on their date of birth out of 29,129 total admissions in areas where the vaccine was provided (implementation areas); 15,032 were vaccine-eligible out of 28,985 total admissions in comparison areas.
23. [200]. Among children eligible to have received all three primary doses of RTS,S/AS01, there was a total of 3,310 admissions with severe malaria (out of 24,076 total age-eligible admissions), 1,457 from implementation areas and 1,853 from comparison areas. Among children who were not eligible there were 3,478 total admissions with severe malaria (out of 22,901 total age-ineligible admissions) to have received any doses of RTS,S/AS01, 1,705 from implementation areas and 1,773 from comparison areas. The incidence rate ratio comparing incidence of admission with severe malaria between implementing and comparison areas was 0.78 (95% CI 0.64 – 0.97) a reduction of 22% (95%CI 3% to 36%); there was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria..
24. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggest there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behaviour, or health worker behaviour in testing and treating for febrile illness.; . **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level for imprecision: few events and large CI. **Publication bias: no serious.**
25, 28. [Impact outcome] Protective efficacy (%) against hospitalization due to severe malaria (modified intention-to-treat analysis). Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
26. [183]. The RTS,S vaccine alone group had 37 severe malaria cases (of which 25 were severe malaria anaemia) over 5535.7 total PYAR for an incidence rate of 6.7 severe malaria cases (95% CI: 4.8 to 9.2) per 1000 PYAR. The SMC alone group had 37 cases (of which 31 were severe malaria anaemia) over 5449.9 total PYAR for a rate of 6.8 cases (95% CI: 4.9 to 9.4) per 1000 PYAR.
27, 50, 53, 66, 69. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
29. [183]. RTS,S + SMC combination group had 11 severe malaria cases (of which 10 were severe malaria anaemia) over 5508 total PYAR for an incidence rate of 2.0 severe malaria cases (95% CI: 1.1 to 3.6) per 1000 PYAR. The SMC alone group has 37 cases (of which 31 were severe malaria anaemia) over 5449.9 total PYAR for a rate of 6.8 cases (95% CI: 4.9 to 9.4) per 1000 PYAR.
30. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI. **Publication bias: no serious.**
31. [Impact outcome] Protective efficacy (%) against severe malaria (per protocol analysis). Severe malaria primary case definition: P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score 2 or lower (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Co-existing illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, sepsis (with positive blood culture), or gastroenteritis with severe dehydration). Laboratory tests and other examinations (chest x-ray, lumbar puncture, blood culture) to exclude co-morbidities were performed only if there was a clinical suspicion/diagnosis justifying additional investigations. Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S). Trial sites receiving seasonal vaccination included Bougouni, Mali (moderate transmission) and Nanoro, Burkina Faso (high transmission).
32. [182]. Protective efficacy reported according to per protocol analysis, 18 months follow-up post dose 3. Absolute effects reported are cases per 1000 vaccinated children, according to modified ITT analysis from month 0 to month 20. The R21 arm had 8 severe malaria cases over 2562.7 total person-years at risk (PYAR) and the control arm had 8 cases over 1279.2 PYAR.
34. [Impact outcome] Protective efficacy (%) against severe malaria anemia (≥1 episode of incident severe malaria anaemia) (modified intention-to-treat analysis). Severe malarial anaemia assessed with: haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a P. falciparum parasitaemia at a density of > 5000 parasites per cubic millimetre. 4-dose intervention group (R3R) received 3 doses of RTS,S/AS01 at months 0, 1, and 2 and a 4th dose at month 20. The control group (R3C) received the comparator vaccine (Rabies vaccine) at months 0, 1, 2, and 20.
35, 44. [179].
36. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder within the project; however, it has not been downgraded for ROB as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large confidence interval. **Publication bias: no serious.**

37. [Impact outcome] Protective efficacy (%) severe malaria anaemia (modified intention-to-treat analysis) Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
38. [183]. The RTS,S vaccine group had 25 severe malaria anemia cases over 5535.7 total person years at risk (PYAR) for an incidence rate of 4.52 cases (95% CI: 3.05 to 6.68) per 1000 PYAR. The SMC alone group has 31 cases over 5449.9 total PYAR for a rate of 5.69 cases (95% CI: 4.00 to 8.09) per 1000 PYAR.
39. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large confidence interval that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
40. Impact outcome] Protective efficacy (%) severe malaria anaemia (modified intention-to-treat analysis). Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
41. [183]. The RTS,S vaccine and SMC combination group had 10 severe malaria anaemia cases over 5508 total person years at risk (PYAR) for an incidence rate of 1.82 cases (95% CI: 0.977 to 3.37) per 1000 PYAR. The SMC alone group had 31 cases over 5449.9 total PYAR for a rate of 5.69 cases (95% CI: 4.00 to 8.09) per 1000 PYAR.
42. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and a very large CI. **Publication bias: no serious.**
43. [Impact outcome] Protective efficacy (%) against blood transfusions (modified intention-to-treat analysis). 4-dose intervention group (R3R) received 3 doses of RTS,S/AS01 at months 0, 1, and 2 and a 4th dose at month 20. The control group (R3C) received the comparator vaccine (Rabies vaccine) at months 0, 1, 2, and 20.
45. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI. **Publication bias: no serious.**
46. [Impact outcome] Protective efficacy (%) against blood transfusions (per protocol analysis). Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S). Low to moderate transmission trial sites receiving age-based vaccination included Dande, Burkina Faso (moderate transmission); Bagamoyo, Tanzania (low transmission) and Kilifi, Kenya (moderate transmission).
47. [182]. Protective efficacy reported according to per protocol analysis, 18 months follow-up post dose 3. Absolute effects reported according to modified ITT analysis from month 0 to month 20. The R21 arm had 9 blood transfusions over 2596.1 total person-years at risk (PYAR) and the control arm had 10 blood transfusions over 1279.0 PYAR.
48. [Impact outcome] Protective efficacy (%) against blood transfusions (modified intention-to-treat analysis) Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
49. [183]. The RTS,S vaccine group had 21 blood transfusion events over 5535.7 total PYAR for an incidence rate of 3.79 events (95% CI: 2.47 to 5.82) per 1000 PYAR. The SMC alone group had 23 events over 5449.9 total PYAR for an incidence rate of 4.22 events (95% CI: 2.80 to 6.35) per 1000 PYAR.
51. [Impact outcome] Protective efficacy (%) against blood transfusions (modified intention-to-treat analysis). Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
52. [183]. The RTS,S vaccine and SMC combination group had 8 blood transfusion events over 5508.0 total PYAR for an incidence rate of 1.45 events (95% CI: 0.726 to 2.90) per 1000 PYAR. The SMC alone group has 23 events over 5449.9 total PYAR for an incidence rate of 4.22 events (95% CI: 2.80 to 6.35) per 1000 PYAR.
54. [Impact outcome] Protective efficacy (%) against blood transfusions (per protocol analysis). Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S). Trial sites receiving seasonal vaccination included Bougouni, Mali (moderate transmission) and Nanoro, Burkina Faso (high transmission).
55. [182]. Protective efficacy reported according to per protocol analysis, 18 months follow-up post dose 3. Absolute effects reported according to modified ITT analysis from month 0 to month 20. The R21 arm had 10 blood transfusions over 2568.5 total person-years at risk (PYAR) and the control arm had 7 blood transfusions over 1284.4 PYAR.
56. [Impact outcome] Protective efficacy (%) against all-cause hospitalisations (modified intention-to-treat analysis). 4-dose intervention group (R3R) received 3 doses of RTS,S/AS01 at months 0, 1, and 2 and a 4th dose at month 20. The control group (R3C) received the comparator vaccine (Rabies vaccine) at months 0, 1, 2, and 20.
57. [179]. Absolute effects reported per 1000 children.
59. [Impact outcome] Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries (Ghana, Kenya, and Malawi), there was a total of 58,114 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 12 July 2023: 14,461 were vaccine-eligible based on their date of birth out of 29,129 total admissions in areas where the vaccine was provided (implementation areas); 15,032 were vaccine-eligible out of 28,985 total

admissions in comparison areas.
60. [200]. Severe malaria represented 15% of all admissions to sentinel hospitals (with at least one overnight stay) in comparison areas among children who were eligible to receive three doses of malaria vaccine. In this age group, there was a total of 11,738 admissions to sentinel hospitals in implementation areas and 12,338 in comparison areas. The rate ratio comparing the incidence of all-cause hospital admission between implementation and comparison areas, for this age group, was 0.92 (95%CI 0.81 – 1.05)..
61. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggest there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behaviour, or health worker behaviour in testing and treating for febrile illness.; . **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: large CI that incorporates the possibility of benefit and harm. Study was powered for a pooled analysis only, country estimates vary but confidence intervals are wide and consistent with pooled effect.. **Publication bias: no serious.**
62. [Impact outcome] Protective efficacy (%) against all-cause hospitalizations (per protocol analysis). Hospitalisation defined as a medical hospitalisation of any cause (excluding planned admissions for procedures/elective surgery or trauma). Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S). Low to moderate transmission trial sites receiving age-based vaccination included Dande, Burkina Faso (moderate transmission); Bagamoyo, Tanzania (low transmission) and Kilifi, Kenya (moderate transmission).
63. [182]. Protective efficacy reported according to per protocol analysis, 18 months follow-up post dose 3. Absolute effects reported according to modified ITT analysis from month 0 to month 20. The R21 arm had 50 hospitalizations over 2596 total person-years at risk (PYAR) and the control arm had 25 hospitalizations over 1279 PYAR.
64, 67. [Impact outcome] Protective efficacy (%) against all-cause hospital admission (excluding external causes and surgery) (modified intention-to-treat analysis). Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
65. [183]. The RTS,S vaccine group had 73 events over 5535.7 total PYAR for an incidence rate of 13.2 events (95% CI: 10.5 to 16.6) per 1000 PYAR. The SMC alone group had 60 events over 5449.9 total PYAR for an incidence rate of 11.0 events (95% CI: 8.55 to 14.2) per 1000 PYAR.
68. [183]. The RTS,S vaccine and SMC combination group had 49 events over 5508 total PYAR for an incidence rate of 8.90 events (95% 6.72 to 11.8) per 1000 PYAR. The SMC alone group had 60 events over 5449.9 total PYAR for an incidence rate of 11.0 events (95% CI: 8.55 to 14.2) per 1000 PYAR. **Supporting references:** [183],
70. [Impact outcome] Protective efficacy (%) against all-cause hospitalizations (per protocol analysis). Hospitalization defined as a medical hospitalisation of any cause (excluding planned admissions for procedures/elective surgery or trauma).
71. [182]. Protective efficacy reported according to per protocol analysis, 18 months follow-up post dose 3. Absolute effects reported according to modified ITT analysis from month 0 to month 20. The R21 arm had 35 hospitalizations over 2568.5 total person-years at risk (PYAR) and the control arm had 21 hospitalizations over 1284.4 PYAR.
72. [Impact outcome] Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries (Ghana, Kenya, and Malawi), there were a total of 58,114 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 12 July 2023: 14,461 were vaccine-eligible based on their date of birth out of 29,129 total admissions in areas where the vaccine was provided (implementation areas); 15,032 were vaccine-eligible out of 28,985 total admissions in comparison areas.
73. [200]. Patients admitted to sentinel hospitals were routinely tested for malaria infection by rapid diagnostic test (RDT) or microscopy. Out of a total of 58,114 patients admitted, test results were available for 91%. Among children eligible to have received three vaccine doses, the number of patients admitted with a positive malaria test was 8,813: 3,865 from implementation areas and 4,948 from comparison areas. The rate ratio comparing the incidence of hospital admission with a positive malaria test between implementation and comparison areas was 0.83 (95%CI 0.73 – 0.95), a reduction of 17% (95%CI 5% to 27%)..
74. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggest there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behaviour, or health worker behaviour in testing and treating for febrile illness.; . **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
75. [Impact outcome] Protective efficacy (%) against malaria hospitalizations (per protocol analysis). Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S). Low to moderate transmission trial sites receiving age-based vaccination included Dande, Burkina Faso (moderate transmission); Bagamoyo, Tanzania (low transmission) and Kilifi, Kenya (moderate transmission).
76. [182]. Protective efficacy reported according to per protocol analysis, 12 months follow-up post dose 3. Absolute effects reported per 1000 children according to modified ITT analysis from month 0 to month 14. The R21 arm had 9 malaria hospitalizations in 1636 children (over 1836.5 total person-years at risk, PYAR) and the control arm had 4 malaria hospitalizations in 815 children (over 907.6 PYAR).
77, 86. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Certainty of evidence downgraded due to serious imprecision; few events and wide confidence interval. **Publication bias: no serious.**

78. [Impact outcome] Protective efficacy (%) against malaria hospitalizations (per protocol analysis). Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S). Trial sites receiving seasonal vaccination included Bougouni, Mali (moderate transmission) and Nanoro, Burkina Faso (high transmission).
79. [182]. Protective efficacy reported according to per protocol analysis, 18 months follow-up post dose 3. Absolute effects reported per 1000 children according to modified ITT analysis from month 0 to month 20. The R21 arm had 8 malaria hospitalizations in 1613 children (over 2564.3 total person-years at risk, PYAR) and the control arm had 8 malaria hospitalizations in 811 children (over 1279.2 PYAR).
80, 97. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Certainty of evidence downgraded due to serious imprecision; few events and wide confidence interval.. **Publication bias: no serious.**
81. [Impact outcome] 4-dose intervention group (R3R) received 3 doses of RTS,S/AS01 at months 0, 1, and 2 and a 4th dose at month 20. The control group (R3C) received the comparator vaccine (Rabies vaccine) at months 0, 1, 2, and 20.
82. [179]. Absolute effect reported per 1000 children. In the 4-dose group, there were 61 deaths (13 malaria) / 2976 children. In the 3-dose group, there were 51 deaths (17 malaria) / 2972 children. In the control group, there were 46 deaths (13 malaria) / 2974 children.
83. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**
84. [Impact outcome]. Protective efficacy (%) against all-cause mortality, excluding trauma and injury (per protocol analysis) Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S). Low to moderate transmission trial sites receiving age-based vaccination included Dande, Burkina Faso (moderate transmission); Bagamoyo, Tanzania (low transmission) and Kilifi, Kenya (moderate transmission).
85. [182]. Absolute effects reported according to modified ITT analysis from month 0 to month 14..
87. Overall, a total of 15,444 deaths in children 1-59 months of age were reported to 28 February 2023 in Ghana and Malawi and to 12 July 2023 in Kenya. Of these deaths, 11,992 were among children eligible to have received three doses of RTS,S/AS01, and 95.8% of these had verbal autopsies completed (or, in the case of facility deaths in Malawi, hospital records obtained), and a cause of death (categorized as due to injury, or other causes) established for 14,097 out of 15,444 deaths (91.3%).
88. [200]. Among children eligible to have received three doses of RTS,S, there were 11,992 deaths: 5,706 in implementation areas and 6,286 in comparison areas. The mortality rate ratio was 0.87 (95%CI 0.77 - 0.97); a reduction of 13% (95%CI 3% to 23%)..
89, 92. [Impact outcome] Protective efficacy (%) against all-cause mortality, excluding external causes and surgery (modified intention-to-treat analysis). Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
90. [183]. In the RTS,S vaccine alone group there were 22 deaths total/1734 participants or 3.97 deaths (95% CI 2.92 to 6.04) per 1000 PYAR. In the SMC alone group, there were 25 deaths total/1716 participants or 4.59 deaths (95% CI 3.10 to 6.79) per 1000 PYAR.
91. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large confidence interval that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**
93. [183]. In the RTS,S vaccine + SMC combination group there were 12 deaths total/1740 children or 2.18 deaths (95% CI 1.24 to 3.84) per 1000 PYAR. In the SMC alone group, there were 25 deaths total/1716 children or 4.59 deaths (95% CI 3.10 to 6.79) per 1000 PYAR.
94. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI.. **Publication bias: no serious.**
95. [Impact outcome] Protective efficacy (%) against all-cause mortality, excluding deaths due to trauma and injury (per protocol analysis). Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S). Trial sites receiving seasonal vaccination included Bougouni, Mali (moderate transmission) and Nanoro, Burkina Faso (high transmission).
96. [182]. Absolute effects reported according to modified ITT analysis from month 0 to month 20..
98. [Impact outcome] Protective efficacy (%) against all-cause mortality, excluding injury and trauma; 3 doses R21 vs. control (seasonal vaccination in highly seasonal settings)
99, 127. [199].
100. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** No reported events in vaccination or control arms. **Publication bias: no serious.**
101. [Safety outcome] Serious adverse events (SAEs), excluding malaria. Intervention group included participants receiving receive 3 doses of RTS,S/AS01 at months 0, 1,and 2 and a fourth dose at month 20 (R3R group); or three doses of RTS,S/AS01 and a dose of comparator vaccine at month 20 (R3C group). The control group received 4 doses of the comparator vaccine at months 0, 1, 2 and 20

(C3C group).
102. [179]. Absolute effect reported per 1000 children. The intervention groups (R3R and R3C) had a total of 1377 serious adverse events (SAEs) in 5948 children and the control group (C3C) had 784 SAEs in 2974 children.
103. [Safety outcome] Serious adverse events (SAEs), excluding malaria. The overall study (in two sites Agogo, Ghana and Siaya, Kenya) included 1609 total participants with 4 dose groups - only group 1 is reported in this table. Group 1 [n=322]: RTS,S/AS01 – 3 standard 0.5 mL doses at months 0, 1 and 2, followed by standard dose at month 20 Group 2 [n=322]: RTS,S/AS01 – 3 standard 0.5 mL doses at months 0, 1 and 2, followed by standard doses at months 14, 26 and 38 Group 3 [n=322]: RTS,S/AS01 – 2 standard 0.5 mL doses at months 0 and 1, followed by fractional doses (0.1 mL) at months 2, 14, 26 and 38 Group 4 [n=322]: RTS,S/AS01 – 2 standard 0.5 mL doses at months 0 and 1, followed by fractional doses (0.1 mL) at months 7, 20 and 32; Group 5 [n=321]: Control received comparator vaccine (Rabies) at month 12
104. [192]. Absolute effect reported per 1000 children. The intervention group had 38 SAEs in 298 children and the control group had 49 SAEs in 293 children. **Comparator:** [192].
105. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Certainty of evidence downgraded due to very wide confidence interval that incorporates the possibility of benefit and harm.. **Publication bias: no serious.**
106, 109. [Safety outcome] Serious adverse events (SAEs), excluding malaria. Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
107. [183]. Absolute effect reported per 1000 children. In the RTS,S alone group there were 3 serious adverse events (SAEs) in 1988 children. In the control group there were 0 SAEs in 1965 children.
108, 122. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded two levels due to serious imprecision, zero events in the control group.. **Publication bias: no serious.**
110. [183]. Absolute effect reported per 1000 children. In the RTS,S + SMC group there were 2 serious adverse events (SAEs) in 1967 children. In the control group there were 0 SAEs in 1965 children.
111, 125. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded two levels for imprecision, zero events in the control group.. **Publication bias: no serious.**
112. [Safety outcome] Serious adverse events (SAEs), excluding malaria, amongst randomized participants receiving at least 1 vaccine dose. Group 1 [n=150]: 3 doses 5 µg R21 adjuvanted with 25 mcg Matrix-M at months 0, 1 and 3 (May – August, prior to the malaria season), with a fourth dose at month 12. Group 2 [n=150]: 3 doses 5 µg R21 adjuvanted with 50 mcg Matrix-M at months 0, 1 and 3 (May – August, prior to the malaria season), with a fourth dose at month 12. Group 3 [n=150]: control group received 3 doses Rabivax-S rabies vaccine at months 0, 1 and 3 (May – August, prior to the malaria season), with a fourth dose at month 12.
113. [199]. Absolute effect reported per 1000 children. In the R21 arm there were 4 serious adverse events (SAEs) in 140 children. In the control group there was 1 SAE in 150 children.
114. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded two levels for imprecision: few events and very wide confidence intervals.. **Publication bias: no serious.**
115. [Safety outcome] Serious adverse events (SAEs), excluding malaria, amongst randomized participants receiving at least 1 vaccine dose. Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S).
116. [182]. Absolute effect reported per 1000 children. In the R21 arm, 88 out of 3252 children experienced one or more serious adverse events (SAEs). In the control group, 41 out of 1626 children experienced one or more SAEs.
117. [Safety outcome] Febrile convulsions within 28 days of vaccination. Intervention group included participants receiving receive 3 doses of RTS,S/AS01 at months 0, 1,and 2 and a fourth dose at month 20 (R3R group); or three doses of RTS,S/AS01 and a dose of comparator vaccine at month 20 (R3C group). The control group received 4 doses of the comparator vaccine at months 0, 1, 2 and 20 (C3C group).
118. [179]. Absolute effect reported per 1000 children. In the RTS,S groups, there were 159 febrile convulsions amongst 2976 children. In the control group, there were 164 febrile convulsions amongst 2974 children.
119. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded two levels due few events and very wide confidence interval that incorporates the possibility of benefit and harm.. **Publication bias: no serious.**
120, 123. [Safety outcome] Febrile convulsions within 28 days of vaccination. Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
121. [183]. Absolute effect reported per 1000 children. In the RTS,S alone group, there were 3 febrile convulsions amongst 1988 children. In the SMC alone group, there were 0 febrile convulsions amongst 1965 children.
124. [183]. Absolute effect reported per 1000 children. In the RTS,S + SMC group, there were 2 febrile convulsions amongst 1967 children. In the SMC alone group, there were 0 febrile convulsions amongst 1965 children.

