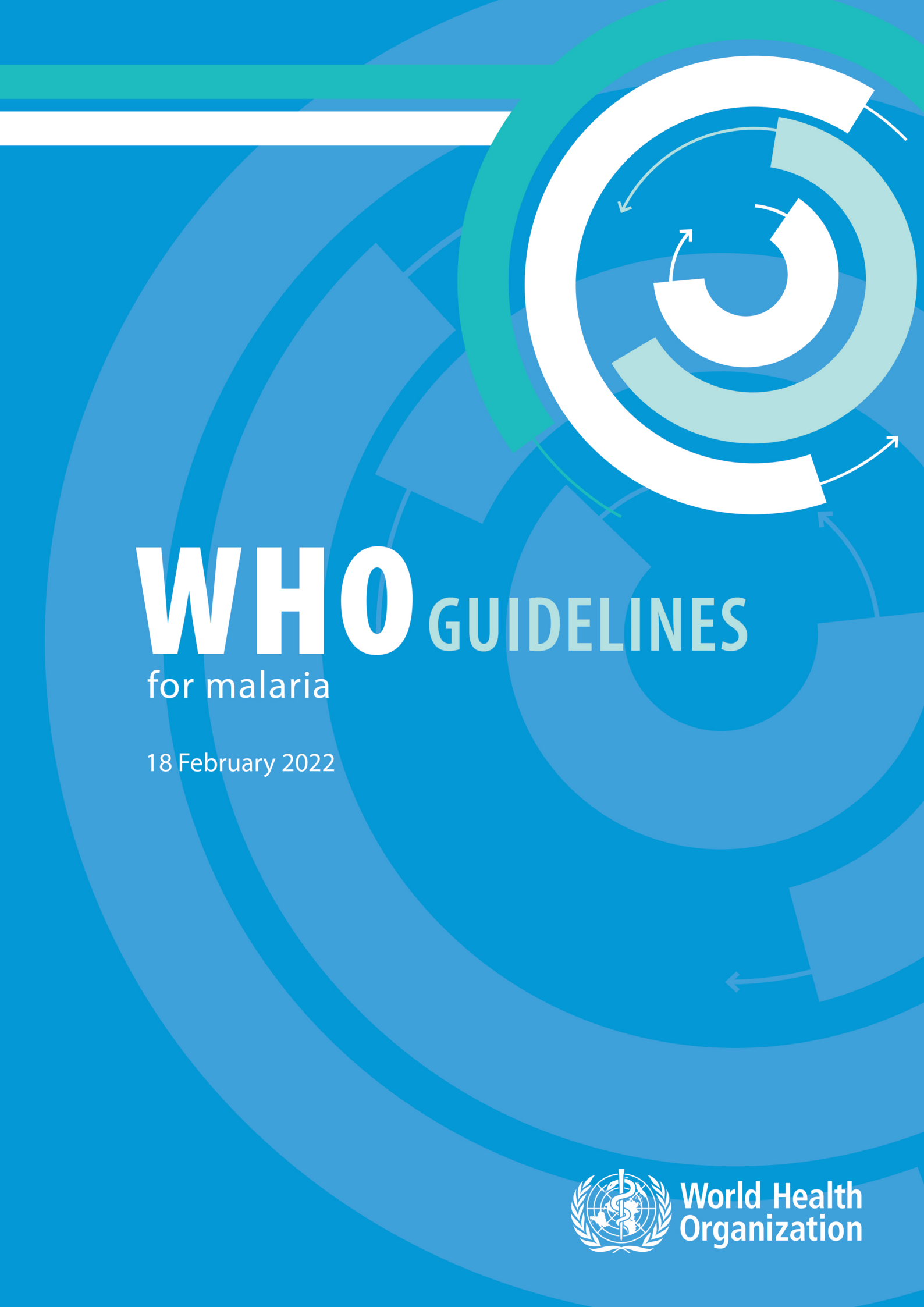

WHO GUIDELINES

for malaria

18 February 2022

World Health Organization

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WHO/UCN/GMP/2022.01

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Disclaimer

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Summary of recommendations

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2. EXECUTIVE SUMMARY

3. INTRODUCTION

4. PREVENTION

4.1 Vector control

4.1.1 Interventions recommended for large-scale deployment

Strong recommendation for , High certainty evidence

Pyrethroid-only nets (2019)

WHO recommends pyrethroid-only long-lasting insecticidal nets (LLINs) that have been prequalified by WHO for deployment for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission.