126. [Safety outcome] Febrile convulsions within 28 days of vaccination. 450 total participants: Two dose groups (only group 2 and 3 used): Group 1 [n=150]: 3 doses 5 µg R21 adjuvanted with 25 mcg Matrix-M at months 0, 1 and 3 (May – August, prior to the malaria season), with a fourth dose at month 12. Group 2 [n=150]: 3 doses 5 µg R21 adjuvanted with 50 mcg Matrix-M at months 0, 1 and 3 (May – August, prior to the malaria season), with a fourth dose at month 12. Group 3 [n=150]: control group received 3 doses Rabivax-S rabies vaccine at months 0, 1 and 3 (May – August, prior to the malaria season), with a fourth dose at month 12.
128. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded two levels for serious imprecision: no events reported in either group and small sample size.. **Publication bias: no serious.**
129. [Safety outcome] Febrile convulsions within 28 days of vaccination Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine, Rabivax-S).
130. [182]. Absolute effect reported per 1000 children. In the R21 arm, there were 8 febrile convulsions amongst 3252 children. In the control arm, there was 1 febrile convulsion amongst 1626 children. A post-hoc analysis of clustering of febrile convulsions within 0-3 days of vaccination vs 4-28 days of vaccination shows the risk difference for the R21/Matrix-M arm is 0.00036 (0.000008 to 0.00071), p=0.004, 95% CI 2.0 to 67.1; risk difference for the control is 0.00016 (-0.00015 to 0.00047), p = 0.28; RI. The risk difference of 0.00036 translates to an attributable risk in the R21/Matrix-M arm of 1/2800 doses administered. This shows evidence of clustering of febrile convulsions in R21/Matrix-M (p=0.004) but not in the control (p=0.28).
131. [Safety outcome] Incidence rate ratio of meningitis (modified intention-to-treat analysis) 4-dose intervention group (R3R) received 3 doses of RTS,S/AS01 at months 0, 1, and 2 and a 4th dose at month 20. The 3-dose intervention group (R3C) received the comparator vaccine (Rabies vaccine) at months 0, 1, 2, and 20. The control group (C3C) received 4 doses of comparator vaccine at months 0, 1, 2, and 20.
132. [179]. In the 4-dose group, there were 11 cases of meningitis out of 2976 children (R3R). In the 3-dose group (R3C), there were 10 meningitis cases out of 2972 children. In the control group (C3C), there was 1 meningitis case out of 2974 children.
133. **Risk of Bias: serious.** This outcome was not pre-specified in the protocol (post-hoc analysis). Study was rated as unclear risk of bias due to heavy involvement of the funder within the project.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large confidence interval; . **Publication bias: no serious.**
134, 161, 164. [Safety outcome] Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
135. [183]. There were 8 cases of clinically suspected meningitis (4 in the SMC alone group, 3 in the RTS,S vaccine alone group, and 1 in the RTS,S + SMC combined group) - all were investigated with the use of lumbar puncture, but none showed proven meningitis.
136. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels for imprecision: no events reported in any groups. **Publication bias: no serious.**
137. [Safety outcome] Pilot implementation study designed to be analysed using cluster randomized control methodology. To rule out an association with meningitis of the magnitude seen in the Phase 3 trial, it would be necessary to exclude rate ratios of about 10.5 (4.5 allowing for coverage and contamination) or more. Across the three countries (Ghana, Kenya and Malawi), there were a total of 58,114 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 12 July 2023: 14,461 were vaccine-eligible based on their date of birth out of 29,129 total admissions in areas where the vaccine was provided (implementation areas); 15,032 were vaccine-eligible out of 28,985 total admissions in comparison areas.
138. [200]. A total of 8,358 suspected cases of meningitis were investigated. Lumbar punctures were performed in 5,862 (70.1%) of these patients, and PCR analysis of samples of cerebrospinal fluid (CSF) was available for 5,091 patients (86.8%). A total of 165 cases of probable or confirmed meningitis were seen in sentinel hospitals among age groups of children eligible for the malaria vaccine: 87 from implementation areas and 78 from comparison areas. Among the age groups that were not eligible for the malaria vaccine, there were 135 probable or confirmed cases of meningitis: 68 from implementation areas and 67 from comparison areas. The incidence rate ratio comparing rates of admission with meningitis in implementation and comparison areas, among vaccine-eligible children, was 0.98 (95%CI 0.63 to 1.52). There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with meningitis. There were a sufficient number of cases and high coverage of the vaccine to detect an excess of the magnitude observed in the Phase 3 trial, if it had occurred. Of the patients with probable or confirmed meningitis in vaccine-eligible age groups from implementation areas, 52% (45 out of 87) had received the RTS,S/AS01 vaccine, compared to 54% (7847 out of 14,640) of all other hospital admissions in this age group from implementation areas. The PCR results showed that only 7% (19/139) of samples from confirmed cases, were of vaccine serotypes preventable by Hib or pneumococcus vaccines (i.e. Haemophilus influenzae type b, or vaccine serotypes of Streptococcus pneumoniae)..
139. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggest there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behaviour, or health worker behaviour in testing and treating for febrile illness. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: large CI that incorporates the possibility of benefit and harm. It was only downgraded by 1 level because the result excludes an effect of the magnitude observed in the Phase 3 trial (RR = 4.5-10.5), after allowing for vaccine uptake levels in the pilot.. **Publication bias: no serious.**
140. [Safety outcome] Incidence of meningitis (confirmed with cerebral spinal fluid examination) in R21/Matrix-M alone vs. control Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination

(a licensed rabies vaccine, Rabivax-S).
141. [182]. Absolute effect reported per 1000 children.
142. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded two levels for imprecision: zero events in the control group. **Publication bias: no serious.**
143. [Safety outcome] Cerebral malaria assessed with positive P. falciparum rapid diagnostic test or by microscopy, with impaired consciousness (Glasgow coma score <11 or Blantyre coma score <3 or assessed as P or U on the AVPU scale (“Alert, Voice, Pain, Unresponsive”). Pilot implementation study designed to be analysed using cluster randomized control methodology; to be able to rule out an association with cerebral malaria of the magnitude seen in the Phase 3 trial it would therefore be necessary to exclude rate ratios of about 2.2 (1.6 allowing for 60% coverage and 5% contamination) or more. Across the three countries (Ghana, Kenya and Malawi), there were a total of 58,1144 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 12 July 2023: 14,461 were vaccine-eligible based on their date of birth out of 29,129 total admissions in areas where the vaccine was provided (implementation areas); 15,032 were vaccine-eligible out of 28,985 total admissions in comparison areas.
144. [200]. There were 418 cases of cerebral malaria among children age-eligible to receive at least one dose of the RTS,S/AS01 malaria vaccine: 197 from implementation areas and 221 from comparison areas. Among children not age-eligible to receive the malaria vaccine, there were 576 cases of cerebral malaria: 282 from implementation areas and 294 from comparison areas. The incidence rate ratio comparing rates of admission to hospital with cerebral malaria in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.94 (95%CI 0.63 to 1.39). The incidence rate ratio for admission with other forms of severe malaria excluding cerebral malaria was 0.80 (95%CI 0.63 to 1.00). There was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria (relative rate ratio 1.09 [95%CI 0.72 to 1.63] and test for interaction p-value: 0.688). When the analysis was restricted to include cases meeting the criteria for cerebral malaria for whom lumbar puncture was performed, there was a total of 172 cases in age-groups eligible to have received at least one dose of the malaria vaccine: 129 from implementation areas and 143 from comparison areas. There were 318 cases in non-eligible age groups: 151 from implementing areas and 167 from comparison areas. The incidence rate ratio comparing rates of admission to hospital with cerebral malaria (with the strict case definition) in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 1.25 (95%CI 0.84 to 1.88). Again, there was no evidence that impact differed between cerebral malaria and other forms of severe malaria (test for interaction p-value: 0.271). There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with cerebral malaria. The incidence rate ratio excludes an effect of the magnitude observed in the Phase 3 trial (RR = 2.2), after allowing for uptake of the vaccine in the pilot..
145. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggest there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behaviour, or health worker behaviour in testing and treating for febrile illness.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: large CI that incorporates the possibility of benefit and harm. Study was powered for a pooled analysis only; country estimates vary but CIs are wide and consistent with pooled effect; .
146. [Safety outcome] Cerebral malaria assessed with severe P. falciparum malaria (positive P. falciparum rapid diagnostic test or by microscopy) with impaired consciousness (Glasgow coma scale < 11, Blantyre coma scale < 3) persisting for > 1 hour after a seizure. Unplanned sub-group analysis of participant groups: 4-dose group received 3 doses of RTS,S/AS01 at months 0, 1, and 2 and a 4th dose at month 20; 3-dose group received 3 doses of RTS,S/AS01 and a dose of comparator vaccine at month 20; Control group received a comparator vaccine at months 0, 1, 2, and 20 (control group).
147. [179]. In the context of an overall decrease in severe malaria, in an unplanned subgroup analysis from study months 0 to 20, 13 cases of possible cerebral malaria by record review and expert opinion occurred in the combined 3- and 4-dose RTS,S/AS01 group compared to 7 in the control group (2:1 randomization). From study month 21 until trial end, there were 7 cerebral malaria cases in the 4-dose RTS,S/AS01 group, 8 cases in the 3-dose RTS,S/AS01 group, and 2 cases in the control group.
148. **Risk of Bias: very serious.** Downgraded two levels for risk of bias: This was a post-hoc analysis based on an imprecise algorithm, followed by record review and expert panel review. Cerebral malaria is a difficult diagnosis to make in real time, and more difficult through record review Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias for this reason. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI. **Publication bias: no serious.**
149. [Safety outcome] Cerebral malaria assessed with severe P. falciparum malaria (positive rapid diagnostic test or by microscopy) with impaired consciousness (Glasgow coma scale < 11, Blantyre coma scale < 3) persisting for > 1 hour after a seizure. Children 5 to 17 months of age were randomized to receive seasonal malaria chemoprevention (SMC) alone (sulfadoxine–pyrimethamine and amodiaquine), RTS,S/AS01 alone, or a combination of RTS,S/AS01 and SMC.
150. [183]. Due to the absence of cases in the reference group, it was not possible to calculate the incidence rate ratio in vaccine recipients. There were no cases of cerebral malaria in the SMC alone group, 4 cases in the RTS,S vaccine alone group (0.723 cases per 1000 PYAR; 95%CI 0.271 to 1.93), and 1 case in the combination of RTS,S vaccine + SMC group (0.182 cases per 1000 PYAR; 95%CI 0.026 to 1.29).
151. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision:

very few events and 0 events in the control arm; . **Publication bias: no serious.**
152. [Safety outcome] Cerebral malaria assessed with positive P. falciparum rapid diagnostic test or by microscopy, with impaired consciousness (Glasgow coma score <11 or Blantyre coma score <3 or assessed as P or U on the AVPU scale ("Alert, Voice, Pain, Unresponsive"). The overall study (in two sites Agogo, Ghana and Siaya, Kenya) included 1609 total participants with 4 dose groups - only group 1 is reported in this table. Group 1 [n=322]: RTS,S/AS01 – 3 standard 0.5 mL doses at months 0, 1 and 2, followed by standard dose at month 20 Group 2 [n=322]: RTS,S/AS01 – 3 standard 0.5 mL doses at months 0, 1 and 2, followed by standard doses at months 14, 26 and 38 Group 3 [n=322]: RTS,S/AS01 – 2 standard 0.5 mL doses at months 0 and 1, followed by fractional doses (0.1 mL) at months 2, 14, 26 and 38 Group 4 [n=322]: RTS,S/AS01 – 2 standard 0.5 mL doses at months 0 and 1, followed by fractional doses (0.1 mL) at months 7, 20 and 32; Group 5 [n=321]: Control received comparator vaccine (Rabies) at month 12
153. [192]. Absolute effect reported per 1000 children.
154. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded two levels due to serious imprecision; very few events and 0 events in the intervention arm. **Publication bias: no serious.**
155. [Safety outcome] Cerebral malaria assessed with severe P. falciparum malaria (positive rapid diagnostic test of microscopy) with impaired consciousness (Glasgow coma scale < 11, Blantyre coma scale < 3) persisting for > 1 hour after a seizure.
156. [182].
157. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded two levels due to serious imprecision: very few events and very wide confidence interval that include the possibility of benefit and harm. **Publication bias: no serious.**
158. [Safety outcome] 4-dose intervention group (R3R) received 3 doses of RTS,S/AS01 at months 0, 1, and 2 and a 4th dose at month 20. The 3-dose intervention group (R3C) received the comparator vaccine (Rabies vaccine) at months 0, 1, 2, and 20. The control group (C3C) received 4 doses of comparator vaccine at months 0, 1, 2, and 20.
159. [179]. Incidence rate ratio (IRR) of 4-dose group + 3-dose group vs Control group: Girls only IRR 2.0 (95% CI: 1.2 - 3.4) vs Boys only IRR 0.8 (95% CI 0.5 - 1.2). Girls only: 4-dose group 35 deaths (9 malaria)/1467 girls + 3-dose group 32 deaths (8 malaria) / 1500 girls vs Control group 17 deaths (4 malaria) / 1503 girls. Boys only 4-dose group 26 deaths (4 malaria) / 1509 boys + 3-dose group 19 deaths (9 malaria) / 1472 boys vs Control group 29 deaths (8 malaria) / 1471 boys.
160. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious.** For this safety outcome we have reported the combined results for children receiving 3 or 4 doses of the vaccine; however, it has not been downgraded for indirectness. **Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**
162. [183]. Gender interaction parameter 1.80 (95%CI: 0.56 to 5.79); Girls only RTS,S vs SMC alone hazard ratio (HR) 1.23 (95% CI: 0.51 to 2.96); there were 11 deaths total or 4.15 deaths per 1000 PYAR (95% CI 2.30 to 7.49) among girls in the RTS,S alone group compared to 9 deaths total or 3.42 deaths per 1000 PYAR (95% CI 1.78 to 6.57) among girls in the SMC alone group. Boys only RTS,S vs SMC alone HR 0.68 (95% CI 0.32 to 1.47); there were 11 deaths total or 3.82 deaths per 1000 PYAR (95% CI 2.11 to 6.89) among boys in the RTS,S alone group compared to 16 deaths total or 5.68 deaths per 1000 PYAR (95% CI 3.48 to 9.27) among boys in the SMC alone group.
163. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**
165. [183]. Gender interaction parameter 0.35 (95%CI 0.06 to 1.98). Girls only RTS,S+SMC combination group vs SMC alone group hazard ratio (HR) 0.22 (95% CI 0.05 to 1.02); there were 2 deaths total or 0.75 deaths per 1000 PYAR (95% CI 0.19 - 3.01) among girls in the RTS,S + SMC combination group compared to 9 deaths total or 3.42 deaths per 1000 PYAR (95% CI 1.78 - 6.57) among girls in the SMC alone group. Boys only RTS,S + SMC combination group vs SMC alone group HR 0.62 (95% CI 0.28 to 1.37); there were 10 deaths total or 3.51 deaths per 1000 PYAR (95% CI 1.89 - 6.52) among boys in the Combination group compared to 16 deaths total or 5.68 deaths per 1000 PYAR (95% CI 3.48 - 9.27) among boys in the SMC alone group.
166. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm;. **Publication bias: no serious.**
167. [Safety outcome] Pilot implementation study designed to be analysed using cluster randomized control methodology. The evaluation was not powered at this time point to assess the overall impact of vaccine introduction on mortality, but the evaluation was well powered to detect gender imbalance in all-cause mortality of the magnitude observed in the Phase 3 trial (mortality ratio = 1.4--1.6), in children up to about 2 years of age. A total of 15,444 deaths among children 1-59 months of age were reported via community-based mortality surveillance across the three countries (Ghana, Kenya, and Malawi) from the start of vaccinations on 23 April 2019 to 12 July 2023 (deaths in April 2021 were excluded because verbal autopsies had not all been completed).
168. [200]. There was no evidence that the effect of RTS,S/AS01 introduction on all-cause mortality differed between girls and boys in this age group. Excluding deaths due to injury in children eligible to have received 3 doses of RTS,S/AS01, there was a total of 11,992 deaths reported: 5,706 from implementing regions and 6,286 from comparison regions. In children who were not eligible to have received the vaccine, there were 7,534 deaths in implementing regions and 7,044 in comparison regions. The mortality ratio in the

vaccine-eligible age group (eligible for 3 doses) between implementing and comparison regions, was 0.87 (95%CI: 0.78 to 0.97), a reduction of 13% (95%CI: 3% to 22%). There was no evidence that the mortality ratio differed between girls and boys (p-value for interaction 0.981). The mortality ratio in girls was 0.86 and in boys 0.87; the relative mortality ratio (girls:boys) was 1.00 (95%CI: 0.89 to 1.12). When analysis was extended to children eligible to have received at least one dose of the vaccine, similar results were obtained (ratio of mortality ratios: 1.04; 95%CI: 0.93 to 1.15; p-value for the interaction: 0.495). The vaccination status of vaccine-eligible children who died in implementation areas was similar in girls and boys (55.6% and 54.5% respectively). According to the endline household surveys (conducted after approximately 30 months of vaccine introduction) in 12-23 month olds, coverage of the first dose of RTS,S/AS01 was slightly higher but not statistically different in boys than in girls (84% in girls and 86% in boys in Ghana; 77% in girls and 77% in boys in Malawi; and 82% in girls and 83% in boys in Kenya). Coverage was similar for the third dose..

References

167. Shattock AJ, Johnson HC, Sim SY, Carter A, Lambach P, Hutubessy RCW, et al. Contribution of vaccination to improved survival and health: modelling 50 years of the Expanded Programme on Immunization. Lancet (London, England) 2024;403(10441):2307-2316 Pubmed Journal

168. WHO Immunization Data Portal. Website

169. WHO review of malaria vaccine clinical development. Geneva: World Health Organization 2024. Website

170. Good MF. Our impasse in developing a malaria vaccine. Cellular and molecular life sciences : CMLS 2011;68(7):1105-13 Pubmed Journal

171. Minassian AM, Silk SE, Barrett JR, Nielsen CM, Miura K, Diouf A, et al. Reduced blood-stage malaria growth and immune correlates in humans following RH5 vaccination. Med (New York, N.Y.) 2021;2(6):701-719.e19 Pubmed Journal

172. Safety and immunogenicity of Pfs25M-EPA/AS01 and Pfs230D1M-EPA/AS01 vaccines, transmission blocking vaccines against Plasmodium falciparum, at full and fractional dosing in adults in Mali. Website

173. Draper SJ, Angov E, Horii T, Miller LH, Srinivasan P, Theisen M, et al. Recent advances in recombinant protein-based malaria vaccines. Vaccine 2015;33(52):7433-43 Pubmed Journal

174. BioNTech SE. Safety and immune responses after vaccination with an investigational RNA-based vaccine against malaria (NCT05581641). U.S National Library of Medicine Website

175. BioNTech SE. A clinical trial to evaluate the safety, efficacy, and immune responses after vaccination with an investigational RNA-based vaccine against malaria. U.S. National Library of Medicine Website

176. Adjuvant development for vaccines and for autoimmune and allergic diseases. Washington (DC): Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) 2020. Website

177. Guidelines on the quality, safety and efficacy of recombinant malaria vaccines targeting the pre-erythrocytic and blood stages of Plasmodium falciparum, Annex 3, TRS No 980. Geneva: World Health Organization 2014. Website

178. Malaria vaccine: WHO position paper - May 2024. Weekly Epidemiological Record,Vol. 99, No. 19, pp. 225-248. 10 May 2024. Geneva: World Health Organization 2024. Website

179. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet (London, England) 2015;386(9988):31-45 Pubmed Journal

180. Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites. PLoS medicine 2014;11(7):e1001685 Pubmed Journal

181. Tinto H, Otieno W, Gesase S, Sorgho H, Otieno L, Liheluka E, et al. Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised controlled trial. The Lancet. Infectious diseases 2019;19(8):821-832 Pubmed Journal

182. Datoo MS, Dicko A, Tinto H, Ouédraogo J-B, Hamaluba M, Olotu A, et al. Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: a multicentre, double-blind, randomised, phase 3 trial. Lancet (London, England) 2024;403(10426):533-544 Pubmed Journal

183. Chandramohan D, Zongo I, Sagara I, Cairns M, Yerbanga R-S, Diarra M, et al. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. The New England journal of medicine 2021;385(11):1005-1017 Pubmed Journal

184. Schmit N, Topazian HM, Natama HM, Bellamy D, Traoré O, Somé MA, et al. The public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine: a mathematical modelling study. The Lancet. Infectious diseases 2024;24(5):465-475 Pubmed Journal

185. Mosquirix: Opinion on medicine for use outside EU. European Medicines Agency 2015. Website

186. Prequalification of Medical Products: Mosquirix. Geneva: World Health Organization 2022. Website

187. Prequalification of Medical Products: R21 Malaria. Geneva: World Health Organization 2023. Website

188. Asante KP, Mathanga DP, Milligan P, Akech S, Oduro A, Mwapasa V, et al. Feasibility, safety, and impact of the RTS,S/AS01E malaria vaccine when implemented through national immunisation programmes: evaluation of cluster-randomised introduction of the vaccine in Ghana, Kenya, and Malawi. Lancet (London, England) 2024;403(10437):1660-1670 Pubmed Journal

189. Vekemans J, Guerra Y, Lievens M, Benns S, Lapierre D, Leach A, et al. Pooled analysis of safety data from pediatric Phase II RTS,S/AS malaria candidate vaccine trials. Human vaccines 2011;7(12):1309-16 Pubmed Journal

190. Baral R, Levin A, Odero C, Pecenka C, Tanko Bawa J, Antwi-Agyei KO, et al. Cost of introducing and delivering RTS,S/AS01 malaria vaccine within the malaria vaccine implementation program. (Supplementary material, Appendix 3). Vaccine 2023;41(8):1496-1502 Pubmed Journal

191. Dicko A, Ouedraogo J-B, Zongo I, Sagara I, Cairns M, Yerbanga RS, et al. Seasonal vaccination with RTS,S/AS01E vaccine with or without seasonal malaria chemoprevention in children up to the age of 5 years in Burkina Faso and Mali: a double-blind, randomised, controlled, phase 3 trial. The Lancet. Infectious diseases 2024;24(1):75-86 Pubmed Journal

192. Samuels AM, Ansong D, Kariuki SK, Adjei S, Bollaerts A, Ockenhouse C, et al. Efficacy of RTS,S/AS01E malaria vaccine administered according to different full, fractional, and delayed third or early fourth dose regimens in children aged 5-17 months in Ghana and Kenya: an open-label, phase 2b, randomised controlled trial. The Lancet. Infectious diseases 2022;22(9):1329-1342 Pubmed Journal

193. Westercamp N, Osei-Tutu L, Schuerman L, Kariuki SK, Bollaerts A, Lee CK, et al. Could Less Be More? Accounting for Fractional-Dose Regimens and Different Number of Vaccine Doses When Measuring the Impact of the RTS,S/AS01E Malaria Vaccine. The Journal of infectious diseases 2024;230(2):e486-e495 Pubmed Journal

194. Kintampo Health Research Centre. Strengthening the Evidence for Policy on the RTS,S/AS01 Malaria Vaccine (MVPE-CC). U.S. National Library of Medicine Website

195. Asante KP, Abdulla S, Agnandji S, Lyimo J, Vekemans J, Soulanoudjingar S, et al. Safety and efficacy of the RTS,S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. The Lancet. Infectious diseases 2011;11(10):741-9 Pubmed Journal

196. Agnandji ST, Asante KP, Lyimo J, Vekemans J, Soulanoudjingar SS, Owusu R, et al. Evaluation of the safety and immunogenicity of the RTS,S/AS01E malaria candidate vaccine when integrated in the expanded program of immunization. The Journal of infectious diseases 2010;202(7):1076-87 Pubmed Journal

197. University of Oxford. Assessment of safety and immunogenicity of a single vial presentation of R21/Matrix-M and co-administration with EPI vaccines. U.S National Library of Medicine Website

198. University of Oxford. Assessment of safety and immunogenicity of R21/Matrix-M in African children living with HIV. U.S. National Library of Medicine Website

199. Datoo MS, Natama MH, Somé A, Traoré O, Rouamba T, Bellamy D, et al. Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. Lancet 2021;397(10287):1809-1818 Pubmed Journal Website

200. Milligan P, Fogelson A. Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 46 months after the vaccine was introduced (unpublished evidence). Geneva: World Health Organization 2024. Website

5. Case management

5.1. Diagnosing malaria

5.2. Treating malaria

5.2.1. Treating uncomplicated malaria

5.2.1.1. Artemisinin-based combination therapy

Clinical question/ PICO

Population: Patients with uncomplicated P. falciparum malaria (malaria-endemic settings in Africa)
Intervention: Dihydroartemisinin + piperaquine once daily for 3 days
Comparator: Artemether + lumefantrine twice daily for 3 days

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the evidence** (Quality of evidence)
Treatment failure - PCR unadjusted [1] 28 days	Relative risk 0.34 (CI 95% 0.3 — 0.39) Based on data from 6,200 participants in 9 studies. (Randomized controlled)	230 per 1000 Difference:	78 per 1000 **152 fewer per 1000** (CI 95% 161 fewer — 140 fewer)	High [2]
Treatment failure - PCR adjusted [3] 28 days	Relative risk 0.42 (CI 95% 0.29 — 0.62) Based on data from 5,417 participants in 9 studies. (Randomized controlled)	30 per 1000 Difference:	13 per 1000 **17 fewer per 1000** (CI 95% 21 fewer — 11 fewer)	High [4]
Treatment failure - PCR unadjusted [5] 63 days	Relative risk 0.71 (CI 95% 0.65 — 0.78) Based on data from 3,200 participants in 2 studies. (Randomized controlled)	450 per 1000 Difference:	320 per 1000 **130 fewer per 1000** (CI 95% 157 fewer — 99 fewer)	High [6]
Treatment failure - PCR adjusted [7] 63 days	Relative risk 0.72 (CI 95% 0.5 — 1.04) Based on data from 2,097 participants in 2 studies. (Randomized controlled)	60 per 1000 Difference:	43 per 1000 **17 fewer per 1000** (CI 95% 30 fewer — 2 more)	High [8]

1, 5. PCR unadjusted
2. **Risk of Bias: no serious.** Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** All the trials had similar results, and statistical heterogeneity was low.. **Indirectness: no serious.** The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** The 95% CI implies appreciable benefit, and the meta-analysis is adequately powered to detect this result.. **Publication bias: no serious.**

3, 7. PCR adjusted
4. **Risk of Bias: no serious.** Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** All the trials had similar results, and statistical heterogeneity was low.. **Indirectness: no serious.** The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** Although there is a benefit in favour of dihydroartemisinin + piperaquine, the PCR-adjusted treatment failure rate was < 5% with both drugs.. **Publication bias: no serious.**
6. **Risk of Bias: no serious.** Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** At this time, there is inconsistency between trials; both show a benefit with dihydroartemisinin + piperaquine, but the size of the benefit differs.. **Indirectness: no serious.** The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** The 95% CI implies appreciable benefit, and the meta-analysis is adequately powered to detect this result.. **Publication bias: no serious.**
8. **Risk of Bias: no serious.** Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** The treatment failure rate with dihydroartemisinin + piperaquine was < 5% in both trials.. **Indirectness: no serious.** The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** Both ACTs performed well in these two trials, with low rates of treatment failure.. **Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with uncomplicated P. falciparum malaria (malaria-endemic settings in Africa)
Intervention: Dihydroartemisinin + piperaquine once daily for 3 days
Comparator: Artesunate + mefloquine once daily for 3 days

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the evidence** (Quality of evidence)
Treatment failure - PCR unadjusted [1] 28 days	Relative risk 1.02 (CI 95% 0.28 — 3.72) Based on data from 3,487 participants in 8 studies. (Randomized controlled)	20 per 1000 Difference:	20 per 1000 **0 fewer per 1000** (CI 95% 14 fewer — 54 more)	High Due to serious inconsistency [2]
Treatment failure - PCR adjusted [3] 28 days	Relative risk 0.41 (CI 95% 0.21 — 0.8) Based on data from 3,467 participants in 8 studies. (Randomized controlled)	10 per 1000 Difference:	4 per 1000 **6 fewer per 1000** (CI 95% 8 fewer — 2 fewer)	High Due to serious inconsistency [4]
Treatment failure - PCR unadjusted [5] 63 days	Relative risk 0.84 (CI 95% 0.69 — 1.03) Based on data from 2,715 participants in 5 studies. (Randomized controlled)	120 per 1000 Difference:	101 per 1000 **19 fewer per 1000** (CI 95% 37 fewer — 4 more)	Moderate Due to serious inconsistency [6]
Treatment failure - PCR adjusted [7] 63 days	Relative risk 0.5 (CI 95% 0.3 — 0.84) Based on data from 2,500	30 per 1000	15 per 1000	High Due to serious inconsistency [8]

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the evidence** (Quality of evidence)
	participants in 5 studies. (Randomized controlled)	Difference:	**15 fewer per 1000** (CI 95% 21 fewer — 5 fewer)	

1, 5. PCR unadjusted
2. **Risk of Bias: no serious.** Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** In six trials, very few recurrences of parasitaemia were found in both groups. Two trials conducted mainly in areas in Thailand with multi-drug resistance showed increased risks for recurrent parasitaemia with artesunate + mefloquine.. **Indirectness: no serious.** The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam.. **Imprecision: no serious.** Overall, no significant difference between treatments; however, dihydroartemisinin + piperaquine may be superior where P. falciparum is resistant to mefloquine.. **Publication bias: no serious.**
3, 7. PCR adjusted
4. **Risk of Bias: no serious.** Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** In six trials, very few recurrences of parasitaemia were found in both groups. Two trials conducted mainly in areas in Thailand with multi-drug resistance showed increased risks for recurrent parasitaemia with artesunate + mefloquine.. **Indirectness: no serious.** The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam.. **Imprecision: no serious.** Overall, a statistically significant benefit with dihydroartemisinin + piperaquine, although the benefit may be present only where there is resistance to mefloquine.. **Publication bias: no serious.**
6. **Risk of Bias: no serious.** Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** Of the five trials, one in Thailand in 2005 showed a statistically significant benefit with dihydroartemisinin + piperaquine, one in Myanmar in 2009 showed a benefit with dihydroartemisinin + piperaquine, and three found no difference.. **Indirectness: no serious.** The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar and Thailand.. **Imprecision: no serious.** Overall, no significant difference between treatments. Although some trials found statistically significant differences, these may not be clinically important.. **Publication bias: no serious.**
8. **Risk of Bias: no serious.** Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** Slight variation among trials, only one showing a statistically significant benefit with dihydroartemisinin + piperaquine.. **Indirectness: no serious.** The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar and Thailand.. **Imprecision: no serious.** Overall, no significant difference between treatments. Although some trials found statistically significant differences, these may not be clinically important.. **Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with uncomplicated P. falciparum malaria (malaria-endemic settings in Africa)
Intervention: Dihydroartemisinin + piperaquine
Comparator: Artemether + lumefantrine

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the evidence** (Quality of evidence)
Serious adverse events (including deaths)	Based on data from 7,022 participants in 8 studies. (Randomized controlled)	6 per 1000 Difference:	10 per 1000 **4 more per 1000**	Moderate Due to serious imprecision [1]

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the evidence** (Quality of evidence)
Early vomiting	Based on data from 2,695 participants in 3 studies. (Randomized controlled)	20 per 1000 Difference:	30 per 1000 **10 more per 1000**	Moderate Due to serious risk of bias [2]
Vomiting	Based on data from 6,761 participants in 9 studies. (Randomized controlled)	90 per 1000 Difference:	90 per 1000 **0 fewer per 1000**	Moderate Due to serious risk of bias [3]
Nausea	Based on data from 547 participants in 2 studies. (Randomized controlled)	20 per 1000 Difference:	20 per 1000 **0 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [4]
Diarrhoea	Based on data from 4,889 participants in 7 studies. (Randomized controlled)	120 per 1000 Difference:	120 per 1000 **0 fewer per 1000**	Moderate Due to serious risk of bias [5]
Abdominal pain	Based on data from 911 participants in 5 studies. (Randomized controlled)	190 per 1000 Difference:	160 per 1000 **30 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [6]
Anorexia	Based on data from 3,834 participants in 5 studies. (Randomized controlled)	150 per 1000 Difference:	140 per 1000 **10 fewer per 1000**	Moderate Due to serious risk of bias [7]
Headache	Based on data from 309 participants in 2 studies. (Randomized controlled)	270 per 1000 Difference:	330 per 1000 **60 more per 1000**	Low Due to serious risk of bias and serious imprecision [8]
Sleeplessness	Based on data from 547 participants in 2 studies. (Randomized controlled)	10 per 1000 Difference:	30 per 1000 **20 more per 1000**	Low Due to serious risk of bias and serious imprecision [9]
Dizziness	Based on data from 547	30 per 1000	40 per 1000	Low Due to serious risk of bias and serious

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the evidence** (Quality of evidence)
	participants in 2 studies. (Randomized controlled)	Difference:	**10 more per 1000**	imprecision [10]
Sleepiness	Based on data from 384 participants in 1 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [11]
Weakness	Based on data from 1,812 participants in 5 studies. (Randomized controlled)	170 per 1000 Difference:	180 per 1000 **10 more per 1000**	Moderate Due to serious risk of bias [12]
Cough	Based on data from 4,342 participants in 5 studies. (Randomized controlled)	420 per 1000 Difference:	420 per 1000 **0 fewer per 1000**	Moderate Due to serious risk of bias [13]
Coryza	Based on data from 832 participants in 2 studies. (Randomized controlled)	680 per 1000 Difference:	660 per 1000 **20 fewer per 1000**	Low Due to serious imprecision [14]
Prolonged QT interval (adverse event)	Based on data from 1,548 participants in 1 studies. (Randomized controlled)	30 per 1000 Difference:	20 per 1000 **10 fewer per 1000**	Low Due to serious imprecision and serious risk of bias [15]
Prolonged QT interval (Bazett correction)	Based on data from 1,548 participants in 1 studies. (Randomized controlled)	70 per 1000 Difference:	90 per 1000 **20 more per 1000**	Low Due to serious imprecision and serious risk of bias [16]
Prolonged QT interval (Fridericia correction)	Based on data from 1,548 participants in 1 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [17]
Pruritus	Based on data from 2,033 participants in 5 studies. (Randomized controlled)	20 per 1000 Difference:	40 per 1000 **20 more per 1000**	Moderate Due to serious risk of bias [18]
Facial oedema	Based on data from 384	0 per 1000	0 per 1000	Low Due to serious risk of bias and serious

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the evidence** (Quality of evidence)
	participants in 1 studies. (Randomized controlled)	Difference:	**0 fewer per 1000**	imprecision [19]

1. **Risk of Bias: no serious.** All but one of the trials were open label; however, we did not downgrade for this outcome.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** No statistically significant difference was detected between treatments; however the sample size does not exclude the possibility of rare but clinically important differences..
2, 3, 5, 7, 12, 13, 18. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No effect found, and the CIs around the absolute effects exclude clinically important differences..
4. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: There are limited data..
6. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** The result does not reach statistical significance..
8. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** The result does not reach statistical significance..
9. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** There are limited data..
10. **Risk of Bias: serious.** The majority of trials were open label.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** There are limited data..
11, 19. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** There are limited data..
14. **Risk of Bias: no serious.** All but one of the trials were open label; however, we did not downgrade for this outcome.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** The result does not reach statistical significance..
15, 16, 17. **Risk of Bias: serious.** This trial was unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Inconsistency: no serious.** **Indirectness: no serious.** This single trial was conducted in children in Burkina Faso, Kenya, Mozambique, Uganda and Zambia.. **Imprecision: serious.** The result does not reach statistical significance..

Clinical question/ PICO

Population: Patients with uncomplicated P. falciparum malaria (malaria-endemic settings in Africa)
Intervention: Dihydroartemisinin + piperaquine
Comparator: Artesunate + mefloquine

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the evidence** (Quality of evidence)
Serious adverse events (including deaths)	Based on data from 3,522 participants in 8 studies. (Randomized controlled)	8 per 1000 Difference:	9 per 1000 **1 more per 1000**	Moderate Due to serious imprecision [1]
Nausea	Based on data from 4,531 participants in 9 studies. (Randomized controlled)	20 per 1000 Difference:	14 per 1000 **6 fewer per 1000**	Moderate Due to serious risk of bias [2]
Early vomiting	Based on data from 4,114 participants in 9 studies. (Randomized controlled)	7 per 1000 Difference:	6 per 1000 **1 fewer per 1000**	Moderate Due to serious risk of bias [3]
Vomiting	Based on data from 2,744 participants in 5 studies. (Randomized controlled)	13 per 1000 Difference:	8 per 1000 **5 fewer per 1000**	Moderate Due to serious risk of bias [4]
Anorexia	Based on data from 3,497 participants in 6 studies. (Randomized controlled)	15 per 1000 Difference:	13 per 1000 **2 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [5]
Diarrhoea	Based on data from 2,217 participants in 5 studies. (Randomized controlled)	6 per 1000 Difference:	8 per 1000 **2 more per 1000**	Moderate Due to serious risk of bias [6]
Abdominal pain	Based on data from 3,887 participants in 7 studies. (Randomized controlled)	11 per 1000 Difference:	11 per 1000 **0 fewer per 1000**	Moderate Due to serious risk of bias [7]
Headache	Based on data from 2,039 participants in 4 studies. (Randomized controlled)	12 per 1000 Difference:	10 per 1000 **2 fewer per 1000**	Low Due to serious risk of bias and serious inconsistency [8]
Dizziness	Based on data from 4,531 participants in 9 studies. (Randomized controlled)	36 per 1000 Difference:	26 per 1000 **10 fewer per 1000**	Moderate Due to serious risk of bias [9]

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the evidence** (Quality of evidence)
Sleeplessness	Based on data from 2,551 participants in 6 studies. (Randomized controlled)	21 per 1000 Difference:	10 per 1000 **11 fewer per 1000**	Moderate Due to serious risk of bias [10]
Fatigue	Based on data from 872 participants in 2 studies. (Randomized controlled)	8 per 1000 Difference:	3 per 1000 **5 fewer per 1000**	Low Due to serious risk of bias and serious indirectness [11]
Nightmares	Based on data from 220 participants in 1 studies. (Randomized controlled)	10 per 1000 Difference:	1 per 1000 **9 fewer per 1000**	Low Due to serious risk of bias and serious indirectness [12]
Anxiety	Based on data from 522 participants in 1 studies. (Randomized controlled)	11 per 1000 Difference:	1 per 1000 **10 fewer per 1000**	Low Due to serious risk of bias and serious indirectness [13]
Blurred vision	Based on data from 464 participants in 1 studies. (Randomized controlled)	9 per 1000 Difference:	4 per 1000 **5 fewer per 1000**	Low Due to serious risk of bias and serious indirectness [14]
Tinnitus	Based on data from 220 participants in 1 studies. (Randomized controlled)	9 per 1000 Difference:	4 per 1000 **5 fewer per 1000**	Low Due to serious risk of bias and serious indirectness [15]
Palpitations	Based on data from 1,175 participants in 3 studies. (Randomized controlled)	18 per 1000 Difference:	11 per 1000 **7 fewer per 1000**	Moderate Due to serious risk of bias [16]
Cough	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	10 per 1000 Difference:	8 per 1000 **2 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [17]
Dyspnoea	Based on data from 220 participants in 1 studies. (Randomized controlled)	9 per 1000 Difference:	3 per 1000 **6 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [18]

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the evidence** (Quality of evidence)
Prolonged QT interval (adverse event)	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	4 per 1000 Difference:	5 per 1000 **1 more per 1000**	Low Due to serious risk of bias and serious imprecision [19]
Prolonged QT interval (Bazett correction)	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	4 per 1000 Difference:	9 per 1000 **5 more per 1000**	Low Due to serious risk of bias and serious imprecision [20]
Prolonged QT interval (Fridericia correction)	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	5 per 1000 Difference:	4 per 1000 **1 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [21]
Arthralgia	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	6 per 1000 Difference:	5 per 1000 **1 fewer per 1000**	Moderate Due to serious risk of bias [22]
Myalgia	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	6 per 1000 Difference:	6 per 1000 **0 fewer per 1000**	Moderate Due to serious risk of bias [23]
Urticaria	Based on data from 719 participants in 2 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 **1 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [24]
Pruritus	Based on data from 872 participants in 2 studies. (Randomized controlled)	3 per 1000 Difference:	2 per 1000 **1 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [25]
Rash	Based on data from 220 participants in 1 studies. (Randomized controlled)	1 per 1000 Difference:	0 per 1000 **1 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [26]

1. **Risk of Bias: no serious.** Only eight of the 11 reports made any comment on serious adverse events. None of these eight trials was blinded. . **Inconsistency: no serious.** None of the eight trials found statistically significant differences.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: serious.** These trials do not exclude the possibility of rare but clinically important adverse effects..
2, 4, 6, 9, 10, 16. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** The result is statistically significant, and

the meta-analysis has adequate power to detect this effect..
3. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** None of the eight trials found statistically significant differences.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** The 95% CI around the absolute effect is narrow and excludes clinically important differences..
5. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: serious.** This result does not reach statistical significance..
7. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No difference was found between treatments, and the sample is large enough for detection of any differences..
8. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: serious.** There is moderate heterogeneity among trials.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
11. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: serious.** Only two trials assessed this outcome.. **Imprecision: no serious.**
12, 13, 14, 15. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: serious.** Only two trials assessed this outcome.. **Imprecision: no serious.**
17. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** This result does not reach statistical significance..
18, 24, 25, 26. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Limited data available, and the result is not statistically significant..
19. **Risk of Bias: serious.** This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Inconsistency: no serious. Indirectness: no serious.** This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.. **Imprecision: serious.** This result does not reach statistical significance..
20, 21. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: no serious.** This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.. **Imprecision: serious.** This result does not reach statistical significance..
22. **Risk of Bias: serious.** All trials were open label. This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear. 15 . **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** No difference was found between treatments, and the sample is large enough for detection of any differences..
23. **Risk of Bias: serious.** All trials were open label. This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** No difference was found between treatments, and the sample is large enough for detection of any differences..

Clinical question/ PICO

Population: Adults and children with uncomplicated P. falciparum malaria (malaria-endemic settings)
Intervention: Artemisinin + naphthoquine; 1-day course
Comparator: Artemether + lumefantrine twice daily for 3 days

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Artemisinin + naphthoquine	**Certainty of the evidence** (Quality of evidence)
Treatment failure on day 28 (PCR-unadjusted)	Relative risk 1.54 (CI 95% 0.27 — 8.96) Based on data from 297	10 per 1000	15 per 1000	Very low Due to serious indirectness and very

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Artemisinin + naphthoquine	**Certainty of the evidence** (Quality of evidence)
	participants in 2 studies. (Randomized controlled)	Difference:	**5 more per 1000** (CI 95% 7 fewer — 80 more)	serious imprecision [1]
Treatment failure on day 28 (PCR-adjusted)	Relative risk 3.25 (CI 95% 0.13 — 78.69) Based on data from 295 participants in 2 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	Very low Due to serious indirectness and very serious imprecision [2]
Fever clearance: fever on day 2	Relative risk 5.9 (CI 95% 0.73 — 47.6) Based on data from 123 participants in 1 studies. (Randomized controlled)	20 per 1000 Difference:	118 per 1000 **98 more per 1000** (CI 95% 5 fewer — 932 more)	Very low Due to serious indirectness and very serious imprecision [3]
Parasite clearance: parasitaemia on day 2	Relative risk 0.15 (CI 95% 0.01 — 2.92) Based on data from 297 participants in 2 studies. (Randomized controlled)	20 per 1000 Difference:	3 per 1000 **17 fewer per 1000** (CI 95% 20 fewer — 38 more)	Very low Due to serious indirectness and very serious imprecision [4]
Gametocytaemia on day 7	Relative risk 1.97 (CI 95% 0.18 — 21.14) Based on data from 123 participants in 1 studies. (Randomized controlled)	20 per 1000 Difference:	39 per 1000 **19 more per 1000** (CI 95% 16 fewer — 403 more)	Very low Due to serious indirectness and very serious imprecision [5]

1, 2. **Risk of Bias: no serious.** One study adequately concealed allocation and thus had a low risk of selection bias. In the other study, the process of randomization and allocation concealment was unclear. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only two studies, in Benin and Cote d'Ivoire, evaluated this comparison. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. Both trials are significantly underpowered.
3, 5. **Risk of Bias: no serious.** This study adequately concealed allocation and thus had a low risk of selection bias. **Indirectness: serious.** Study in Cote d'Ivoire. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** This trial was small and the result has a very wide 95% confidence interval, including appreciable benefit and harm.
4. **Risk of Bias: no serious.** One study adequately concealed allocation and thus had a low risk of selection bias. In the other study, the process of randomization and allocation concealment was unclear. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only two studies, in Benin and Cote d'Ivoire, evaluated this comparison. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** The result has a very wide 95% confidence interval, including appreciable benefit and harm.

Clinical question/ PICO

Population: Adults and children with uncomplicated P. falciparum malaria (malaria-endemic settings)

Intervention: Artemisinin + naphthoquine; 1-day course
Comparator: Dihydroartemisinin + piperaquine; 3-day course

Outcome Timeframe	**Study results and measurements**	**Comparator** Dihydroartemisinin + piperaquine	**Intervention** Artemisinin + naphthoquine	**Certainty of the evidence** (Quality of evidence)
Treatment failure on day 28 (PCR-unadjusted)	Based on data from 143 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000	Very low Due to serious indirectness and very serious imprecision [1]
Treatment failure on day 28 (PCR-adjusted)	Based on data from 143 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000	Very low Due to serious indirectness and very serious imprecision [2]
Treatment failure on day 42 (PCR-unadjusted)	Relative risk 0.91 (CI 95% 0.13 — 6.26) Based on data from 143 participants in 1 studies. (Randomized controlled)	30 per 1000 Difference:	27 per 1000 **3 fewer per 1000** (CI 95% 26 fewer — 158 more)	Very low Due to serious indirectness and very serious imprecision [3]
Treatment failure on day 42 (PCR-adjusted)	Relative risk 0.19 (CI 95% 0.01 — 3.82) Based on data from 141 participants in 1 studies. (Randomized controlled)	30 per 1000 Difference:	6 per 1000 **24 fewer per 1000** (CI 95% 30 fewer — 85 more)	Very low Due to serious indirectness and very serious imprecision [4]
Fever clearance: fever on day 2	Based on data from 144 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000	Very low Due to serious indirectness and very serious imprecision [5]
Parasite clearance: parasitaemia on day 2	Relative risk 6.29 (CI 95% 0.33 — 119.69) Based on data from 144 participants in 1 studies. (Randomized controlled)	0 per 1000	40 per 1000	Very low Due to serious indirectness and very serious imprecision [6]
Gametocytaemia: on day 7	Relative risk 1.38 (CI 95% 0.52 — 3.7) Based on data from 144 participants in 1 studies. (Randomized controlled)	80 per 1000 Difference:	110 per 1000 **30 more per 1000** (CI 95% 38 fewer — 216 more)	Very low Due to serious indirectness and very serious imprecision [7]

1, 2, 3, 4. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at

low risk of selection bias. **Inconsistency: no serious. Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. This trial is significantly underpowered.
5. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Inconsistency: no serious. Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** This trial is small. No participants in either group had fever on day 2.
6, 7. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Inconsistency: no serious. Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** The result has a very wide 95% confidence interval, including appreciable benefit and harm.

Clinical question/ PICO

Population: Adults and children with uncomplicated P. falciparum malaria in malaria transmission settings
Intervention: Artesunate-pyronaridine
Comparator: artemether-lumefantrine

Outcome Timeframe	**Study results and measurements**	**Comparator** AL	**Intervention** ASPY	**Certainty of the evidence** (Quality of evidence)	**Summary**
Total failure: day 28 (PCR-adjusted)	Relative risk 0.59 (CI 95% 0.26 — 1.31) Based on data from 3,068 participants in 4 studies. [1] (Randomized controlled)	15 per 1000 Difference:	9 per 1000 **6 fewer per 1000** (CI 95% 11 fewer — 5 more)	Low Due to serious indirectness, Due to serious imprecision. Certainty of the evidence grade differs from the 2014 review version due to additional data: the previous review reported no substantial difference between ASPY and AL in reference to this outcome and therefore did not downgrade for imprecision. In this update we report a reduced rate in the ASPY arm. Because we concluded that there may be a difference, we necessarily downgraded for the imprecision. [2]	Compared to AL, ASPY may have fewer PCR-adjusted failures at day 28.
Total failure: day 42 (PCR-adjusted)	Relative risk 0.86 (CI 95% 0.49 — 1.51) Based on data from 2,575 participants in 4	23 per 1000 Difference:	20 per 1000 **3 fewer per 1000**	Low Due to serious indirectness, Due to serious	There may be little or no difference in PCR-adjusted failures at day 42 between ASPY and

Outcome Timeframe	**Study results and measurements**	**Comparator** AL	**Intervention** ASPY	**Certainty of the evidence** (Quality of evidence)	**Summary**
	studies. [3] (Randomized controlled)		(CI 95% 12 fewer — 12 more)	imprecision [4]	AL.
Total failure: day 28 (unadjusted)	Relative risk 0.27 (CI 95% 0.13 — 0.58) Based on data from 3,149 participants in 4 studies. [5] (Randomized controlled)	126 per 1000 Difference:	34 per 1000 **92 fewer per 1000** (CI 95% 110 fewer — 53 fewer)	Low Due to serious indirectness, Due to serious inconsistency, Certainty of the evidence grade differs from the 2014 review version due to additional data: the introduction of more data increased the heterogeneity between the included trials. [6]	Compared to AL, ASPY may have fewer unadjusted failures at day 28.
Total failure: day 42 (unadjusted)	Relative risk 0.61 (CI 95% 0.46 — 0.82) Based on data from 3,080 participants in 4 studies. [7] (Randomized controlled)	254 per 1000 Difference:	155 per 1000 **99 fewer per 1000** (CI 95% 137 fewer — 46 fewer)	Low Due to serious inconsistency, Due to serious indirectness, Certainty of the evidence grade differs from the 2014 review version due to additional data: the introduction of more data increased the heterogeneity between the included trials. [8]	Compared to AL, ASPY may have fewer unadjusted failures at day 42.
Serious adverse events (42 days)	Relative risk 1.16 (CI 95% 0.3 — 4.5) Based on data from 2,004 participants in 3 studies. [9] (Randomized controlled)	3 per 1000 Difference:	3 per 1000 **0 fewer per 1000** (CI 95% 2 fewer — 11 more)	Low Due to very serious imprecision [10]	We do not know if there is a difference in serious adverse events between ASPY and AL.
First treatment, abnormal ALT increase (42 days)	Relative risk 3.34 (CI 95% 1.33 — 8.39) Based on data from 3,415 participants in 4 studies. [11] (Randomized controlled)	3 per 1000 Difference:	10 per 1000 **7 more per 1000** (CI 95% 1 more — 22 more)	Low Due to serious indirectness, Due to serious imprecision [12]	Compared to AL, ASPY may lead to higher events of abnormal ALT increase. (Aggregate analysis indicates this estimate may be accurate).
First treatment, AST increase (42 days)	Relative risk 3.12 (CI 95% 1.23 — 7.94) Based on data from 3,415 participants in 4 studies. [13] (Randomized	3 per 1000 Difference:	9 per 1000 **6 more per 1000** (CI 95% 1 more	Low Due to serious indirectness, Due to serious imprecision [14]	Compared to AL, ASPY may lead to higher events of abnormal AST increase.

Outcome Timeframe	**Study results and measurements**	**Comparator** AL	**Intervention** ASPY	**Certainty of the evidence** (Quality of evidence)	**Summary**
	controlled)		— 21 more)		
First treatment, abnormal bilirubin increase (42 days)	Relative risk 0.82 (CI 95% 0.33 — 2.04) Based on data from 3,130 participants in 3 studies. [15] (Randomized controlled)	6 per 1000 Difference:	5 per 1000 **1 fewer per 1000** (CI 95% 4 fewer — 6 more)	Low Due to serious indirectness, Due to serious imprecision [16]	We do not know if there is a difference in bilirubin between ASPY and AL.

1. Systematic review [224] with included studies: Roth 2018a, Kayentao 2012, Sagara 2018 (Bougoula, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Kolle, Mali), Tshefu 2010.
2, 4, 12, 14. **Inconsistency: no serious. Indirectness: serious.** The trials included adults and children and had sites in Africa and Asia. However, across the trials, only 115 children and 0 adults were randomized to ASPY in Asia. Further adequately powered studies in adults and children in Asia would be needed to fully apply this result.. **Imprecision: serious.** The CIs are wide and include both almost no effect and clinically significant effect..
3. Systematic review [224] with included studies: Kayentao 2012, Sagara 2018 (Kolle, Mali), Sagara 2018 (Sotuba, Mali), Tshefu 2010, Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Roth 2018a, Sagara 2018 (Bougoula, Mali).
5. Systematic review [224] with included studies: Roth 2018a, Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Sotuba, Mali), Tshefu 2010, Sagara 2018 (Kolle, Mali), Kayentao 2012.
6, 8. **Inconsistency: serious.** There was quantitative heterogeneity between studies.. **Indirectness: serious.** The trials included adults and children and had sites in Africa and Asia. However, across the trials, only 115 children and 0 adults were randomized to ASPY in Asia. Further adequately powered studies in adults and children in Asia would be needed to fully apply this result.. **Imprecision: no serious.**
7. Systematic review [224] with included studies: Tshefu 2010, Sagara 2018 (Sotuba, Mali), Kayentao 2012, Roth 2018a, Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Kolle, Mali).
9. Systematic review [224] with included studies: Tshefu 2010, Roth 2018a, Kayentao 2012.
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** The low number of events recorded in the studies is insufficient for confidently estimating the effect size. .
11. Systematic review [224] with included studies: Kayentao 2012, Roth 2018a, Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Kolle, Mali), Tshefu 2010, Sagara 2018 (Bougoula, Mali).
13. Systematic review [224] with included studies: Roth 2018a, Sagara 2018 (Bougoula, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Sotuba, Mali), Kayentao 2012, Tshefu 2010, Sagara 2018 (Kolle, Mali).
15. Systematic review [224] with included studies: Sagara 2018 (Bougoula, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Sotuba, Mali), Kayentao 2012, Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Tshefu 2010.
16. **Inconsistency: no serious. Indirectness: serious.** The trials included adults and children and had sites in Africa and Asia. However, across the trials, only 115 children and 0 adults were randomized to ASPY in Asia. Further adequately powered studies in adults and children in Asia would be needed to fully apply this result.. **Imprecision: serious.** The CIs include both no effect and clinically significant effect.

Clinical question/ PICO

Population: Adults and children with uncomplicated P. falciparum malaria (malaria transmission settings)
Intervention: Artesunate-pyronaridine
Comparator: Artesunate-amodiaquine

Outcome Timeframe	**Study results and measurements**	**Comparator** AS-AQ	**Intervention** ASPY	**Certainty of the evidence** (Quality of evidence)	**Summary**
Total failure: day 28 (PCR-adjusted)	Relative risk 0.55 (CI 95% 0.11 — 2.77) Based on data from 1,245 participants in 1 studies. [1] (Randomized controlled)	8 per 1000 Difference:	4 per 1000 **4 fewer per 1000** (CI 95% 7 fewer — 14 more)	Low Due to serious indirectness, Due to serious imprecision [2]	Compared to AS-AQ, ASPY may have fewer PCR-adjusted failures at day 28.
Total failure: day 42 (PCR-adjusted)	Relative risk 0.98 (CI 95% 0.2 — 4.83) Based on data from 1,091 participants in 1 studies. [3] (Randomized controlled)	6 per 1000 Difference:	5 per 1000 **0 fewer per 1000** (CI 95% 5 fewer — 23 more)	Low Due to serious indirectness, Due to serious imprecision [4]	There may be little or no difference in PCR-adjusted failures at day 42 between ASPY and AS-AQ.
Total failure: day 28 (unadjusted)	Relative risk 0.49 (CI 95% 0.3 — 0.81) Based on data from 1,257 participants in 1 studies. [5] (Randomized controlled)	75 per 1000 Difference:	37 per 1000 **38 fewer per 1000** (CI 95% 52 fewer — 14 fewer)	Moderate Due to serious indirectness [6]	Compared to AS-AQ, ASPY probably has fewer unadjusted failures at day 28.
Total failure: day 42 (unadjusted)	Relative risk 0.98 (CI 95% 0.78 — 1.23) Based on data from 1,235 participants in 1 studies. [7] (Randomized controlled)	195 per 1000 Difference:	192 per 1000 **4 fewer per 1000** (CI 95% 43 fewer — 45 more)	Moderate Due to serious indirectness [8]	There is probably little or no difference in unadjusted failures at day 42 between ASPY and AS-AQ.
First treatment, abnormal ALT increase (42 days)	Relative risk 1.41 (CI 95% 0.28 — 7.09) Based on data from 1,317 participants in 1 studies. [9] (Randomized controlled)	1 per 1000 Difference:	1 per 1000 **0 fewer per 1000** (CI 95% 1 fewer — 6 more)	Low Due to serious indirectness, Due to serious imprecision [10]	Compared to AL, ASPY may lead to higher events of abnormal ALT increase. (Aggregate analysis indicates this estimate may be accurate).
First treatment, abnormal AST increase (42 days)	Relative risk 0.43 (CI 95% 0.08 — 2.07) Based on data from 1,317 participants in 1 studies. [11] (Randomized controlled)	4 per 1000 Difference:	2 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 4 more)	Very low Due to serious indirectness, Due to very serious imprecision [12]	We do not know if there is a difference in AST between ASPY and AS-AQ.
First treatment, abnormal bilirubin increase (42 days)	Relative risk 0.99 (CI 95% 0.06 — 15.76) Based on data from 1,317 participants in 1 studies. [13] (Randomized controlled)	1 per 1000 Difference:	1 per 1000 **0 fewer per 1000** (CI 95% 1 fewer — 15 more)	Very low Due to serious indirectness, Due to very serious imprecision [14]	We do not know if there is a difference in bilirubin between ASPY and AS-AQ
Serious adverse					Serious adverse events data were not available

Outcome Timeframe	Study results and measurements	Comparator AS-AQ	Intervention ASPY	Certainty of the evidence (Quality of evidence)	Summary
events [15]					disaggregated by site to allow inclusion in this comparison.

1. Systematic review [224] with included studies: Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Kolle, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Sotuba, Mali).
2. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: serious.** The CI is large and includes both no effect and clinically important effects..
3. Systematic review [224] with included studies: Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Djoliba, Mali).
4. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: serious.** The effect estimate is close to no effect, but the CI is wide..
5. Systematic review [224] with included studies: Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Djoliba, Mali).
6, 8. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: no serious.**
7. Systematic review [224] with included studies: Sagara 2018 (Djoliba, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Bougoula, Mali).
9. Systematic review [224] with included studies: Sagara 2018 (Bougoula, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Kolle, Mali), Sagara 2018 (Djoliba, Mali).
10. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: serious.** The low number of events recorded in the study is insufficient for confidently estimating the effect size. However, aggregate analysis of ALT increase across different comparator drugs provides indirect evidence that the point estimate may be accurate..
11. Systematic review [224] with included studies: Sagara 2018 (Bougoula, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Mafrinyah, Guinea).
12, 14. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: very serious.** The CI is very large and includes both no effect and clinically important effects..
13. Systematic review [224] with included studies: Sagara 2018 (Bougoula, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Mafrinyah, Guinea).
15. Serious adverse events data were not available disaggregated by site to allow inclusion in this comparison.

References

224. Pryce J, Taylor M, Fox T, Hine P. Pyronaridine-artesunate for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database Syst Rev 2022;6(6) Pubmed Journal

Clinical question/ PICO

Population: Adults and children with uncomplicated P. falciparum malaria (malaria transmission settings)

Intervention: Artesunate-pyronaridine

Comparator: Mefloquine plus artesunate

Outcome Timeframe	**Study results and measurements**	**Comparator** MQ+AS	**Intervention** ASPY	**Certainty of the evidence** (Quality of evidence)	**Summary**
Total failure: day 28 (PCR-adjusted)	Relative risk 0.37 (CI 95% 0.13 — 1.05) Based on data from 1,117 participants in 1 studies. [1] (Randomized controlled)	22 per 1000 Difference:	8 per 1000 **14 fewer per 1000** (CI 95% 19 fewer — 1 more)	Low Due to serious indirectness, Due to serious imprecision, Certainty of the evidence grade differs from the 2014 review version due to alterations in the data extraction protocol: the CI has become less precise, and our decision has greater consistency with other outcome certainty grades. [2]	Compared to MQ+AS, ASPY may have fewer PCR-adjusted failures at day 28.
Total failure: day 42 (PCR-adjusted)	Relative risk 1.8 (CI 95% 0.9 — 3.57) Based on data from 1,037 participants in 1 studies. [3] (Randomized controlled)	29 per 1000 Difference:	52 per 1000 **23 more per 1000** (CI 95% 3 fewer — 75 more)	Low Due to serious indirectness, Due to serious imprecision [4]	Compared to MQ+AS, ASPY may have more PCR-adjusted failures at day 42.
Total failure: day 28 (unadjusted)	Relative risk 0.36 (CI 95% 0.17 — 0.78) Based on data from 1,120 participants in 1 studies. [5] (Randomized controlled)	41 per 1000 Difference:	15 per 1000 **26 fewer per 1000** (CI 95% 34 fewer — 9 fewer)	Moderate Due to serious indirectness [6]	Compared to MQ+AS, ASPY probably has fewer unadjusted failures at day 28.
Total failure: day 42 (unadjusted)	Relative risk 0.84 (CI 95% 0.54 — 1.31) Based on data from 1,059 participants in 1 studies. [7] (Randomized controlled)	83 per 1000 Difference:	70 per 1000 **13 fewer per 1000** (CI 95% 38 fewer — 26 more)	Low Due to serious indirectness, Due to serious imprecision, Certainty of the evidence grade differs from the 2014 review version due to alterations in the data extraction protocol: the CI has become less precise, and our decision has greater consistency with other outcome certainty grades. [8]	There is probably little or no difference in unadjusted failures at day 42 between ASPY and MQ+AS.
Serious adverse events (42 days)	Relative risk 1 (CI 95% 0.25 — 3.97) Based on data from 1,271 participants in 1	7 per 1000 Difference:	7 per 1000 **0 fewer per 1000**	Low Due to serious indirectness, Due to serious	There may be little or no difference in serious adverse events between ASPY and MQ+AS

Outcome Timeframe	**Study results and measurements**	**Comparator** MQ+AS	**Intervention** ASPY	**Certainty of the evidence** (Quality of evidence)	**Summary**
	studies. [9] (Randomized controlled)		(CI 95% 5 fewer — 21 more)	imprecision [10]	
Adverse events leading to withdrawal	Relative risk 0.62 (CI 95% 0.17 — 2.31) Based on data from 1,271 participants in 1 studies. [11]	9 per 1000 Difference:	6 per 1000 **3 fewer per 1000** (CI 95% 7 fewer — 12 more)		
First treatment, abnormal ALT increase (42 days)	Relative risk 7.48 (CI 95% 0.99 — 56.45) Based on data from 1,271 participants in 1 studies. [12] (Randomized controlled)	2 per 1000 Difference:	18 per 1000 **13 more per 1000** (CI 95% 0 fewer — 111 more)	Low Due to serious indirectness, Due to serious imprecision [13]	Compared to MQ+AS, ASPY may lead to higher events of abnormal ALT increase. (Aggregate analysis indicates this estimate may be accurate).
First treatment, abnormal AST increase (42 days)	Relative risk 9.49 (CI 95% 0.55 — 162.64) Based on data from 1,271 participants in 1 studies. [14] (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	Very low Due to very serious imprecision, Due to serious indirectness [15]	We do not know if there is a difference in AST between ASPY and MQ+AS.
First treatment, abnormal bilirubin increase (42 days)	Relative risk 3.49 (CI 95% 0.43 — 28.29) Based on data from 1,271 participants in 1 studies. [16] (Randomized controlled)	2 per 1000 Difference:	7 per 1000 **5 more per 1000** (CI 95% 1 fewer — 55 more)	Very low Due to serious indirectness, Due to very serious imprecision [17]	We do not know if there is a difference in bilirubin between ASPY and MQ+AS.

1, 3, 5, 7, 9, 11, 12, 14, 16. Systematic review [224] with included studies: Rueangweerayut 2012.
2. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: serious.** The CI is large and includes both no effect and clinically important effects.
4, 8, 10. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: serious.** The CI is large and includes both no effect and clinically important effects..
6. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: no serious.**
13. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: serious.** The low number of events recorded in the study is insufficient for confidently estimating the effect size. However, aggregate analysis of ALT increase across different comparator drugs provides indirect evidence that the point estimate may be accurate..

15, 17. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: very serious.** The CI is very large and includes both no effect and clinically important effects..

References

224. Pryce J, Taylor M, Fox T, Hine P. Pyronaridine-artesunate for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database Syst Rev 2022;6(6) Pubmed Journal

Clinical question/ PICO

Population: Adults and children with uncomplicated malaria (high and low transmission settings for P. falciparum and P. vivax malaria)

Intervention: Artesunate-pyronaridine

Comparator: other antimalarials for all malaria subtypes (safety outcomes only)

Outcome Timeframe	**Study results and measurements**	**Comparator** other antimalarials	**Intervention** ASPY	**Certainty of the evidence** (Quality of evidence)	**Summary**
Serious adverse events	Relative risk 1.24 (CI 95% 0.54 — 2.84) Based on data from 3,941 participants in 7 studies. [1] (Randomized controlled)	5 per 1000 Difference:	7 per 1000 **1 more per 1000** (CI 95% 2 fewer — 9 more)	Moderate Due to serious imprecision [2]	There is probably little or no difference in the rate of serious adverse events with ASPY compared to other antimalarials.
First treatment, abnormal ALT increase	Relative risk 3.59 (CI 95% 1.76 — 7.33) Based on data from 6,669 participants in 8 studies. [3] (Randomized controlled)	2 per 1000 Difference:	7 per 1000 **5 more per 1000** (CI 95% 2 more — 13 more)	High [4]	Abnormal ALT increase is more frequent with ASPY compared to other antimalarials.
First treatment, abnormal AST increase	Relative risk 2.22 (CI 95% 1.12 — 4.41) Based on data from 6,669 participants in 14 studies. [5] (Randomized controlled)	3 per 1000 Difference:	7 per 1000 **4 more per 1000** (CI 95% 0 fewer — 10 more)	Moderate Due to serious imprecision [6]	There is probably an increased risk of abnormal AST increase with ASPY compared to other antimalarials.
First treatment, abnormal bilirubin increase	Relative risk 1.03 (CI 95% 0.49 — 2.18) Based on data from 6,417 participants in 7 studies. [7] (Randomized controlled)	4 per 1000 Difference:	4 per 1000 **0 fewer per 1000** (CI 95% 2 fewer — 5 more)	Moderate Due to serious imprecision [8]	There is probably little or no difference for bilirubin between ASPY and other antimalarials.
Subsequent treatment(s),	Relative risk 2.18 (CI 95% 0.76 — 6.27)	4	8	Low Due to serious	There may be an increased risk of raised

Outcome Timeframe	**Study results and measurements**	**Comparator** other antimalarials	**Intervention** ASPY	**Certainty of the evidence** (Quality of evidence)	**Summary**
abnormal ALT increase	Based on data from 1,649 participants in 1 studies. [9] (Randomized controlled)	per 1000 Difference:	per 1000 **5 more per 1000** (CI 95% 1 fewer — 21 more)	indirectness, Due to serious imprecision [10]	ALT with subsequent treatments with ASPY compared to other antimalarials.
Subsequent treatment(s), abnormal AST increase	Relative risk 1.82 (CI 95% 0.74 — 4.44) Based on data from 1,649 participants in 1 studies. [11] (Randomized controlled)	6 per 1000 Difference:	11 per 1000 **5 more per 1000** (CI 95% 2 fewer — 21 more)	Low Due to serious indirectness, Due to serious imprecision [12]	There may be an increased risk of raised AST with subsequent treatments with ASPY compared to other antimalarials.
Subsequent treatment(s), abnormal bilirubin increase	Relative risk 1.13 (CI 95% 0.42 — 3.01) Based on data from 1,649 participants in 1 studies. [13] (Randomized controlled)	8 per 1000 Difference:	9 per 1000 **1 more per 1000** (CI 95% 5 fewer — 16 more)	Low Due to serious indirectness, Due to serious imprecision [14]	There may be little or no difference for bilirubin between ASPY and other antimalarials.

1. Systematic review [224] with included studies: Shin 2011, Nelwan 2015, Kayentao 2012, Roth 2018a, Rueangweerayut 2012, Tshefu 2010, Poravuth 2011.
2, 8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The CI includes both no effect and clinically important effects..
3. Systematic review [224] with included studies: Poravuth 2011, Shin 2011, Sagara 2018 (Mafrinyah, Guinea), Kayentao 2012, Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bougoula, Mali), Tshefu 2010, Sagara 2018 (Sotuba, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Rueangweerayut 2012, Sagara 2018 (Bougoula, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Djoliba, Mali), Nelwan 2015, Sagara 2018 (Kolle, Mali), Roth 2018a.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Although the CI is wide, there were few events..
5. Systematic review [224] with included studies: Kayentao 2012, Sagara 2018 (Kolle, Mali), Nelwan 2015, Shin 2011, Sagara 2018 (Bougoula, Mali), Poravuth 2011, Sagara 2018 (Sotuba, Mali), Roth 2018a, Sagara 2018 (Kolle, Mali), Rueangweerayut 2012, Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Bougoula, Mali), Tshefu 2010, Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Sotuba, Mali).
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The CI includes both almost no effect and clinically important effects.
7. Systematic review [224] with included studies: Sagara 2018 (Sotuba, Mali), Sagara 2018 (Kolle, Mali), Tshefu 2010, Shin 2011, Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Rueangweerayut 2012, Sagara 2018 (Djoliba, Mali), Poravuth 2011, Sagara 2018 (Bougoula, Mali), Sagara 2018 (Bougoula, Mali), Nelwan 2015, Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Kolle, Mali), Sagara 2018 (Sotuba, Mali), Kayentao 2012.
9. Systematic review [224] with included studies: Sagara 2018 (Bougoula, Mali), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Ouagadougou, Burkina Faso).
10. **Inconsistency: no serious. Indirectness: serious.** The CI includes both no effect and clinically important effects.. **Imprecision: serious.**
11. Systematic review [224] with included studies: Sagara 2018 (Bougoula, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Kolle, Mali), Sagara 2018 (Sotuba, Mali).
12, 14. **Inconsistency: no serious. Indirectness: serious. Imprecision: serious.**

13. Systematic review [224] with included studies: Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Kolle, Mali), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Kolle, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bougoula, Mali).

References

224. Pryce J, Taylor M, Fox T, Hine P. Pyronaridine-artesunate for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database Syst Rev 2022;6(6) Pubmed Journal

5.2.1.1.1. Duration of treatment

Clinical question/ PICO

Population: Adults and children with uncomplicated malaria (malaria-endemic settings)

Intervention: Artesunate 4 mg/kg bw once daily for 3 days plus sulfadoxine–pyrimethamine on day 1

Comparator: Artesunate 4 mg/kg bw once daily for 1 day plus sulfadoxine–pyrimethamine on day 1

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate 1 day plus sulfadoxine-pyrimethamine	**Intervention** Artesunate 3 days plus sulfadoxine-pyrimethamine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Parasitological failure 14 days	Relative risk 0.36 (CI 95% 0.27 — 0.5) Based on data from 1,276 participants in 4 studies. (Randomized controlled)	19 per 1000 Difference:	7 per 1000 **12 fewer per 1000** (CI 95% 14 fewer — 9 fewer)	High 1	
Parasitological failure - PCR-unadjusted 28 days	Relative risk 0.62 (CI 95% 0.54 — 0.71) Based on data from 1,260 participants in 4 studies. (Randomized controlled)	47 per 1000 Difference:	29 per 1000 **18 fewer per 1000** (CI 95% 22 fewer — 14 fewer)	High 2	*Corresponding risk calculated is different than what is reported in WHO document*
Parasitological failure - PCR-adjusted 28 days	Relative risk 0.45 (CI 95% 0.36 — 0.55) Based on data from 1,202 participants in 4 studies. (Randomized controlled)	33 per 1000 Difference:	15 per 1000 **18 fewer per 1000** (CI 95% 21 fewer — 15 fewer)	High 3	*Corresponding risk calculated is different than what is reported in WHO document*
Gametocytaemia 7 days	Relative risk 0.74 (CI 95% 0.58 — 0.93) Based on data from 1,260 participants in 4	20 per 1000	15 per 1000	High 4	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate 1 day plus sulfadoxine-pyrimethamine	**Intervention** Artesunate 3 days plus sulfadoxine-pyrimethamine	**Certainty of the evidence** (Quality of evidence)	**Summary**
	studies. (Randomized controlled)	Difference:	**5 fewer per 1000** (CI 95% 8 fewer — 1 fewer)		
Gametocytaemia 14 days	Relative risk 0.8 (CI 95% 0.57 — 1.14) Based on data from 1,199 participants in 4 studies. (Randomized controlled)	11 per 1000 Difference:	9 per 1000 **2 fewer per 1000** (CI 95% 5 fewer — 2 more)	High [5]	*Corresponding risk calculated is different than what is reported in WHO document*
Gametocytaemia 28 days	Relative risk 0.36 (CI 95% 0.14 — 0.92) Based on data from 898 participants in 4 studies. (Randomized controlled)	3 per 1000 Difference:	1 per 1000 **2 fewer per 1000** (CI 95% 3 fewer — 0 fewer)	Moderate Due to serious imprecision [6]	

1, 2, 3, 4. **Inconsistency: no serious.** All four studies found reductions with 3 days of artesunate, although there was some variation in the size of this effect. **Indirectness: no serious.** The four trials were conducted in children with uncomplicated P. falciparum malaria in the Gambia, Kenya, Malawi and Uganda. The same screening methods and inclusion criteria were used. Sulfadoxine–pyrimethamine was the partner antimalarial drug in all four trials. Resistance to sulfadoxine–pyrimethamine was noted at three study sites, parasitological failure with sulfadoxine–pyrimethamine alone being seen in 10–13% of participants in the Gambia, 27% in Kenya and 25% in Uganda. **Imprecision: no serious.** The confidence intervals are narrow, and the intervals comprise clinically important effects. No serious imprecision: The confidence intervals are narrow and do not include no effect.
5. **Inconsistency: no serious.** All four studies found reductions with 3 days of artesunate, although there was some variation in the size of this effect. **Imprecision: no serious.** The confidence intervals are narrow, and the intervals comprise clinically important effects. No serious imprecision: The confidence intervals are narrow and do not include no effect.
6. **Inconsistency: no serious.** All four studies found reductions with 3 days of artesunate, although there was some variation in the size of this effect. **Imprecision: serious.** The confidence intervals are narrow, and the intervals comprise clinically important effects. Downgraded by 1 for serious imprecision: As gametocytaemia at this time was rare in both groups, the studies have inadequate power to confidently detect important differences.

5.2.1.1.2. Dosing of ACTs

5.2.1.2. Recurrent falciparum malaria

5.2.1.3. Reducing the transmissibility of treated P. falciparum infections in areas of low-intensity transmission

Clinical question/ PICO

Population: People with symptomatic malaria in malaria-endemic areas

Intervention: Short-course primaquine plus malaria treatment including an artemisinin derivative

Comparator: Malaria treatment with an artemisinin derivative alone

Outcome Timeframe	**Study results and measurements**	**Comparator** ACT	**Intervention** ACT + primaquine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Malaria incidence, prevalence or entomological inoculation rate	Relative risk Based on data from 0 participants in 0 studies.		CI 95%		
People infectious to mosquitoes	Relative risk Based on data from 0 participants in 0 studies.		CI 95%		Limited observational data from mosquito feeding studies suggests that 0.25 mg/kg bw may rapidly reduce the infectivity of gametocytes to mosquitoes.
Participants with gametocytes on microscopy or PCR (day 8) (dose < 0.4 mg/kg bw) [1]	Relative risk 0.67 (CI 95% 0.44 — 1.02) Based on data from 223 participants in 1 studies. (Randomized controlled)	34 per 1000 Difference:	23 per 1000 **11 fewer per 1000** (CI 95% 19 fewer — 1 more)	Low Due to very serious imprecision [2]	
Participants with gametocytes on microscopy or PCR (day 8) (dose 0.4–0.6 mg/kg bw) [3]	Relative risk 0.3 (CI 95% 0.16 — 0.56) Based on data from 219 participants in 1 studies. (Randomized controlled)	35 per 1000 Difference:	11 per 1000 **24 fewer per 1000** (CI 95% 29 fewer — 15 fewer)	Low Due to serious imprecision and serious indirectness [4]	
Participants with gametocytes on microscopy or PCR (day 8) (dose > 0.6 mg/kg bw) [5]	Relative risk 0.29 (CI 95% 0.22 — 0.37) Based on data from 1,380 participants in 7 studies. (Randomized controlled)	30 per 1000 Difference:	9 per 1000 **21 fewer per 1000** (CI 95% 23 fewer — 19 fewer)	High [6]	
Mean percentage change in	Based on data from 101 participants in 1 studies. (Randomized controlled)			Low Due to very serious	ACT: 15% mean drop in Hb from baseline in the control group. ACT +

Outcome Timeframe	Study results and measurements	Comparator ACT	Intervention ACT + primaquine	Certainty of the evidence (Quality of evidence)	Summary
haemoglobin (Hb) [7]				indirectness [8]	primaquine: Mean drop in Hb from baseline in the intervention groups was 3% lower (10% lower to 4% higher).

1, 3, 5. AUC estimates (log10 AUC for days 1–43) are included as footnotes for each dosing stratum.
2. **Risk of Bias: no serious.** Includes one trial with no risk of bias detected. **Imprecision: very serious.** One small trial with CIs that include 50% reduction and no effect.
4. **Risk of Bias: no serious.** Includes one trial with no risk of bias detected. **Indirectness: serious.** This is a single trial in a single setting. **Imprecision: serious.** A single trial with few events.
6. **Indirectness: no serious.** While there is marked quantitative heterogeneity, the studies with no demonstrable effect had few events. Not downgraded.
7. One trial reported a relative decrease in haemoglobin against baseline in both groups on days 8, 15, 29 and 43 in all participants irrespective of G6PD status. No difference at any time between participants receiving primaquine and those that not did not. We present the data for day 43 in this table.
8. **Indirectness: very serious.** The percentage of people with large drops in haemoglobin, not the mean change in the population, is the important safety outcome, and the estimates are averages in a small population (N = 99) that includes people with normal G6PD function. The study is therefore unlikely to detect effects in a small subgroup with a relatively uncommon adverse event.

5.2.1.4. Special risk groups

5.2.1.4.1. Pregnant and lactating women

Clinical question/ PICO

Population: Treating malaria in pregnancy during their first trimester in prospective cohort studies
Intervention: artemisinin derivatives
Comparator: antimalarial not including artemisinin derivative and recommended in the first trimester

Outcome Timeframe	Study results and measurements	Comparator antimalarial not including artemisinin derivative and recommende	Intervention artemisinin derivatives	Certainty of the evidence (Quality of evidence)	Summary
Composite	Relative risk 0.71 (CI 95% 0.49 — 1.03) Based on data from 1,810 participants in 12 studies. (Observational (non-randomized))	89 per 1000 Difference:	64 per 1000 **25 fewer per 1000** (CI 95% 45 fewer — 3 more)	Low	ABT may reduce adverse fetal events
Miscarriage	Relative risk 0.74 (CI 95% 0.47 — 1.17) Based on data from	71 per 1000	53 per 1000	Low	ABT may reduce miscarriage

Outcome Timeframe	**Study results and measurements**	**Comparator** antimalarial not including artemisinin derivative and recommende	**Intervention** artemisinin derivatives	**Certainty of the evidence** (Quality of evidence)	**Summary**
	1,739 participants in 12 studies.	Difference:	**18 fewer per 1000** (CI 95% 37 fewer — 12 more)		
Stillbirth	Relative risk 0.71 (CI 95% 0.32 — 1.57) Based on data from 1,389 participants in 12 studies.	16 per 1000 Difference:	11 per 1000 **5 fewer per 1000** (CI 95% 11 fewer — 9 more)	Low	ABT may reduce stillbirth
Fetal loss	Relative risk 0.7 (CI 95% 0.47 — 1.02) Based on data from 1,810 participants in 12 studies.	82 per 1000 Difference:	58 per 1000 **24 fewer per 1000** (CI 95% 43 fewer — 2 more)	Low	ABT may reduce fetal loss
Major congenital anomalies	Relative risk 0.6 (CI 95% 0.13 — 2.87) Based on data from 1,810 participants in 12 studies.	7 per 1000 Difference:	4 per 1000 **3 fewer per 1000** (CI 95% 6 fewer — 14 more)	Low	ABT may reduce congenital abnormalities

Clinical question/ PICO

Population: Treating malaria in pregnancy during their first trimester in prospective cohort studies
Intervention: Artemether-lumefantrine
Comparator: Quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether-lumefantrine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Composite	Relative risk 0.58 (CI 95% 0.36 — 0.92) Based on data from 1,439 participants in 12 studies.	92 per 1000 Difference:	54 per 1000 **37 fewer per 1000** (CI 95% 58 fewer — 7 fewer)	Low	AL may reduce adverse fetal events

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether-lumefantrine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Miscarriage	Relative risk 0.67 (CI 95% 0.37 — 1.23) Based on data from 1,377 participants in 12 studies.	74 per 1000 Difference:	51 per 1000 **24 fewer per 1000** (CI 95% 46 fewer — 16 more)	Low	AL may reduce miscarriage
Stillbirth	Relative risk 0.53 (CI 95% 0.22 — 1.24) Based on data from 1,078 participants in 12 studies.	20 per 1000 Difference:	11 per 1000 **10 fewer per 1000** (CI 95% 16 fewer — 5 more)	Low	AL may reduce stillbirth
Fetal loss	Relative risk 0.56 (CI 95% 0.35 — 0.9) Based on data from 1,439 participants in 12 studies.	87 per 1000 Difference:	50 per 1000 **37 fewer per 1000** (CI 95% 56 fewer — 8 fewer)	Low It is not appropriate to upgrade here. Whilst very large effects may “upgrade” by one point, this is only when the CI do not overlap with smaller effects, which is not the case here. Indeed, GRADE state that a large effect is only considered with the RR is <0.5, and this is based on direct evidence with no plausible confounders.	AL may reduce fetal loss
Major congenital anomalies	Based on data from 1,439 participants in 12 studies.	4 per 1000		Low	AL may reduce congenital abnormalities

5.2.1.4.2. Young children and infants

5.2.1.4.3. Patients co-infected with HIV

5.2.1.4.4. Non-immune travellers

5.2.1.4.5. Uncomplicated hyperparasitaemia

5.2.1.5. Uncomplicated malaria caused by P. vivax, P. ovale, P. malariae or P. knowlesi

Clinical question/ PICO

Population: Adults and children with uncomplicated P. vivax malaria (Malaria-endemic areas in which chloroquine is still effective for the first 28 days)

Intervention: Artemisinin-based combination therapy

Comparator: Chloroquine

Outcome Timeframe	**Study results and measurements**	**Comparator** Chloroquine	**Intervention** ACT	**Certainty of the evidence** (Quality of evidence)
Remaining parasitaemia at 24 h	Relative risk 0.42 (CI 95% 0.36 — 0.5) Based on data from 1,652 participants in 4 studies. (Randomized controlled)	520 per 1000 Difference:	218 per 1000 **302 fewer per 1000** (CI 95% 333 fewer — 260 fewer)	High [1]
Still febrile after 24 h	Relative risk 0.55 (CI 95% 0.43 — 0.7) Based on data from 990 participants in 2 studies. (Randomized controlled)	290 per 1000 Difference:	160 per 1000 **130 fewer per 1000** (CI 95% 165 fewer — 87 fewer)	Moderate Due to serious inconsistency [2]
Effective treatment of blood-stage infection as assessed by recurrent parasitaemia before day 28	Relative risk 0.58 (CI 95% 0.18 — 1.9) Based on data from 1,622 participants in 5 studies. (Randomized controlled)	30 per 1000 Difference:	17 per 1000 **13 fewer per 1000** (CI 95% 25 fewer — 27 more)	High [3]
Post-treatment prophylaxis as assessed by recurrent parasitaemia between day 28 and day 42, 56 or 63 - with primaquine	Relative risk 0.27 (CI 95% 0.08 — 0.94) Based on data from 376 participants in 1 studies. (Randomized controlled)	60 per 1000 Difference:	16 per 1000 **44 fewer per 1000** (CI 95% 55 fewer — 4 fewer)	Low Due to serious indirectness and serious imprecision [4]

Outcome Timeframe	**Study results and measurements**	**Comparator** Chloroquine	**Intervention** ACT	**Certainty of the evidence** (Quality of evidence)
Post-treatment prophylaxis as assessed by recurrent parasitaemia between day 28 and day 42, 56 or 63 - without primaquine	Relative risk 0.57 (CI 95% 0.4 — 0.82) Based on data from 1,066 participants in 3 studies. (Randomized controlled)	400 per 1000 Difference:	228 per 1000 **172 fewer per 1000** (CI 95% 240 fewer — 72 fewer)	Moderate Due to serious indirectness [5]
Serious adverse events	Relative risk 1 (CI 95% 0.14 — 7.04) Based on data from 1,775 participants in 5 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	High [6]

1. **Risk of Bias: no serious.** Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result. **Inconsistency: no serious.** The findings of all the trials are consistent. **Indirectness: no serious.** The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns. **Imprecision: no serious.** The studies show a clinically and statistically significant benefit of ACT. **Publication bias: no serious.**
2. **Risk of Bias: no serious.** Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result. **Inconsistency: serious.** In one additional trial which could not be included in the meta-analysis, fever clearance was not significantly different between groups. **Indirectness: no serious.** The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns. **Imprecision: no serious.** The studies show a clinically and statistically significant benefit of ACT.
3, 6. **Risk of Bias: no serious.** Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result. **Inconsistency: no serious.** The findings of all the trials are consistent. **Indirectness: no serious.** The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns. **Imprecision: no serious.** No clinically important difference between ACTs and chloroquine. Although the 95% CI around the relative effect is very wide, recurrent parasitaemia before day 28 and serious adverse events were very rare; consequently, the 95% CI around the absolute effect is very narrow.
4. **Indirectness: serious.** This study delayed primaquine until day 28; therefore, the course was not completed until day 42, the last day of the trial. The effect might not be present if primaquine is given in the usual way (on completion of 3 days of ACT). The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes. **Imprecision: serious.** Although the result is statistically significant, the 95% CI is wide and includes the possibility of no appreciable benefit.
5. **Inconsistency: no serious.** The findings of all the trials are consistent. **Indirectness: serious.** Both studies were conducted in Afghanistan where primaquine is not recommended because of a high prevalence of G6PD deficiency. The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes. **Imprecision: no serious.** The studies show a clinically and statistically significant benefit of ACT.

Clinical question/ PICO

Population: Adults and children with uncomplicated P. vivax malaria (Settings with high transmission of P. vivax (chloroquine resistance is also reported as high))

Intervention: Dihydroartemisinin + piperaquine

Comparator: Alternative ACTs

Outcome Timeframe	**Study results and measurements**	**Comparator** Alternative ACT	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the evidence** (Quality of evidence)
Effective treatment of blood-stage parasites as assessed by recurrent parasitaemia before day 28	Relative risk 0.2 (CI 95% 0.08 — 0.49) Based on data from 334 participants in 3 studies. (Randomized controlled)	350 per 1000 Difference:	70 per 1000 **280 fewer per 1000** (CI 95% 322 fewer — 178 fewer)	Moderate Due to serious inconsistency [1]
Post-treatment prophylaxis as assessed by recurrent parasitaemia between days 28 and 42 - with primaquine	Relative risk 0.21 (CI 95% 0.1 — 0.46) Based on data from 179 participants in 2 studies. (Randomized controlled)	340 per 1000 Difference:	71 per 1000 **269 fewer per 1000** (CI 95% 306 fewer — 184 fewer)	Low Due to serious risk of bias and serious indirectness [2]
Post-treatment prophylaxis as assessed by recurrent parasitaemia between days 28 and 42 - without primaquine	Relative risk 0.4 (CI 95% 0.14 — 1.1) Based on data from 66 participants in 1 studies. (Randomized controlled)	330 per 1000 Difference:	132 per 1000 **198 fewer per 1000** (CI 95% 284 fewer — 33 more)	Very low Due to serious risk of bias, serious indirectness and serious imprecision [3]

1. **Risk of Bias: no serious.** Allocation was adequately concealed in these studies, resulting in a low risk of bias. **Inconsistency: serious.** There was some clinical heterogeneity between trials. Dihydroartemisinin + piperaquine did not perform as well in Papua New Guinea as it has elsewhere; however, it was still superior to artemether + lumefantrine and artesunate+sulfadoxine–pyrimethamine. **Indirectness: no serious.** Studies included adults and children and were conducted in areas where transmission is high and chloroquine resistance is well documented. **Imprecision: no serious.** Both limits of the 95% CI suggest an appreciable clinical benefit with dihydroartemisinin + piperaquine.
2. **Risk of Bias: serious.** Losses to follow-up were high (> 20% at this time). **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** One trial delayed administration of primaquine until day 28; therefore, the course will not have been completed until the last day of the trial. The second trial offered unsupervised primaquine to all participants on completion of ACT. This reflects normal practice, but it is not clear how many participants completed their course. The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes.
3. **Risk of Bias: serious.** Losses to follow-up were high (> 20% at this time). **Indirectness: serious.** Only one study assessed this outcome. Recurrent parasitaemia was higher with all three ACTs than seen elsewhere, and the results are therefore not easily extrapolated to other sites. **Imprecision: serious.** The 95% CI of the effect estimate is wide and includes an important clinical benefit and no difference between treatments.

5.2.1.6. Testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency

Clinical question/ PICO

Population: Patients with confirmed P. vivax or P. ovale malaria undergoing G6PD testing to inform treatment with primaquine to prevent relapses

Intervention: Qualitative near-patient tests for G6PD

Comparator: Quality-assured spectrophotometric assay

Summary

Key questions

In patients undergoing G6PD activity testing, how accurate are qualitative near-patient tests for G6PD deficiency compared to quantitative spectrophotometric G6PD testing to distinguish patients with G6PD activity below or above the threshold of 30% of normal G6PD activity, critical to informing administration of specific regimens of 8-aminoquinolines to prevent relapses of *P. vivax* and *P. ovale*?

PIRT

- **Patients** with confirmed *P. vivax* or *P. ovale* malaria undergoing G6PD testing to inform treatment with primaquine to prevent relapses.
- **Index test** is qualitative near-patient tests for G6PD.
- **Reference standard** is quality assured spectrophotometric assay for G6PD. The reference standard value for the studies included in the systematic review was based on the adjusted male median (AMM) G6PD activity (100% G6PD activity) calculated for each G6PD spectrophotometric assay. The AMM is defined as the median G6PD activity of all male participants after excluding samples with less than 10% of the overall median activity *[313]*. If biased recruiting were used in a study the 100% G6PD activity will be the average of all normal males in the study.
- **Target condition**: true positives, false positives, false negatives and true negatives; the overall aim of testing is to prevent severe hemolysis due to daily primaquine intake in case of G6PD deficient patients (<30% of normal G6PD activity).

Summary of evidence from the systematic review (Weeratunga *et al.*, unpublished evidence)

Summary sensitivity and sensitivity of the qualitative tests by threshold

Threshold	Studies	Participants	Cases	Pooled sensitivity % (95% CI)	Pooled specificity % (95% CI)	Numbers in a cohort of 1000 patients tested (95% CI)		
						Prevalence of 5%	Prevalence of 10%	Prevalence of 20%
30%	19	11456	1103	94.9 (89.4, 97.6)	96.2 (93.5, 97.8)	TP=47 (45, 49) FP=36 (21, 62) FN=3 (1, 5) TN=914 (888, 929)	TP=95 (89, 98) FP=34 (20, 58) FN=5 (2, 11) TN=866 (842, 880)	TP=190 (179, 195) FP=30 (18, 52) FN=10 (5, 21) TN=770 (748, 782)

Espino 2016 (b) and Espino 2016 (c) were excluded from meta-analysis, because Espino 2016 (a), (b), (c) use the same participants. Difference between the three studies is that (a) consists of 621 participants assessed by G6PD Qualitative FST, (b) consists of 302 participants assessed by CareStart G6PD using venous blood samples and (c) consists of 302 participants assessed by CareStart G6PD using capillary blood samples. Espino 2016 (a) was chosen, due to having a more complete sample size.

Henriques 2018 (b) and (d) were excluded from meta-analysis, because Henriques 2018 (a) and (b) use the same participants, and Henriques 2018 (c) and (d) use the same participants. Difference between (a) and (b) is that (a) consists of 505 participants assessed by G6PD Qualitative FST and (b) consists of 498 participants assessed by CareStart G6PD enrolled in Cambodia. Difference between © and (d) is that (c) consists of 757 participants assessed by G6PD Qualitative FST and (d) consists of 753 participants assessed by CareStart G6PD enrolled in the Lao People's Democratic Republic. Henriques 2018 (a) and (c) were chosen, due to having a more complete sample size.

Bancone 2015(a)excluded from meta-analysis, because Bancone 2015 (a) and (b) use the same participants. Difference between two studies are that(a) uses capillary blood and (b) uses venous blood samples. Bancone 2015(a) was excluded, due to majority of studies using venous blood sample in the meta-analysis for this test.

Adu-Gyasi 2015 (b) and Adu-Gyasi 2015 (c) were excluded from meta-analysis, because Adu-Gyasi 2015 (a), (b), (c) use the same participants. Difference between the three studies is that (a) consists of 205 participants assessed by CareStart G6PD, (b) consists of 119 male participants assessed by CareStart G6PD and (c) consists of 86 female participants assessed by CareStart G6PD. Espino 2016 (a) was chosen, due to having a more complete sample size.

These summary estimates were based on the CareStart G6PD qualitative test (Access Bio, Inc.) as the majority of evaluation studies included this test (at least 10 of 19 studies). Only four studies evaluated the fluorescent spot test (FST).

Clinical question/ PICO

Population: Patients with malaria undergoing G6PD testing to inform treatment with primaquine or tafenoquine to prevent relapses of P. vivax and P. ovale

Intervention: Semi-quantitative near-patient tests for G6PD

Comparator: Quality-assured G6PD spectrophotometric assay

Summary

Key question

In patients undergoing G6PD activity testing, how accurate are semi-quantitative near-patient tests for G6PD deficiency compared to quantitative spectrophotometric G6PD testing at the thresholds of 30% and 70% of normal G6PD activity, critical to informing administration of specific regimens of 8-aminoquinolines to prevent relapses of *P. vivax* and *P. ovale*?

PIRT

- **Patients** with malaria who undergoing G6PD testing to inform treatment with primaquine or tafenoquine to prevent relapses of *P. vivax* and *P. ovale*.
- **Index test** is semi-quantitative near-patient tests for G6PD.
- **Reference standard** is the quality assured G6PD spectrophotometric assay using the adjusted male median (AMM) as the standardised metric of 100% G6PD activity. For the Standard G6PD biosensor used with the STANDARD G6PD Analyzer (SB Biosensor, Inc) a supplementary analysis was performed using manufacturer references to calculate relevant thresholds.
- **Target conditions**: true positives, false positives, false negatives and true negatives; the overall aim of testing is to prevent severe haemolysis due to tafenoquine or high daily primaquine intake in case of G6PD deficient patients (<30% and ≥ 70% of normal G6PD activity).

Summary of evidence from the systematic review (Weeratunga et al., unpublished evidence)

Summary sensitivity and sensitivity of the semiquantitative tests by threshold as defined by the adjusted male median (AMM)

Threshold	Studies	Participants	Cases	Pooled sensitivity % (95% CI)	Pooled specificity % (95% CI)	Numbers in a cohort of 1000 patients tested (95% CI)		
						Prevalence of 5%	Prevalence of 10%	Prevalence of 20%
30% AMM	11	6507	399	47.6 (17.8,79.2) †	99.4 (98.5,99.8)	TP=24 (9, 40) FP=6 (2, 14) FN=26 (10, 41) TN=944 (936,948)	TP=48 (18, 79) FP=5 (2, 14) FN=52 (21, 82) TN=895 (887,898)	TP=95 (36,158) FP=5 (2, 12) FN=105 (42, 164) TN=795 (788,798)
70% AMM	11	6507	886	73.6 (58.1,84.9)	93.6 (88.8,96.5)	TP=37 (29, 42) FP=61 (33, 106) FN=13 (8, 21) TN=889 (844,917)	TP=74 (58, 85) FP=58 (32,101) FN=26 (15, 42) TN=842 (799,869)	TP=147 (116, 170) FP=51 (28, 90) FN=53 (30, 84) TN=749 (710,772)

30%-70% AMM, females	11	3185	238	45.5 (26.5,65.9) †	92.8 (87.0,96.1)	TP=23 (13, 33) FP=68 (37,123) FN=27 (17, 37) TN=882 (826,913)	TP=46 (27, 66) FP=65 (35,117) FN=54 (34, 73) TN=835 (783,865)	TP=91 (53, 132) FP=58 (31,104) FN=109 (68,147) TN=742 (696,769)

This analysis was performed on data from **Alam 2018, Aung 2023, Bancone 2018, Hamid 2018, Ley 2017, Wepelmann 2017, Adissu 2023 Ethiopia and India, Pal 2021, Zobrist 2021 and Pal 2018**.

Where study arms were reported for both venous blood and capillary blood the arm with higher sample size was included as some patient samples were represented in both arms.

Alam 2018 and Pal 2018 was classified as high risk of bias due to convenience, non-random sampling. Alam 2018 was also classified as high risk of bias in flow and timing domain. Regarding applicability Pal 2021 contains a set of contrived specimens.

Data relating to Adissu 2023 Ethiopia and India were not published as standalone papers. Therefore, risk of bias analysis and applicability assessment was performed based on manufacturer supplied study protocols.

TP: true positive; FP: false positive; FN: false negative; TN: true negative

† High variability in sensitivity between studies.

Standard G6PDby SD Biosensor – Manufacturer determined thresholds, as per the instructions for use

Threshold	Studies	Participants	Cases	Pooled sensitivity % (95% CI)	Pooled specificity % (95% CI)	Numbers in a cohort of 1000 patients tested (95% CI)		
						Prevalence of 5%	Prevalence of 10%	Prevalence of 20%
30% Manufacturer	6	4613	204	100.0 (98.2,100.0) †	97.0 (96.5, 97.5)	TP=50 (49, 50) FP=29 (24, 33) FN=0 (0, 1) TN=922 (917,926)	TP=100 (98,100) FP=27 (23, 32) FN=0 (0, 2) TN=873 (869,878)	TP=200 (196,200) FP=24 (20, 28) FN=0 (0, 4) TN=776 (772,780)
70% Manufacturer	6	4613	430	91.4 (75.5, 97.4)	93.7 (85.8, 97.4)	TP=46 (38, 49) FP=60 (25, 135) FN=4 (1, 12) TN=890 (815,925)	TP=91 (76, 97) FP=57 (23,128) FN=9 (3, 24) TN=843 (772,877)	TP=183 (151,195) FP=50 (21,114) FN=17 (5, 49) TN=750 (686,779)
30%-70% Manufacturer, females	6	2209	53	52.9 (28.9, 75.7)†	94.7 (86.3, 98.0)	TP=26 (14, 38) FP=50 (19,130) FN=24 (12, 36) TN=900 (820,931)	TP=53 (29, 76) FP=48 (18,123) FN=47 (24, 71) TN=852 (777,882)	TP=106 (58,151) FP=42 (16,110) FN=94 (49, 142) TN=758 (690,784)

Notes – Studies included in this analysis were **Adissu 2023 Ethiopia and India, Alam 2018, Pal 2021, Zobrist 2021 and Pal 2018**.

Where study arms were reported for both venous blood and capillary blood the arm with higher sample size was included as some patient samples were represented in both arms

Alam 2018 and Pal 2018 was classified as high risk of bias due to convenience, non-random sampling. Alam 2018 was also classified as high risk of bias in flow and timing domain. Regarding applicability Pal 2021 contains a set of contrived specimens.

5.2.1.7. Anti-relapse treatment of P. vivax and P. ovale

Clinical question/ PICO

Population: People aged ≥ 16 years with P. vivax malaria and normal G6PD activity

Intervention: TQ plus CQ

Comparator: no treatment plus CQ

Summary

PICO research question: Should single-dose TQ be an alternative to standard dose PQ (3.5 mg/kg total dose) for preventing relapse in patients with ≥ 70% G6PD activity who previously received chloroquine?

To evaluate the efficacy and safety of tafenoquine 300 mg (single dose) compared to primaquine or placebo in preventing *P. vivax* relapses.

Methods
Criteria for considering studies for this review
Types of studies: Randomized controlled trials (RCTs)

Types of participants: Patients with a Glucose-6-phosphate dehydrogenase (G6PD) activity of > =70% treated with chloroquine for confirmed P. *vivax* malaria.

Types of interventions
Intervention: Tafenoquine (single dose 300 mg)

Control: Standard primaquine treatment 0.25 mg/kg daily for 14 days or 0.5 mg/kg daily for 7 days or placebo

Co-interventions: Chloroquine 25 mg/kg given over 3 days

Types of outcome measures
Primary outcomes

- First recurrent episode (as a proxy measure of relapse when patients remained in the endemic area during follow-up) of *P. vivax* parasitaemia by six months.

Secondary outcomes

- Serious adverse events: death, symptomatic haemolysis, symptomatic methaemoglobinaemia, or any other potentially life-threatening observation or complaint that required treatment and monitoring by further investigations.
- Any adverse events: all adverse effects either reported by participants or elicited by investigators during treatment and follow-up.

Evidence synthesis
The Cochrane Infectious Diseases Group (CIDG) assembled the review following the steps and activities below:

Tafenoquine (single dose)
- The existing published Cochrane Review of Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria (search date June 2020) was updated. This update identified no further published randomized controlled trials (RCTs) relating to efficacy and safety.
- An additional systematic review was performed of all study types relating to efficacy, safety, feasibility, and cost of tafenoquine up to search date 1 August 2023.

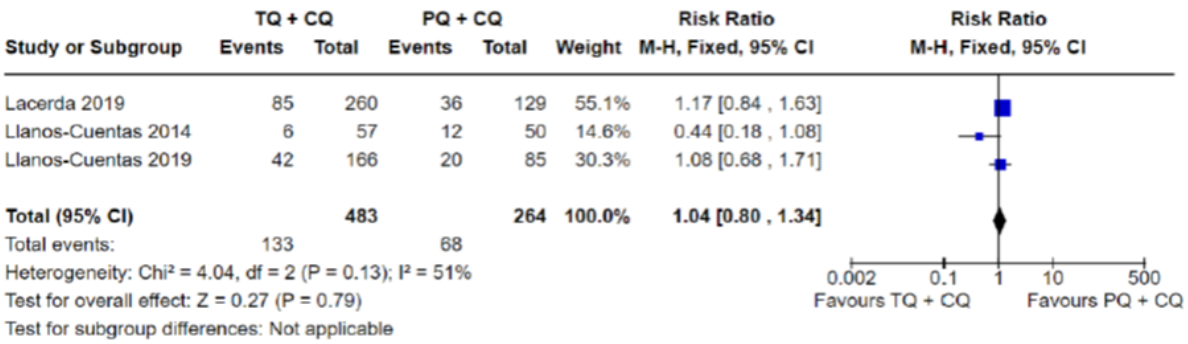
Search methods
For each systematic review, the following databases were searched up to 31 July 2023 (for RCT review) and 01 August 2023 (for review of all study types): the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library, Issue 7 of 12, July 2023; MEDLINE (OVID, from 1946); Embase (OVID, from 1947); WHO Global Index Medicus; Science Citation index-Expanded (Web of Science, from 1900). The WHO International Clinical Trials Registry Platform (ICTRP) (who.int/ictrp/en/), ClinicalTrials.gov (clinicaltrials.gov/ct2/home), and the ISRCTN registry (isrctn.com/) were searched to identify trials in progress.

Synthesizing results
Two review authors independently assessed the literature search results. Included studies were described, assessed, and data presented. GRADE was used to assess the certainty of the evidence.

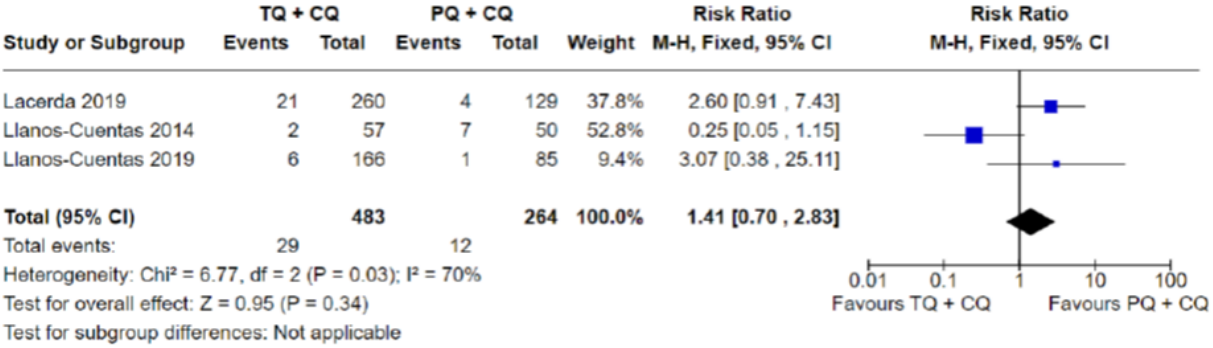
Results: Effects of the intervention

Analysis: Tafenoquine plus chloroquine versus primaquine plus chloroquine

TQ + CQ versus PQ + CQ: recurrent *P. vivax* parasitaemia by six months



TQ + CQ versus PQ + CQ: serious adverse events



Outcome Timeframe	**Study results and measurements**	**Comparator** no treatment plus CQ	**Intervention** TQ plus CQ	**Certainty of the evidence** (Quality of evidence)	**Summary**
Recurrent P. vivax parasitaemia by 6 months	Relative risk 0.32 (CI 95% 0.12 — 0.88) Based on data from 504 participants in 2 studies.	636 per 1000 Difference:	204 per 1000 **432 fewer per 1000** (CI 95% 76 fewer — 560 more)	Moderate Downgraded one level for high heterogeneity: one of the trials was small and had few events during six months, as such this result is at high risk of overestimating the true effect. [1]	TQ + CQ reduces relapse of P. vivax infections compared to CQ alone. However, there is moderate uncertainty around effect size.
Serious adverse events	Relative risk 1.34 (CI 95% 0.63 — 2.84) Based on data from 504 participants in 2 studies.	53 per 1000 Difference:	72 per 1000 **18 more per 1000** (CI 95% 34 fewer — 152 more)	Low All trials when combined enrolled adults with P. vivax malaria in Peru, Thailand, India, Ethiopia, Cambodia, Philippines and Brazil. CQ was given in the	TQ + CQ may cause more serious adverse events than CQ alone.

Outcome Timeframe	**Study results and measurements**	**Comparator** no treatment plus CQ	**Intervention** TQ plus CQ	**Certainty of the evidence** (Quality of evidence)	**Summary**
				standard adult dose to all participants. Downgraded two levels for serious imprecision (wide CI of risk estimate). [2]	
Any adverse event	Relative risk 0.96 (CI 95% 0.81 — 1.13)	567 per 1000 Difference:	544 per 1000 **23 fewer per 1000** (CI 95% 459 fewer — 641 more)	High [3]	TQ + CQ probably has little or no difference in overall occurrence of adverse events compared to CQ alone.

1. **Risk of Bias: no serious.** All trials were at low risk of selection and reporting bias. **Indirectness: no serious.** All trials when combined enrolled adults with P. vivax malaria in Peru, Thailand, India, Ethiopia, Cambodia, Philippines, and Brazil. CQ was given in the standard adult dose to all participants.
2, 3. **Risk of Bias: no serious.** All trials were at low risk of selection and reporting bias.

Clinical question/ PICO

Population: People aged ≥ 16 years with P. vivax malaria and normal G6PD activity
Intervention: TQ plus CQ
Comparator: PQ plus CQ

Outcome Timeframe	**Study results and measurements**	**Comparator** PQ plus CQ	**Intervention** TQ plus CQ	**Certainty of the evidence** (Quality of evidence)	**Summary**
P. vivax parasitaemia during 6 months of follow-up	Relative risk 1.04 (CI 95% 0.8 — 1.34) Based on data from 747 participants in 3 studies.	258 per 1000	268 per 1000 (CI 95% 206 fewer — 345 more)	Moderate Downgraded one level for high heterogeneity. [1]	TQ is probably as effective as PQ for P. vivax relapse prevention up to 6 months.
Serious adverse events	Relative risk 1.41 (CI 95% 0.7 — 2.83) Based on data from 747 participants in 3 studies.	45 per 1000	64 per 1000 (CI 95% 32 fewer — 129 more)	Low Downgraded by two levels for serious imprecision. Point estimate indicated 41% increase in harms, but there were wide CI of risk estimate. [2]	TQ + CQ may cause more serious adverse events than standard-dose PQ + CQ.
Any adverse	Relative risk 1.01 (CI 95% 0.89 — 1.14)	591	597	High	TQ + CQ probably has little or no difference in

Outcome Timeframe	Study results and measurements	Comparator PQ plus CQ	Intervention TQ plus CQ	Certainty of the evidence (Quality of evidence)	Summary
event		per 1000	per 1000 (CI 95% 526 fewer — 674 more)	[3]	adverse events (any type) compared to standard-dose PQ + CQ.

1. **Risk of Bias: no serious.** Two trials were at low risk of selection bias (selection bias in Llanos-Cuentas 2019 was unclear), while all trials were at low risk of reporting bias. **Indirectness: no serious.** All trials when combined enrolled adults with P. vivax malaria in Peru, Thailand, India, Ethiopia, Cambodia, Philippines, Colombia, Viet Nam and Brazil. CQ was given in the standard adult dose to all participants. However, 75% of sample size data were from the South America study sites.
2, 3. **Risk of Bias: no serious.** Two trials were at low risk of selection bias (selection bias in Llanos-Cuentas 2019 was unclear), while all trials were at low risk of reporting bias.

Clinical question/ PICO

Population: People with P. vivax malaria

Intervention: 7 mg/kg dose primaquine (high total dose including 7-day and 14-day regimens)

Comparator: 3.5 mg/kg dose primaquine (low total dose including 7-day and 14-day regimens)

Summary

Summary of evidence from the systematic review
The summary of findings table is based on data from the two new individual patient data meta-analyses *[276][280]*.

Efficacy (7 mg/kg versus 3.5 mg/kg total dose primaquine)

- **Question:** Is high (7 mg/kg) total dose primaquine more efficacious than low (3.5 mg/kg) total dose primaquine at preventing relapses to day 180 in patients with uncomplicated vivax malaria?
- **Population:** People with *P. vivax* malaria
- **Intervention:** 7 mg/kg dose primaquine (high total dose including 7-day and 14-day regimens)
- **Comparison:** 3.5 mg/kg dose primaquine (low total dose including 7-day and 14-day regimens)

See PICO table

References

276. Commons RJ, Rajasekhar M, Edler P, Abreha T, Awab GR, Baird JK, et al. Effect of primaquine dose on the risk of recurrence in patients with uncomplicated Plasmodium vivax: a systematic review and individual patient data meta-analysis. The Lancet. Infectious diseases 2024;24(2):172-183 Pubmed Journal

280. Rajasekhar M, Simpson JA, Ley B, Edler P, Chu CS, Abreha T, et al. Primaquine dose and the risk of haemolysis in patients with uncomplicated Plasmodium vivax malaria: a systematic review and individual patient data meta-analysis. The Lancet. Infectious diseases 2024;24(2):184-195 Pubmed Journal

Clinical question/ PICO

Population: People with P. vivax malaria

Intervention: 7 mg/kg dose primaquine (high total dose including 7-day and 14-day regimens)

Comparator: 3.5 mg/kg dose primaquine (low total dose including 7-day and 14-day regimens)

Summary

Summary of evidence from the systematic review
The summary of findings table is based on data from the two new individual patient data meta-analyses *[276][280]*.

Tolerability and safety (1 mg/kg/day versus 0.25 mg/kg/day primaquine)

- **Question:** Does high (1 mg/kg) daily dose primaquine cause more gastrointestinal symptoms or adverse haemoglobin changes compared to low (0.25 mg/kg) daily dose primaquine?
- **Population:** People with *P. vivax* malaria
- **Intervention:** 1 mg/kg/day primaquine (high daily dose)
- **Comparison:** 0.25 mg/kg/day primaquine (low daily dose)

See PICO table

References

276. Commons RJ, Rajasekhar M, Edler P, Abreha T, Awab GR, Baird JK, et al. Effect of primaquine dose on the risk of recurrence in patients with uncomplicated Plasmodium vivax: a systematic review and individual patient data meta-analysis. The Lancet. Infectious diseases 2024;24(2):172-183 Pubmed Journal

280. Rajasekhar M, Simpson JA, Ley B, Edler P, Chu CS, Abreha T, et al. Primaquine dose and the risk of haemolysis in patients with uncomplicated Plasmodium vivax malaria: a systematic review and individual patient data meta-analysis. The Lancet. Infectious diseases 2024;24(2):184-195 Pubmed Journal

Clinical question/ PICO

Population: Malaria-endemic areas
Intervention: Chloroquine prophylaxis
Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Chloroquine prophylaxis	**Certainty of the evidence** (Quality of evidence)
Clinical malaria	Relative risk		CI 95%	
P. vivax parasitaemia	Relative risk 0.02 (CI 95% 0 — 0.26) Based on data from 951 participants in 1 studies. (Randomized controlled)	70 per 1000 Difference:	1 per 1000 **69 fewer per 1000** (CI 95% 70 fewer — 52 fewer)	Moderate Due to serious imprecision [1]
Severe anaemia in third trimester	Relative risk		CI 95%	

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Chloroquine prophylaxis	**Certainty of the evidence** (Quality of evidence)
Anaemia in third trimester	Relative risk 0.95 (CI 95% 0.9 — 1.01) Based on data from 951 participants in 1 studies. (Randomized controlled)	509 per 1000 Difference:	484 per 1000 **25 fewer per 1000** (CI 95% 51 fewer — 5 more)	Moderate Due to serious imprecision [2]
Adverse events	Relative risk		CI 95%	

1. **Risk of Bias: no serious.** This study had a low risk of bias in all domains. **Indirectness: no serious.** This study was conducted in Thailand between 1998 and 2001. Chloroquine was administered as four tablets at enrolment, followed by two tablets once a week until delivery. **Imprecision: serious.** Although the intervention appeared to prevent all episodes of P. vivax malaria, there were few events, even in the control group.
2. **Risk of Bias: no serious.** This study had a low risk of bias in all domains. **Indirectness: no serious.** This study was conducted in Thailand between 1998 and 2001. Chloroquine was administered as four tablets at enrolment, followed by two tablets once a week until delivery. **Imprecision: serious.** The finding of a small clinical benefit did not reach statistical significance.

5.2.2. Treating severe malaria

5.2.2.1. Artesunate

Clinical question/ PICO

Population: Children with severe malaria (malaria-endemic areas)
Intervention: Artesunate
Comparator: Quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artesunate	**Certainty of the evidence** (Quality of evidence)
Death	Relative risk 0.76 (CI 95% 0.65 — 0.9) Based on data from 5,765 participants in 4 studies. (Randomized controlled)	109 per 1000 Difference:	83 per 1000 **26 fewer per 1000** (CI 95% 38 fewer — 11 fewer)	High [1]

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artesunate	**Certainty of the evidence** (Quality of evidence)
Neurological sequelae on day 28	Relative risk 1.23 (CI 95% 0.74 — 2.03) Based on data from 4,857 participants in 1 studies. (Randomized controlled)	11 per 1000 Difference:	14 per 1000 **3 more per 1000** (CI 95% 3 fewer — 11 more)	Moderate Due to serious risk of bias [2]
Neurological sequelae at discharge	Relative risk 1.36 (CI 95% 1.01 — 1.83) Based on data from 5,163 participants in 3 studies. (Randomized controlled)	28 per 1000 Difference:	38 per 1000 **10 more per 1000** (CI 95% 0 fewer — 23 more)	Moderate Due to serious imprecision [3]
Hypoglycaemia episodes	Relative risk 0.62 (CI 95% 0.45 — 0.87) Based on data from 5,765 participants in 4 studies. (Randomized controlled)	30 per 1000 Difference:	19 per 1000 **11 fewer per 1000** (CI 95% 16 fewer — 4 fewer)	High [4]
Time to hospital discharge (days)	Based on data from 113 participants in 3 studies. (Randomized controlled)	See comment.		Moderate Due to serious imprecision [5]

1. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** There was no statistical heterogeneity between the trials (I^2 = 0%). **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of the Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: no serious.** Both limits of the 95% CI of the pooled effect imply an appreciable clinical benefit with artesunate. The number of people who must be treated to prevent one childhood death is 38.
2. **Risk of Bias: serious.** 41/170 (24%) patients with neurological sequelae at discharge were not available for assessment at day 28. **Indirectness: no serious.** This trial was conducted in 11 centres in Africa, with standard dosing of artesunate and quinine. The nature of the neurological sequelae is not described. **Imprecision: no serious.** The 95% CI around the absolute effect is narrow. The worst-case scenario is a 1.2% increase in neurological sequelae at day 28.
3. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** There was no statistical heterogeneity between the trials (I^2 = 0%). **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of the Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: serious.** The effect estimate indicates clinically important harm; however, the 95% CI includes the possibility of no clinically important difference between the two interventions.
4. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** There was no statistical heterogeneity between the trials (I^2 = 0%). **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: no**

serious. The result is statistically significantly in favour of artesunate. The sample size is adequate to detect a 40% risk reduction with 80% power and 95% confidence.
5. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** None of the trials found evidence of a large difference between the two treatment groups. **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of the Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: serious.** We were unable to pool the data as they were reported only as medians and range or intraquartile range. There is no evidence of a clinically important benefit with artesunate on this outcome.

Clinical question/ PICO

Population: Adults with severe malaria (malaria-endemic areas)
Intervention: Artesunate
Comparator: Quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artesunate	**Certainty of the evidence** (Quality of evidence)
Death	Relative risk 0.61 (CI 95% 0.5 — 0.75) Based on data from 1,664 participants in 5 studies. (Randomized controlled)	241 per 1000 Difference:	147 per 1000 **94 fewer per 1000** (CI 95% 120 fewer — 60 fewer)	High 1
Neurological sequelae at day 28	Relative risk		CI 95%	
Neurological sequelae at discharge	Relative risk 2.97 (CI 95% 0.6 — 14.64) Based on data from 1,259 participants in 1 studies. (Randomized controlled)	3 per 1000 Difference:	9 per 1000 **6 more per 1000** (CI 95% 1 fewer — 41 more)	Moderate Due to serious imprecision [2]
Hypoglycaemia episodes	Relative risk 0.62 (CI 95% 0.45 — 0.87) Based on data from 5,765 participants in 4 studies. (Randomized controlled)	30 per 1000 Difference:	19 per 1000 **11 fewer per 1000** (CI 95% 16 fewer — 4 fewer)	High 3
Time to hospital discharge (days)	Based on data from 113 participants in 2 studies. (Randomized controlled)	See comment.		Moderate Due to serious imprecision [4]

1. **Risk of Bias: no serious.** Two of the smaller studies did not conceal allocation, and none of the studies was blinded; however, most data are from studies in which allocation was concealed, and the lack of blinding is unlikely to introduce bias for an objective outcome such as death. **Inconsistency: no serious.** The point estimates of all five trials favoured artesunate. No significant statistical heterogeneity was detected (I^2 = 0%). **Indirectness: no serious.** All five trials were conducted in Asia but in a variety of settings (Bangladesh, India, Indonesia, Myanmar, Thailand and Viet Nam), and included age groups > 15–16 years. Of the four small trials, two did not give the loading dose of quinine, but there was no statistical heterogeneity between these two trials and the large multicentre trial, in which the loading dose was given. **Imprecision: no serious.** Both limits of the 95% CI imply a clinically important benefit with artesunate.
2. **Risk of Bias: no serious.** This trial was unblinded, but the nature of the sequelae makes observer or reporting bias unlikely. **Inconsistency: no serious.** Not applicable, as only one trial. **Indirectness: no serious.** This trial was conducted in sites in four countries in Asia with the standard doses of artesunate and quinine (with loading dose). Of the 10 sequelae that occurred in this trial (the additional two were in children), five were psychiatric sequelae, four were a persistent problem with balance, and two were hemiparesis. **Imprecision: serious.** Neurological sequelae appear to be rare after severe malaria in adults; however, the 95% CI includes the possibility of clinically important harm with artesunate.
3. **Risk of Bias: no serious.** The large multicentre study adequately concealed allocation and can be considered at low risk of bias. The smaller trial did not. Neither trial was blinded. **Inconsistency: no serious.** There was no statistical heterogeneity (I^2 = 0%). **Indirectness: no serious.** This evidence is from multiple sites in Asia (Bangladesh, India, Indonesia and Myanmar), and both trials used standard drug doses. **Imprecision: no serious.** This result is statistically significantly in favour of artesunate. The sample size was adequate to detect a 75% risk reduction with 80% power and 95% confidence..

4. **Risk of Bias: no serious.** The large multicentre study adequately concealed allocation and can be considered at low risk of bias. The smaller trial did not. Neither trial was blinded. **Inconsistency: no serious.** Neither trial found a statistically significant difference in time to hospital discharge. **Indirectness: no serious.** This evidence is from multiple sites in Asia (Bangladesh, India, Indonesia and Myanmar), and both trials used standard drug doses. **Imprecision: serious.** We were unable to pool data because of the way in which they were presented, but there is no evidence of a benefit on this outcome with artesunate.

5.2.2.2. Parenteral alternatives when artesunate is not available

Clinical question/ PICO

Population: Adults with severe malaria (malaria-endemic countries)
Intervention: Intramuscular artemether
Comparator: Intravenous or intramuscular artesunate

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate	**Intervention** Artemether	**Certainty of the evidence** (Quality of evidence)
Death	Relative risk 0.55 (CI 95% 0.34 — 0.92) Based on data from 494 participants in 2 studies. (Randomized controlled)	148 per 1000 Difference:	81 per 1000 **67 fewer per 1000** (CI 95% 98 fewer — 12 fewer)	Moderate Due to serious imprecision [1]
Neurological sequelae at discharge	Relative risk		CI 95%	
Coma resolution time	Based on data from 494 participants in 2 studies. (Randomized controlled)	Not pooled.		Moderate Due to serious imprecision [2]
Parasite clearance time	Based on data from 494 participants in 2 studies. (Randomized controlled)	Not pooled.		Moderate Due to serious imprecision [3]
Fever clearance time	Based on data from 494 participants in 2 studies. (Randomized controlled)	Not pooled.		Low Due to serious imprecision [4]

1. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no serious.** There is no statistical heterogeneity. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These trials and the

meta-analysis have inadequate power to detect a difference in mortality or to prove equivalence.
2. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no serious.** Both studies suggest an advantage with artesunate, although this was statistically significant only in the small trial. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These data could not be pooled.
3. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no serious.** Neither study found a difference between treatments. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These data could not be pooled.
4. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no serious.** One trial found no statistically significant difference, and the other, small trial found a benefit with artesunate. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These data could not be pooled.

Clinical question/ PICO

Population: Children with severe malaria (malaria-endemic countries)
Intervention: Intramuscular artemether
Comparator: Intravenous or intramuscular quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether	**Certainty of the evidence** (Quality of evidence)
Death	Relative risk 0.96 (CI 95% 0.76 — 1.2) Based on data from 1,447 participants in 12 studies. (Randomized controlled)	170 per 1000 Difference:	163 per 1000 **7 fewer per 1000** (CI 95% 41 fewer — 34 more)	Moderate Due to serious imprecision [1]
Neurological sequelae at discharge	Relative risk 0.84 (CI 95% 0.66 — 1.07) Based on data from 968 participants in 7 studies. (Randomized controlled)	220 per 1000 Difference:	185 per 1000 **35 fewer per 1000** (CI 95% 75 fewer — 15 more)	Low Due to very serious imprecision [2]
Coma resolution time	Based on data from 358 participants in 6 studies. (Randomized controlled)	Quinine: The mean time in control groups ranged from 17.4 to 42.4 h. Artemether: The mean time was 5.45 h shorter in the intervention groups (7.90 to 3.00 h shorter).		Low Due to very serious risk of bias [3]
Parasite clearance time	Based on data from 420 participants in 7 studies. (Randomized controlled)	Quinine: The mean time in control groups ranged from 22.4 to 61.3 h. Artemether: The mean time was 9.03 h shorter in the intervention groups (11.43 to 6.63 h shorter).		Moderate Due to serious inconsistency [4]
Fever clearance time	Based on data from 457 participants in 8 studies. (Randomized controlled)	Quinine: The mean time in control groups ranged from 18 to 61 h. Artemether: The mean time was 3.73 h shorter in the intervention groups (6.55 to 0.92 h shorter).		Low Due to serious risk of bias and serious inconsistency [5]

1. **Risk of Bias: no serious.** Various risks of bias, but exclusion of trials with high or unclear risk of selection bias did not change this result. **Inconsistency: no serious.** None of the individual trials found statistically significant effects, and there was no statistical heterogeneity between trials. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: serious.** These trials and the meta-analysis had inadequate power to detect a difference or to prove equivalence.
2. **Risk of Bias: no serious.** Various risks of bias, but exclusion of trials with high or unclear risk of selection bias did not change this result. **Inconsistency: no serious.** None of the individual trials found statistically significant effects, and there was no statistical heterogeneity between trials. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: very serious.** These trials and the meta-analysis have inadequate power to detect a difference or to prove equivalence. The 95% CI is very wide and includes clinically important differences and no effect.
3. **Risk of Bias: very serious.** Four of the six trials had unclear risk of selection bias. When these four trials are excluded, the result becomes nonsignificant. **Inconsistency: no serious.** Statistically significant differences were seen in only two of the six trials; however, statistical heterogeneity between trials was low, and the result of the meta-analysis is significant. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect.
4. **Risk of Bias: no serious.** Various risks of bias, but exclusion of trials with high or unclear risk of selection bias did not change this result. **Inconsistency: serious.** The mean difference in parasite clearance time ranged from a 2 h increase with

artemether to a 15 h decrease. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect.
5. **Risk of Bias: serious.** Four of the seven trials had unclear risks of selection bias. When these four trials are excluded, the result becomes nonsignificant. **Inconsistency: serious.** The mean difference in fever clearance time ranged from a 25 h increase with artemether to an 18 h decrease. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: no serious.** The meta-analysis has adequate power to detect this effect. The result is statistically significant but may not be clinically important.

Clinical question/ PICO

Population: Adults with severe malaria (malaria-endemic countries)
Intervention: Intramuscular artemether
Comparator: Intravenous or intramuscular quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether	**Certainty of the evidence** (Quality of evidence)
Death	Relative risk 0.59 (CI 95% 0.42 — 0.83) Based on data from 716 participants in 4 studies. (Randomized controlled)	208 per 1000 Difference:	123 per 1000 **85 fewer per 1000** (CI 95% 121 fewer — 35 fewer)	Moderate Due to serious imprecision [1]
Neurological sequelae at discharge	Relative risk 2.92 (CI 95% 0.31 — 27.86) Based on data from 560 participants in 1 studies. (Randomized controlled)	4 per 1000 Difference:	12 per 1000 **8 more per 1000** (CI 95% 3 fewer — 107 more)	Moderate Due to serious imprecision [2]
Coma resolution time	Based on data from 683 participants in 3 studies. (Randomized controlled)	Not pooled.		Low Due to serious inconsistency and serious imprecision [3]
Parasite clearance time	Based on data from 716 participants in 4 studies.	Not pooled.		Moderate Due to serious imprecision [4]
Fever clearance time	Based on data from 716 participants in 4 studies.	Not pooled.		Moderate Due to serious imprecision [5]

1. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: no serious.** Statistically significant differences were seen in only one of the four studies; however, statistical heterogeneity among the trials

was low, and the results of the meta-analysis are statistically significant. **Indirectness: no serious.** All four trials compared intramuscular artemether with intravenous quinine in adults: two studies in Thailand, one each in Papua New Guinea and Viet Nam. **Imprecision: serious.** These trials and the meta-analysis had inadequate power to detect a difference in mortality or to prove equivalence.
2. **Risk of Bias: no serious.** This single trial had a low risk of bias. **Imprecision: serious.** Neurological sequelae in adults were uncommon. This trial had inadequate power to detect or exclude clinically important differences.
3. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: serious.** One trial found a shorter median coma resolution time with quinine, and one trial found no difference; the third trial reported mean coma recovery time incompletely. **Imprecision: serious.** The data could not be pooled.
4. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: no serious.** The two largest studies both found shorter median clearance times with artemether. **Indirectness: no serious.** All four trials compared intramuscular artemether with intravenous quinine in adults: two studies in Thailand, one each in Papua New Guinea and Viet Nam. **Imprecision: serious.** The data could not be pooled.
5. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: no serious.** One trial found a shorter median fever clearance time with quinine, and two trials found a shorter time with artemether. **Indirectness: no serious.** All four trials compared intramuscular artemether with intravenous quinine in adults: two studies in Thailand, one each in Papua New Guinea and Viet Nam. **Imprecision: serious.** The data could not be pooled.

5.2.2.3. Pre-referral treatment options

Clinical question/ PICO

Population: Children aged < 5 years with severe malaria (rural settings in Africa and Asia where parenteral treatment is not available)

Intervention: Rectal artesunate plus referral for definitive treatment

Comparator: Placebo plus referral for definitive treatment

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Rectal artesunate	**Certainty of the evidence** (Quality of evidence)
All-cause mortality (in Asia) 7-30 days	Relative risk 0.44 (CI 95% 0.23 — 0.82) Based on data from 2,010 participants in 1 studies. (Randomized controlled)	31 per 1000 Difference:	14 per 1000 **17 fewer per 1000** (CI 95% 24 fewer — 6 fewer)	Low Due to serious inconsistency and serious imprecision [1]
All-cause mortality (in Africa) 7-30 days	Relative risk 0.81 (CI 95% 0.63 — 1.04) Based on data from 6,040 participants in 1 studies. (Randomized controlled)	44 per 1000 Difference:	36 per 1000 **8 fewer per 1000** (CI 95% 16 fewer — 2 more)	Low Due to serious inconsistency and serious imprecision [2]
All-cause mortality (overall) 7-30 days	Relative risk 0.74 (CI 95% 0.59 — 0.93) Based on data from 8,050 participants in 1 studies. (Randomized controlled)	41 per 1000 Difference:	30 per 1000 **11 fewer per 1000** (CI 95% 17 fewer — 3 fewer)	Moderate Due to serious inconsistency [3]

1. **Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** In Asia, older children and adults were also randomized to artesunate or placebo, and mortality was significantly higher in those given rectal artesunate; the cause is unclear. **Indirectness: no serious.** This trial was conducted in community settings in Bangladesh, Ghana and the United Republic of Tanzania. **Imprecision: serious.** The number of events was low.
2. **Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** In Asia, older children and adults were also randomized to artesunate or placebo, and mortality was significantly higher in those given rectal artesunate; the cause is unclear. **Indirectness: no serious.** This trial was conducted in community settings in Bangladesh, Ghana and the United Republic of Tanzania. **Imprecision: serious.** The 95% confidence interval is wide and includes no difference.
3. **Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** In Asia, older children and adults were also randomized to artesunate or placebo, and mortality was significantly higher in those given rectal artesunate; the cause is unclear. **Indirectness: no serious.** This trial was conducted in community settings in Bangladesh, Ghana and the United Republic of Tanzania. **Imprecision: no serious.** The result is statistically significant, and the study had adequate power to detect this effect.

Clinical question/ PICO

Population: Children aged > 6 years and adults with severe malaria (rural settings where parenteral treatment is not available)

Intervention: Rectal artesunate plus referral for definitive treatment

Comparator: Placebo plus referral for definitive treatment

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Rectal artesunate	Certainty of the evidence (Quality of evidence)
All-cause mortality 7-30 days	Relative risk 2.21 (CI 95% 1.18 — 4.15) Based on data from 4,018 participants in 1 studies. (Randomized controlled)	7 per 1000 Difference:	15 per 1000 **8 more per 1000** (CI 95% 1 more — 22 more)	Low Due to serious inconsistency and serious imprecision [1]

1. **Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** Rectal artesunate appears beneficial in children < 5 years and harmful in older children and adults. This finding is difficult to explain. **Indirectness: no serious.** This trial was conducted in a single setting in Bangladesh. **Imprecision: serious.** There were few deaths in adults in this trial: 31/2009 in treated and 14/2009 in controls.

5.2.3. Other considerations in treating malaria

5.2.3.1. Management of malaria cases in special situations

5.2.3.2. Quality of antimalarial drugs

5.2.3.3. Monitoring efficacy and safety of antimalarial drugs and resistance

5.3. National adaptation and implementation

6. Interventions in the final phase of elimination and prevention of re-establishment

6.1. Interventions recommended for mass implementation in delimited geographical areas

6.1.1. Mass testing and treatment (MTaT)

Clinical question/ PICO

Population: Adults and children in a delimited geographic area

Intervention: Mass testing and treatment

Comparator: No MTaT

Summary

Seven studies of MTaT were included in the systematic review: four cRCTs, conducted in Kenya, Indonesia, Zambia and Burkina Faso; and three NRSs in Senegal, Ghana and India (Bhamani *et al* *unpublished evidence*).

All four of the cRCTs conducted 2–3 rounds of MTaT over a period of up to one year, with the exception of the study in Kenya that carried out six rounds of MTaT over two years. The studies in Kenya and Burkina Faso were conducted in areas of moderate to high transmission while those in Indonesia and Zambia were areas of low transmission. The overall risk of bias for community-level outcomes in these studies was low. Meta-analyses of the results found little to no reductions in community-level incidence or prevalence of infection. However, there was a small reduction of the incidence of clinical malaria found in two studies.

The certainty of evidence from the NRSs was GRADEd as very low.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MTaT	**Intervention** Mass testing and treatment	**Certainty of the evidence** (Quality of evidence)	**Summary**
2 months - Prevalence	Relative risk 0.93 (CI 95% 0.82 — 1.04) Based on data from 3,660 participants in 1 studies. (Randomized controlled) Follow up: one study with 2 cohorts (year 1 & 2). pooled for both the cohorts.	377 per 1000 Difference:	351 per 1000 **26 fewer per 1000** (CI 95% 68 fewer — 15 more)	High	MTaT does not reduce the prevalence of malaria at 2 months.
0 - 12 months - Incidence	Rate ratio 0.95 (CI 95% 0.87 — 1.04) Based on data from 857 participants in 1 studies. (Randomized controlled)	2,331 per 1000 Difference:	2,214 per 1000 **117 fewer per 1000** (CI 95% 303 fewer — 93 more)	High	MTaT does not reduce incidence of malaria infection between 0-12 months.
0 - 12 months - Incidence of clinical malaria	Relative risk 0.81 (CI 95% 0.7 — 0.95) Based on data from 332,454 participants in 2 studies. (Randomized controlled)	233 per 1000 Difference:	189 per 1000 **44 fewer per 1000** (CI 95% 70 fewer — 12 fewer)	High	MTaT reduces the incidence of clinical malaria between 0-12 months.
6 - 12 months - Incidence	Relative risk 1.27 (CI 95% 0.51 — 3.14) Based on data from 2,349 participants in 2 studies. (Randomized controlled) Follow up: One study has two intervention arms. Both intervention arms are pooled with another study and compared with the control. Control arm is inflated in value because it's the same comparison group for the two different intervention arm in one study.	4 per 1000 Difference:	5 per 1000 **1 more per 1000** (CI 95% 2 fewer — 11 more)	Moderate Due to serious imprecision [1]	MTaT likely results in little to no difference in the incidence of malaria infection between 6-12 months (outcome measured only in children).
Adverse event (group targeted by the intervention)	Based on data from 6,373 participants in 1 studies. (Randomized controlled)		5 per 1000	Low Due to serious indirectness, and serious imprecision [2]	The evidence is very uncertain about the effect of MTaT on adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MTaT	**Intervention** Mass testing and treatment	**Certainty of the evidence** (Quality of evidence)	**Summary**
Serious adverse event (SAE) (group targeted by the intervention)	Based on data from 6,373 participants in 1 studies. (Randomized controlled) Follow up: not estimable.			Low Due to serious indirectness, and serious imprecision [3]	The evidence is very uncertain about the effect of MTaT on serious adverse events.
6 months - Prevalence (group targeted by the intervention)	Odds ratio 0.47 (CI 95% 0.24 — 0.9) Based on data from 1,024 participants in 1 studies. (Randomized controlled)	440 per 1000 Difference:	270 per 1000 **170 fewer per 1000** (CI 95% 281 fewer — 26 fewer)	Moderate Due to serious imprecision [4]	MTaT likely reduces prevalence of infection at six months among those receiving the intervention.
9 months - Prevalence (group targeted by the intervention)	Relative risk 0.91 (CI 95% 0.82 — 1.01) Based on data from 2,838 participants in 1 studies. (Randomized controlled)	378 per 1000 Difference:	344 per 1000 **34 fewer per 1000** (CI 95% 68 fewer — 4 more)	Moderate Due to serious imprecision [5]	MTaT likely does not reduce the prevalence of infection at nine months among the group targeted by the intervention.
2 months - Prevalence (group targeted by the intervention)	Odds ratio 0.03 (CI 95% 0.02 — 0.07) Based on data from 8,508 participants in 1 studies. (Observational (non-randomized))	34 per 1000	1 per 1000	Very low Due to serious inconsistency, serious indirectness, and serious imprecision [6]	The evidence is very uncertain about the effect of MTaT on the prevalence of infection at two months in the group receiving the intervention.
12 months - Prevalence (group targeted by the intervention)	Odds ratio 0.91 (CI 95% 0.67 — 1.38) Based on data from 416 participants in 1 studies. (Observational (non-randomized))	438 per 1000	415 per 1000	Very low Due to serious inconsistency, serious indirectness, and serious imprecision [7]	The evidence is very uncertain about the effect of MTaT on the prevalence of infection at 12 months in the group targeted by the intervention.
12 months - Prevalence (group targeted by the intervention)	Odds ratio 0.76 (CI 95% 0.67 — 0.85) Based on data from 8,907 participants in 1 studies. (Observational (non-randomized))	363 per 1000 Difference:	302 per 1000 **61 fewer per 1000** (CI 95% 87 fewer — 37 fewer)	Very low Due to serious inconsistency, serious indirectness, and serious imprecision [8]	The evidence is very uncertain about the effect of MTaT on the prevalence of infection in the group targeted by the intervention.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MTaT	**Intervention** Mass testing and treatment	**Certainty of the evidence** (Quality of evidence)	**Summary**
Adverse event (group targeted by the intervention)	Based on data from 6,373 participants in 1 studies. (Randomized controlled)	Most common AEs during treatment were fever (0.023/person-day), headache (0.008/person-day), vomiting (0.006/person-day), cough (0.004/ person-day), shivering (0.003/person-day), and nasal congestion (0.002/ person-day).		Low Due to serious risk of bias, and serious imprecision [9]	The evidence is very uncertain about the effect of MTaT on adverse events.
Prevalence (group targeted by the intervention)	Based on data from 633 participants in 1 studies. (Observational (non-randomized))	Three rounds of MTaT were conducted to determine prevalence in the asymptomatic reservoir. MTaT was compared with detection through passive surveillance prevalence. 1st round-moderate to high burden areas -50/28,527 i.e. 0.18% vs 0.06% from passive surveillance; 2nd round-low to high burden areas - 7/11,363 i.e. 0.06% vs 0.03% from passive surveillance; 3rd round- RCD of cryptic cases in 50 households -3/8,467 i.e. 0.03%.		Very low Due to serious risk of bias [10]	The evidence is very uncertain about the effect of MTaT on the prevalence of infection among the group targeted by the intervention.

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Used as a proxy for incidence of infection at the community level.
2, 3. **Inconsistency: no serious. Indirectness: serious.** SAEs and AEs are not classified based on intervention and control arms; unable to calculate control measures in absence of control measure. **Imprecision: serious.** SAEs and AEs are not classified based on intervention and control arms; unable to calculate control measures in absence of control measure.
4, 5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Used as a proxy for prevalence of infection at the community level.
6. **Inconsistency: serious.** Study did not control for one confounding domain and missing register from health facility in intervention village - the analysis is unlikely to have removed the risk of bias arising from the missing data. **Indirectness: serious.** Study did not control for one confounding domain and missing register from health facility in intervention village - the analysis is unlikely to have removed the risk of bias arising from the missing data. **Imprecision: serious.** Study did not control for one confounding domain and missing register from health facility in intervention village - the analysis is unlikely to have removed the risk of bias arising from the missing data.
7. **Inconsistency: serious.** Critical overall risk of bias due to inherent biases associated with study design. **Indirectness: serious.** Critical overall risk of bias due to inherent biases associated with study design. **Imprecision: serious.** Critical overall risk of bias due to inherent biases associated with study design.
8. **Inconsistency: serious.** Used as a proxy for prevalence of infection at the community level; critical overall risk of bias due to inherent biases associated with study design . **Indirectness: serious.** Used as a proxy for prevalence of infection at the community level; critical overall risk of bias due to inherent biases associated with study design. **Imprecision: serious.** Used as a proxy for prevalence of infection at the community level; critical overall risk of bias due to inherent biases associated with study design.
9. **Risk of Bias: serious.** Common AEs are reported for the whole study, however no break-up is provided for different arms. **Imprecision: serious.** Common AEs are reported for the whole study, however no break-up is provided for different arms.
10. **Risk of Bias: serious.** Critical overall risk of bias due to inherent biases associated with study design.

6.2. Interventions targeting infections in people at higher-risk

6.2.1. Targeted drug administration (TDA)

Clinical question/ PICO

Population: Adults and children at increased risk of malaria infection relative to the general population living in areas of very low to low transmission or post-elimination settings

Intervention: Targeted drug administration (TDA)

Comparator: no TDA

Summary

No studies from areas approaching elimination were identified in the systematic review (Tusell *et al* *unpublished evidence*). Two studies conducted in post-elimination settings identified imported infections in migrant workers with onward transmission to the local population. In both studies, the migrant workers were provided with a full therapeutic dose of chloroquine and 14 days of primaquine in a single round (the study from Greece conducted one round per year for three years). No additional infections among the migrant workers or the community were identified for five months (Sri Lanka) or two years (Greece) after the last round of TDA. Adverse events were monitored in both studies: a single serious case of haemolysis was identified in the study from Greece due to an incorrect G6PD test result; the remaining adverse events were relatively minor side effects.

Outcome Timeframe	**Study results and measurements**	**Comparator** no TDA	**Intervention** Targeted drug administration (TDA)	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prevalence of malaria infection	Relative risk 0.85 (CI 95% 0.73 — 1) Based on data from 8,922 participants in 1 studies. (Randomized controlled)	219 per 1000 Difference:	186 per 1000 **33 fewer per 1000** (CI 95% 59 fewer — 0 more)	High	TDA results in little to no difference in the prevalence of malaria
Serious Adverse Events (cRCTs)	Based on data from 10,079 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000	Very low Due to very serious risk of bias, Due to very serious imprecision [1]	The evidence is very uncertain about the effect of TDA on serious adverse events
Serious adverse events (cRCTs)	Relative risk 4.19 (CI 95% 1.43 — 12.31) Based on data from 4,916 participants in 1 studies. (Randomized controlled)	2 per 1000 Difference:	7 per 1000 **6 more per 1000** (CI 95% 1 more — 23 more)	Low Due to very serious imprecision [2]	TDA may result in little to no difference in serious adverse events
Serious adverse events (NRS)	Based on data from 31 participants in 1 studies. (Observational (non-randomized))	0 per 1000	0 per 1000	Very low Due to serious risk of bias, Due to serious imprecision [3]	The evidence is very uncertain about the effect of TDA on serious adverse events
Adverse events (cRCTs)	Relative risk 1.48 (CI 95% 0.12 — 18.02) Based on data from 4,916 participants in 1 studies. (Randomized controlled)	19 per 1000 Difference:	28 per 1000 **9 more per 1000** (CI 95% 17 fewer — 325 more)	Low Due to very serious imprecision [4]	TDA may have little to no effect on adverse events

Outcome Timeframe	**Study results and measurements**	**Comparator** no TDA	**Intervention** Targeted drug administration (TDA)	**Certainty of the evidence** (Quality of evidence)	**Summary**
Adverse events (NRS)	Based on data from 1,094 participants in 1 studies. (Observational (non-randomized))	0 per 1000	0 per 1000	Very low Due to serious risk of bias [5]	The evidence is very uncertain about the effect of TDA on adverse events
Prevalence among those targeted by the intervention (cRCTs)	Relative risk 0.15 (CI 95% 0.06 — 0.38) Based on data from 5,970 participants in 2 studies. (Randomized controlled)	406 per 1000 Difference:	61 per 1000 **345 fewer per 1000** (CI 95% 381 fewer — 251 fewer)	Moderate Due to serious indirectness [6]	TDA probably reduces the prevalence of malaria among those targeted by the intervention
Prevalence among those targeted by the intervention (NRS)	Relative risk 0.35 (CI 95% 0.22 — 0.57) Based on data from 348 participants in 1 studies. (Observational (non-randomized))	315 per 1000 Difference:	110 per 1000 **205 fewer per 1000** (CI 95% 246 fewer — 135 fewer)	Low Due to serious risk of bias, Due to serious indirectness [7]	TDA may reduce the prevalence of malaria among those targeted by the intervention
Incidence of malaria in the community	Based on data from 0 participants in 2 studies. (Observational (non-randomized))	Both studies reported no malaria cases during the follow-up periods.		Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [8]	The evidence is very uncertain about the effect of TDA on the prevalence of malaria among those targeted by the intervention

1. **Risk of Bias: very serious.** Outcome was collected in intervention arm only. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Unable to calculate effect measure in absence of control measures. **Publication bias: no serious.**
2, 4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals. **Publication bias: no serious.**
3. **Risk of Bias: serious.** Critical overall risk of bias due to inherent biases associated with study design. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Few patients and few events. **Publication bias: no serious.**
5. **Risk of Bias: serious.** Critical overall risk of bias due to inherent biases associated with study design. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Inconsistency: no serious. Indirectness: serious.** Used as a surrogate for prevalence of infection at the community level. **Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: serious.** Moderate risk of bias due to bias due to confounding, bias due to deviations from intended interventions, and no information about bias in measurement of outcomes. **Inconsistency: no serious. Indirectness: serious.** Used as a surrogate for prevalence of infection at the community level. **Imprecision: no serious. Publication bias: no serious.**
8. **Risk of Bias: serious.** Critical overall risk of bias due to inherent biases associated with study design. **Inconsistency: no serious. Indirectness: serious.** Used as a surrogate for prevalence of infection at the community level. **Imprecision: serious.** Few patients and few events. **Publication bias: no serious.**

6.2.2. Targeted testing and treatment (TTaT)

Clinical question/ PICO

Population: Adults and children at increased risk of malaria infection relative to the general population living in very low to low or post-elimination transmission settings

Intervention: Targeted testing and treatment

Comparator: No TTaT

Summary

The systematic review identified three studies for inclusion: two cRCTs in Ghana and Kenya and one NRS in Malawi (Allen *et al* unpublished evidence). No studies were conducted in very low to low transmission or post-elimination settings. The GDG determined that the TTaT strategy would be most relevant in very low to low transmission or post-elimination settings and, therefore, decided that the PICO question should be modified and the setting limited to such areas. As a result, the GDG did not consider any of the studies identified by the systematic review to fit the revised PICO.

Outcome Timeframe	**Study results and measurements**	**Comparator** No TTaT	**Intervention** Targeted testing and treatment	**Certainty of the evidence** (Quality of evidence)	**Summary**
0 - 24 months - Adverse events (group targeted by intervention)	Based on data from 2,030 participants in 1 studies. (Randomized controlled) Follow up: not estimable.		45 per 1000	Moderate Due to serious imprecision [1]	TTaT likely results in little to no difference in adverse events among the group targeted by intervention between 0-24 months.
0 - 24 months - Incidence	Rate ratio 1.13 (CI 95% 0.82 — 1.55) Based on data from 3,046 participants in 1 studies. (Randomized controlled)	666 per 1000	752 per 1000	Moderate Due to serious risk of bias [2]	TTaT probably results in little to no difference in the incidence of malaria infection between 0-24 months.
12 months - Prevalence (group targeted by intervention)	Relative risk 0.71 (CI 95% 0.46 — 1.11) Based on data from 4,382 participants in 1 studies. (Randomized controlled)	143 per 1000 Difference:	102 per 1000 **41 fewer per 1000** (CI 95% 77 fewer — 16 more)	Moderate Due to serious imprecision [3]	TTaT probably has little to no effect on malaria prevalence in the group targeted by the intervention at 12 months.
Mortality (group targeted by intervention)	Relative risk 0.73 (CI 95% 0.08 — 6.95) Based on data from 8,222 participants in 2 studies. (Randomized controlled)	7 per 1000 Difference:	5 per 1000 **2 fewer per 1000** (CI 95% 6 fewer — 42 more)	Moderate Due to serious imprecision [4]	TTaT likely results in little to no difference in severe adverse events among group targeted by intervention.
24 months - Prevalence (group targeted by intervention)	Relative risk 1.53 (CI 95% 0.89 — 2.62) Based on data from 4,140 participants in 1 studies. (Randomized controlled)	84 per 1000 Difference:	129 per 1000 **45 more per 1000** (CI 95% 9 fewer — 136 more)	Moderate Due to serious imprecision [5]	TTaT probably results in little to no difference in prevalence in the group targeted by intervention at 24 months.
6 weeks -	Relative risk 0.43	255	110	Moderate	TTAT reduces the

Outcome Timeframe	**Study results and measurements**	**Comparator** No TTaT	**Intervention** Targeted testing and treatment	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prevalence (group targeted by intervention)	(CI 95% 0.33 — 0.55) Based on data from 1,317 participants in 1 studies. (Observational (non-randomized))	per 1000 Difference:	per 1000 **145 fewer per 1000** (CI 95% 171 fewer — 115 fewer)	Due to serious risk of bias, serious imprecision, and large magnitude of effect [6]	prevalence of malaria among the group targeted by intervention at six weeks.

1. **Risk of Bias: serious.** Outcome not measured in control arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Outcome not measured in control arm.
2. **Risk of Bias: serious.** High risk of bias for domain 5 of RoB2 assessment - Selection of reported result. Study assessed incidence of malaria; episodes of malaria and accounted for repeat illnesses, but did not assess number of children in intervention and control arms that had malaria. Incidence was instead categorized by all episodes, episodes after first fever and repeat malaria and prevalence or number of clinical cases was not reported. Conducted a multi-level poisson to calculate incidence and rate ratios for comparison in study arms, but did not perform a generalized model accounting for potential demographics and confounders to assess risk of malaria infection in study arms. Incidence among high-risk population within the community used as a surrogate for community level impact. **Inconsistency: no serious. Indirectness: no serious.** Incidence among high-risk population within the community used as a surrogate for community level impact. **Imprecision: no serious.**
3, 5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Absolute effect estimates both appreciable risk and appreciable benefit.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Imprecision due to wide confidence intervals; crude data used for mortality unadjusted for additional criteria or potential confounders. Absolute effect estimates both appreciable risk and appreciable benefit.
6. **Risk of Bias: serious.** Moderate risk of bias in D7 of ROBINS-I, bias in selection of the reported result. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Absolute effect estimates both appreciable risk and appreciable benefit. **Upgrade: large magnitude of effect.**

6.2.3. Testing and treatment at points of entry to reduce importation of malaria

Clinical question/ PICO

Population: Adults and children arriving at points of entry (land, sea or air)
Intervention: Testing and treatment at points of entry
Comparator: no intervention

Summary

The systematic review identified seven NRSs in six countries (Cambodia, China, Equatorial Guinea, Greece, Myanmar and the United Arab Emirates that reported on TTaT at points of entry (Coma-Cros *et al unpublished evidence*). None of the studies provided information on the outcome considered critical by the GDG, i.e. the number of positive cases identified by the strategy as a proportion of all imported cases found in the country during the same period.

Outcome Timeframe	**Study results and measurements**	**Comparator** no intervention	**Intervention** Testing and treatment at points of entry	**Certainty of the evidence** (Quality of evidence)
Prevalence (group targeted by the intervention, test done	Based on data from 0 participants in 1 studies. (Observational (non-	Results indicate the highest prevalence in passengers younger than 15 years old travelling in the direction from the mainland to Bioko, 70.4%		Very low Due to serious risk of bias [1]

Outcome Timeframe	**Study results and measurements**	**Comparator** no intervention	**Intervention** Testing and treatment at points of entry	**Certainty of the evidence** (Quality of evidence)
at POE)	randomized))	(95% CI 58.4 - 80.7; p-value 0.017). A lower prevalence was observed for the same age range in the opposite direction, 38.1% (95% CI 26.1 - 51.2; p-value 0.017). For passengers older than 15 years a prevalence of 35.7% (95% CI 30.1 - 41.6; p-value 0.001) was observed between the mainland and Bioko and a prevalence of 22.6% (95% CI 17.3 - 28.6; p-value 0.001) in the opposite direction.		
Prevalence (positivity rate) (group targeted by the intervention, test done at POE)	Based on data from 0 participants in 4 studies. (Observational (non-randomized))	For UAE, where indigenous cases were zero, importation among arrivals applying for resident or work permits was between 4.6 and 9.1% for the study period. In Myanmar, among migrant workers, the positivity rate decreased over the years from 13.1% to 3.1%. In Cambodia, official border points identified different positivity rates depending on the neighbouring country, 0.6% with Thailand, 3.6% with Vietnam and 11.5% with Laos. Mobile malaria posts identified a decrease in the positivity rate over the years, from 9.2% to 0.09%.		Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness [2]
Prevalence (positivity rate) (group targeted by the intervention, test done after entry)	Based on data from 0 participants in 2 studies. (Observational (non-randomized))	Results in Shanglin County, China, showed a positivity rate of 21.6%. Targeted test and treat was done to persons with overseas travel history, mainly coming from Ghana where they work in the gold mining sector, within an 8-day median interval (range 0-28 days; interquartile range 4-18 days) between return date and diagnosis date. Results in Evrotas area in Greece, showed a positivity rate of 1.6% in 2012 and 2015, 1.4% in 2016 and 1.5% in 2017. During 2013 and 2014 there were no cases because an MDA was implemented in the area. The median time period from the migrants arriving in Greece to the day of their first contact with the field team and their registration in the database was much higher for the years 2012–2014 (90, 60 and 10 days respectively), compared with the years 2015–2017 (5, 15 and 7 days respectively).		Very low Due to serious risk of bias [3]

1. **Risk of Bias: serious.** Observational study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
2. **Risk of Bias: serious.** Observational study. **Inconsistency: serious.** Big differences among positivity rates (from 0.0 to 21.0). **Indirectness: serious.** Outcome expressed in positivity rate no prevalence. **Imprecision: no serious. Publication bias: no serious.**
3. **Risk of Bias: serious.** Observational study. **Inconsistency: no serious. Indirectness: no serious.** Outcome expressed in positivity rate no prevalence. **Imprecision: no serious. Publication bias: no serious.**

6.3. Interventions in response to detection of confirmed malaria cases

6.3.1. Reactive drug administration (RDA)

Clinical question/ PICO

Population: Adults and children residing with or near a confirmed malaria case or having the same risk of acquiring infection as the index case in areas of very low to low transmission or in post-elimination settings

Intervention: Reactive drug administration

Comparator: No RDA

Summary

The systematic review identified six cRCTs assessing the impact of RDA in four countries of sub-Saharan Africa (Eswatini, Gambia, Namibia and Zambia) (Steinhardt *et al* *unpublished evidence (c)*). All studies used DP for treatment, with the exception of the study from Namibia that provided AL. One NRS assessing the impact of RDA was identified; the study, conducted in Peru, provided chloroquine plus seven days of primaquine at a dosage of 0.5mg/kg. All studies except for one were from low-transmission settings. Three of the cRCTs compared RDA to no RDA and three compared RDA to RACDT.

In the cRCTs, the people around the index case included in the RDA programme ranged from household and compound members (of the index case to people living within 500 meters of the index case.

Evidence of low to moderate certainty from the cRCTs suggested that RDA may reduce malaria prevalence and incidence slightly but probably results in little to no difference in the incidence of clinical malaria. Adverse events were often not measured in both arms, which complicated interpretation of the findings, but reported rates of adverse events or serious adverse events were low.

Outcome Timeframe	**Study results and measurements**	**Comparator** No RDA	**Intervention** Reactive drug administration	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prevalence of parasitemia - cRCTs	Odds ratio 0.76 (CI 95% 0.53 — 1.09) Based on data from 9,822 participants in 4 studies. (Randomized controlled)	20 per 1000 Difference:	16 per 1000 **5 fewer per 1000** (CI 95% 9 fewer — 2 more)	Low Due to serious indirectness, Due to serious imprecision [1]	RDA may reduce malaria prevalence
Incidence of parasitemia - cRCTs	Rate ratio 0.73 (CI 95% 0.36 — 1.47) Based on data from 18,354 participants in 2 studies. (Randomized controlled)	27 per 1000 Difference:	20 per 1000 **7 fewer per 1000** (CI 95% 17 fewer — 13 more)	Moderate Due to serious imprecision [2]	RDA probably reduces the incidence of malaria parasitaemia
Incidence of clinical malaria - cRCTs	Rate ratio 0.91 (CI 95% 0.8 — 1.03) Based on data from 3,013,320 participants in 6 studies. (Randomized controlled)	18 per 1000 Difference:	16 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 1 more)	Moderate Due to serious indirectness [3]	The evidence is very uncertain about the effect of RDA on the incidence of clinical malaria
Incidence of clinical malaria - NRS	Rate ratio 0.59 (CI 95% 0.4 — 0.86) Based on data from 400,430 participants in 1 studies. (Observational (non-randomized))	6 per 1000 Difference:	3 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 1 fewer)	Very low Due to serious risk of bias [4]	The evidence is very uncertain about the effect of RDA on the incidence of clinical malaria
Adverse events (AEs) [5]	Based on data from participants in 4 studies. (Randomized controlled)	Four randomized trials reported on adverse events (AEs); however, AEs were typically only actively solicited from the RDA arm and not from the comparison or RACD arm. In the Zambia trial comparing RDA using dihydroartemisinin-piperaquine (DP) with RACD using artemether-		Very low Most studies focused adverse event reporting only in the RDA arm; in three of the four studies no adverse events	

Outcome Timeframe	**Study results and measurements**	**Comparator** No RDA	**Intervention** Reactive drug administration	**Certainty of the evidence** (Quality of evidence)	**Summary**
		lumefantrine (AL), 123 (6.9%) mild AEs occurred in 1,775 people treated with DP (Bridges 2021); all resolved. In the Namibia trial (Hsiang 2020) of RDA with AL compared to RACD with AL, 17 of 4,247 treated participants (0.4%) in the RDA arm experienced an AE versus 1 participant of 98 (1.0%) treated in the RACD arm; 11 AEs were considered unrelated, 6 possibly related, and 6 probably related. In The Gambia (Okebe 2021), 75 AEs (7.6%) among 979 participants receiving DP in the RDA arm reported AEs; 69 were considered mild and 6 moderate. In Eswati, 68 (3.8%) of 1,776 participants receiving RDA with DP experienced AEs; 54 were rated as mild and 14 as moderate.		were reported from the comparison arm receiving RACD. We are unable to calculate an effect measure for AEs since they were measured in most studies only in the RDA arm	

1. **Inconsistency: no serious. Indirectness: serious.** Two studies (Hsiang 2020 and Okebe 2021) lack a true control group. The comparison in Hsiang 2020 is RACD and the comparison in Okebe 2021 is a modified version of RACD (testing and treating symptomatic household members of the index case). Although we rated down for indirectness, any bias would be towards the null if RACD has an effect on reducing malaria transmission., thus these effect sizes might underestimate the true effect of RDA. The pooled estimate ranges from averting 9 cases of parasitemia per 1,000 to having 2 more. **Imprecision: serious.** Two studies (Hsiang 2020 and Okebe 2021) lack a true control group. The comparison in Hsiang 2020 is RACD and the comparison in Okebe 2021 is a modified version of RACD (testing and treating symptomatic household members of the index case). Although we rated down for indirectness, any bias would be towards the null if RACD has an effect on reducing malaria transmission., thus these effect sizes might underestimate the true effect of RDA. The pooled estimate ranges from averting 9 cases of parasitemia per 1,000 to having 2 more.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The pooled effect estimate ranges from 0.36 (substantial benefit of RDA) to 1.47, indicating potential harm of RDA.
3. **Inconsistency: no serious. Indirectness: serious.** Only two studies (Eisele 2020--LOW and Eisele 2020--HIGH) had a true control group; three (Bridges 2021, Hsiang 2020, and VIlakati 2021) compared RDA to reactive case detection (RACD), and the fourth (Okebe 2021) compares RDA to a modified version of RACD (testing and treating symptomatic household members of the index case). Although we rated down for indirectness, any bias would be towards the null if RACD has an effect on reducing malaria transmission., thus these effect sizes might underestimate the true effect of RDA. **Imprecision: no serious.**
4. **Risk of Bias: serious.** There is a general lack of information about many aspects of this dissertation using data from Tumbes, Peru. We rated as 'Some concerns' most aspects of the study and consider the bias overall to be serious.
5. Four randomized trials reported on adverse events (AEs); however, AEs were typically only actively solicited from the RDA arm and not from the comparison or RACD arm. In the Zambia trial comparing RDA using dihydroartemisinin-piperaquine (DP) with RACD using artemether-lumefantrine (AL), 123 (6.9%) mild AEs occurred in 1,775 people treated with DP (Bridges 2021); all resolved. In the Namibia trial (Hsiang 2020) of RDA with AL compared to RACD with AL, 17 of 4,247 treated participants (0.4%) in the RDA arm experienced an AE versus 1 participant of 98 (1.0%) treated in the RACD arm; 11 AEs were considered unrelated, 6 possibly related, and 6 probably related. In The Gambia (Okebe 2021), 75 AEs (7.6%) among 979 participants receiving DP in the RDA arm reported AEs; 69 were considered mild and 6 moderate. In Eswati, 68 (3.8%) of 1,776 participants receiving RDA with DP experienced AEs; 54 were rated as mild and 14 as moderate.

6.3.2. Reactive case detection and treatment (RACDT)

Clinical question/ PICO

Population: Adults and children residing with or near a confirmed malaria case or having the same risk of acquiring infection as the index case in areas nearing elimination or in post-elimination settings

Intervention: Reactive case detection and treatment

Comparator: No RACDT

Summary

The systematic review identified three cRCTs in three countries of sub-Saharan Africa (Eswatini, Namibia and Zambia) (Steinhardt *et al unpublished evidence (d)*). However, all three studies were intended to evaluate the impact of RDA, and RACDT was the comparator. As RDA is likely to be a more effective strategy than RACDT, no conclusions could be drawn from these studies. The two NRSs identified from Brazil and Zambia reported on outcomes among those receiving the intervention, but did not evaluate impact at the community level.

Outcome Timeframe	**Study results and measurements**	**Comparator** No RACDT	**Intervention** Reactive case detection and treatment	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prevalence of parasitemia	Odds ratio 1.85 (CI 95% 0.96 — 3.57) Based on data from 3,926 participants in 1 studies. (Randomized controlled)	31 per 1000 Difference:	56 per 1000 **26 more per 1000** (CI 95% 1 fewer — 80 more)	Very low Due to very serious indirectness, and serious imprecision [1]	The evidence is very uncertain about the effect of RACDT on the prevalence of malaria
Incidence of clinical malaria	Rate ratio 1.3 (CI 95% 0.94 — 1.79) Based on data from 215,146 participants in 3 studies. (Randomized controlled)	9 per 1000 Difference:	12 per 1000 **3 more per 1000** (CI 95% 1 fewer — 17 more)	Very low Due to very serious indirectness, and serious imprecision [2]	The evidence is very uncertain about the effect of RACDT on the incidence of clinical malaria
Parasitemia prevalence among those receiving the intervention	Based on data from participants in 2 studies. (Observational (non-randomized))	Results from a difference-in-differences analysis of the Brazil study indicate a slight increase (by 0.8 percentage(%)-points, 3.8%-points, and 2.3%-points at 30, 60, and 180 days, respectively) in parasitemia over time in RACD households compared to control households. The Zambia study indicated a slight decrease (by 0.9%-points and 2.1%-points at 30 and 90 days after RACD, respectively) in parasitemia in RACD households, but no control households were included.		Very low Due to serious risk of bias, and serious inconsistency [3]	The evidence is very uncertain about the effect or RACDT on parasite prevalence among people who participate in RACDT.
Adverse events	Based on data from participants in 3 studies. (Randomized controlled)	Three randomized trials reported on adverse events (AEs); however, AEs were typically only actively solicited from the RDA arm and not from the RACD arm. In the Zambia trial comparing RACD using artemether-lumefantrine (AL) with RDA using dihydroartemisinin-piperaquine (DP) (Bridges 2021(16)), 123 (6.9%) mild AEs occurred in 1,775 people treated with DP (all resolved); no events were reported from the RACD arm. In the Namibia trial (Hsiang 2020(23)) of RACD with AL compared to RDA with AL, the authors reported that 1 participant of 98 (1.0%) treated in the RACD arm experienced an AE compared to 17 of 4,247 treated participants (0.4%) in the RDA arm; 11		Very low Due to very serious risk of bias, serious indirectness, and very serious imprecision [4]	The evidence is very uncertain about the effect of RACDT on adverse events.

Outcome Timeframe	**Study results and measurements**	**Comparator** No RACDT	**Intervention** Reactive case detection and treatment	**Certainty of the evidence** (Quality of evidence)	**Summary**
		AEs were considered unrelated, 6 possibly related, and 6 probably related. In the Eswati trial (Vilakati 2021(18)), no AEs were reported from participants who received AL in the RACD arm and 68 (3.8%) of 1,776 participants receiving RDA with DP were reported to experience AEs; 54 were rated as mild and 14 as moderate.			

1. **Inconsistency: no serious. Indirectness: very serious.** The study on which this effect estimate is based compared RACD to reactive drug administration (RDA), which is hypothesized to be a more effective intervention. Thus any effect favoring RACD (vs. RDA) is likely to be underestimated, and any effect favoring the comparison should not necessarily be interpreted as evidence that RACD has a harmful effect or no beneficial effect.. **Imprecision: serious.** The actual odds ratio for the effect size = 1.85 (95% CI: 0.96, 20.00) and is therefore quite imprecise, spanning no effect to a large harmful effect. (RevMan can only accommodate balanced confidence intervals but this effect size was calculated by study authors using non-linear model post-estimation combinations.).
2. **Inconsistency: no serious. Indirectness: very serious.** The studies on which this effect estimate is based all compared RACD to reactive drug administration (RDA), which is hypothesized to be a more effective intervention. Thus any effect favoring RACD (vs. RDA) is likely to be underestimated, and any effect favoring the comparison should not necessarily be interpreted as evidence that RACD has a harmful effect or no beneficial effect. **Imprecision: serious.** The pooled rate ratio spans no effect to a substantial absolute effect in a low-transmission setting.
3. **Risk of Bias: serious.** These data come from non-randomized studies. One of the studies has a before-and-after design with no control group. **Inconsistency: serious.** One study showed a slightly beneficial effect of RACD and the other study showed a slightly negative effect. **Indirectness: no serious. Imprecision: no serious.**
4. **Risk of Bias: very serious.** Two of the three studies included here focused adverse event reporting only in the RDA arm; in these studies no adverse events were reported from the RACD arm. **Indirectness: serious.** Two of the three studies included here focused adverse event reporting only in the RDA arm; in these studies no adverse events were reported from the RACD arm. **Imprecision: very serious.** We are unable to calculate an effect measure for AEs since they were measured in most studies only in the RDA arm.

6.3.3. Reactive indoor residual spraying

Clinical question/ PICO

Population: Adults and children residing with or near a confirmed malaria case in areas nearing elimination or in post-elimination settings

Intervention: Reactive indoor residual spraying

Comparator: no Reactive IRS

Summary

The systematic review identified two cRCTs in Namibia and South Africa (Gimnig *et al* *unpublished evidence*). The study from Namibia (superiority trial design) was conducted as a 2x2 factorial design with RACDT alone, RDA alone, RACDT plus RIRS, and RDA plus RIRS. The study from South Africa was designed as a non-inferiority trial comparing RIRS to standard IRS (used in defined priority areas) that reached one third of houses. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available in the Research evidence.

Beneficial outcomes

- RIRS results in a large reduction in the prevalence of malaria (RD: -27 per 1000 persons; 95% CI: -35 to -8 per 1000 persons; one cRCT [superiority design]; high-certainty evidence).
- RIRS may reduce the incidence of clinical malaria. However, the effects of RIRS on clinical malaria vary and it is possible that RIRS makes little or no difference (RD: -14 per 1000 p-y; 95% CI: -32 to 4 per 1000 p-y; one cRCT [superiority design]; moderate-certainty evidence).
- RIRS probably results in little to no difference in incidence of clinical malaria (mean difference: 0.1 per 1000 p-y; 95% CI: -0.38 to 0.59 per 1000 p-y; one cRCT [non-inferiority design]; moderate-certainty evidence).

Adverse events

- RIRS results in little to no difference in reported adverse events (RD: 2 per 1000 persons; 95% CI: -2 to 1 per 1000 persons; one cRCT [superiority design]; high-certainty evidence).
- RIRS results in little to no difference in serious adverse events (deaths) (one cRCT [non-inferiority design]; high-certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** no Reactive IRS	**Intervention** Reactive indoor residual spraying	**Certainty of the evidence** (Quality of evidence)	**Summary**
Prevalence of malaria (superiority trial) 7 Critical	Odds ratio 0.32 (CI 95% 0.15 — 0.8) Based on data from 4,082 participants in 1 studies. (Randomized controlled)	41 per 1000 Difference:	13 per 1000 **28 fewer per 1000** (CI 95% 35 fewer — 8 fewer)	High	Reactive IRS reduces malaria prevalence
Incidence of clinical malaria (superiority design) 9 Critical	Relative risk 0.65 (CI 95% 0.19 — 1.11) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	39 per 1000 Difference:	25 per 1000 **14 fewer per 1000** (CI 95% 32 fewer — 4 more)	Moderate Due to serious imprecision [1]	Reactive IRS probably reduces the incidence of clinical malaria
Adverse events (superiority trial)	Relative risk 0.48 (CI 95% 0.18 — 1.27) Based on data from 8,948 participants in 1 studies. (Randomized controlled)	3 per 1000 Difference:	1 per 1000 **2 fewer per 1000** (CI 95% 2 fewer — 1 more)	High	Reactive IRS results in little to no difference in adverse events
Serious adverse events (deaths, non-inferiority trial)	Relative risk 0.69 (CI 95% 0.29 — 1.6) Based on data from 393,387 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000	High	Reactive IRS results in little to no difference in serious adverse events (deaths) compared with standard IRS
Incidence of clinical malaria (non-inferiority design) 6 Important	High better Based on data from 0 participants in 1 studies. (Randomized controlled)	0 (Mean) Difference:	0.1 (Mean) **MD 0.1 higher** (CI 95% 0.38 lower — 0.59 higher)	Moderate Due to serious indirectness [2]	Reactive IRS probably results in little to no difference in incidence of clinical malaria compared with standard IRS

Outcome Timeframe	**Study results and measurements**	**Comparator** no Reactive IRS	**Intervention** Reactive indoor residual spraying	**Certainty of the evidence** (Quality of evidence)	**Summary**
Adverse Events 5 Important	Based on data from 0 participants in 2 studies. (Randomized controlled)	One study (Hsiang 2020) reported adverse events among persons receiving reactive IRS versus those not receiving reactive IRS. A total of 23 adverse events were reported among 18 participants. In the the reactive IRS arm, 6/4579 participants (0.13%) reported an adverse event compared to 12/4369 participants (0.27%) in the arm that received reactive case detection alone. None of the adverse events were considered related to IRS. In the study by Bath 2021, comparing reactive IRS versus standard IRS over two years, 9 deaths due to malaria were reported in the reactive IRS arm out of a population of 204,237. In the standard IRS arm, a total of 12 malaria deaths were reported out of a population of 189,150.		High	

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval of adjusted estimate overlaps 1. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: serious.** Study was designed as a non-inferiority study compared to standard IRS. **Imprecision: no serious. Publication bias: no serious.**

7. Surveillance

8. Methods

9. Glossary

10. Contributors and interests

10.1. Recommendations for vector control

10.2. Recommendations for chemoprevention

10.3. Recommendation for malaria vaccines

10.4. Recommendations for treatment

10.5. Recommendations for interventions in the final phase of elimination and prevention of re-establishment

For further information, contact:
Global Malaria Programme
World Health Organization
20 avenue Appia
1211 Geneva 27
Switzerland
Email: GMPinfo@who.int
Website: www.who.int/teams/global-malaria-programme