Remark: WHO recommends ITNs that have been prequalified by WHO for use in protecting populations at risk of malaria, including in areas where malaria has been eliminated or transmission interrupted but the risk of reintroduction remains.

ITNs are most effective where the principal malaria vector(s) bite predominantly at night after people have retired under their nets. ITNs can be used both indoors and outdoors, wherever they can be suitably hung (though hanging nets in direct sunlight should be avoided, as sunlight can affect insecticidal activity).

Conditional recommendation , Moderate certainty evidence

Pyrethroid-PBO nets (2019)

WHO conditionally recommends pyrethroid-PBO nets prequalified by WHO for deployment instead of pyrethroid-only ITNs for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission where the principal malaria vector(s) exhibit pyrethroid resistance that is: a) confirmed, b) of intermediate level, and c) conferred (at least in part) by a monooxygenase-based resistance mechanism, as determined by standard procedures.

Good practice statement

Achieving and maintaining optimal coverage with ITNs for malaria prevention and control (2019)

To achieve and maintain optimal ITN coverage, WHO recommends that countries apply mass free net distribution through campaigns, combined with other locally appropriate delivery mechanisms such as continuous distribution using antenatal care (ANC) clinics and the Expanded Programme on Immunization (EPI).

Recipients of ITNs should be advised (through appropriate communication strategies) to continue using their nets beyond the three-year expected lifespan of the net, irrespective of the condition and age of the net, until a replacement net is available.

Good practice statement

Management of old ITNs (2019)

WHO recommends that old ITNs should only be collected where there is assurance that: i) communities are not left without nets, i.e., new ITNs are distributed to replace old ones; and ii) there is a suitable and sustainable plan in place for safe disposal of the collected material.

If ITNs and their packaging (bags and baling materials) are collected, the best option for disposal is high-temperature incineration. They should not be burned in the open air. In the absence of appropriate facilities, they should be buried away from water sources and preferably in non-permeable soil.

WHO recommends that recipients of ITNs be advised (through appropriate communication strategies) not to dispose of their nets in any water body, as the residual insecticide on the net can be toxic to aquatic organisms (especially fish).

Strong recommendation for , Low certainty evidence

Indoor residual spraying (2019)

WHO recommends IRS using a product prequalified by WHO for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission

Remark:
DDT, which has not been prequalified, may be used for IRS if no equally effective and efficient alternative is available, and if it is used in line with the Stockholm Convention on Persistent Organic Pollutants.

IRS is considered an appropriate intervention where:

- 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 malaria transmission pattern is such that the population can be protected by one or two rounds of IRS per year;
- the majority of structures are suitable for spraying; and
- structures are not scattered over a wide area, resulting in high transportation and other logistical costs.

Good practice statement

Access to ITNs or IRS at optimal coverage levels (2019)

WHO recommends ensuring access to effective vector control using ITNs or IRS at optimal coverage levels for all populations at risk of malaria in most epidemiological and ecological settings.

4.1.2 Combining ITNs and IRS

Conditional recommendation against , Moderate certainty evidence

Prioritize optimal coverage with either ITNs or IRS over combination (2019)

WHO recommends against combining ITNs and IRS and that priority be given to delivering either ITNs or IRS at optimal coverage and to a high standard, rather than introducing the second intervention as a means to compensate for deficiencies in the implementation of the first intervention.

Remark:

In settings where optimal ITN coverage, as specified in the strategic plan, has been achieved and where ITNs remain effective, additionally implementing IRS may have limited utility in reducing malaria morbidity and mortality. Given the resource constraints across malaria-endemic countries, it is recommended that effort be focused on good-quality implementation of either ITNs or IRS, rather than deploying both in the same area. However, the combination of these interventions may be considered for resistance prevention, mitigation or management should sufficient resources be available.

Good practice statement

No scale-back in areas with ongoing local malaria transmission (2019)

In areas with ongoing local malaria transmission (irrespective of both the pre-intervention and current level of transmission), WHO recommends that vector control interventions should not be scaled back. Ensuring access to effective malaria vector control at optimal levels for all inhabitants of such areas should be pursued and maintained.

4.1.3 Supplementary interventions

Conditional recommendation , Low certainty evidence

Larviciding (2019)

WHO conditionally recommends the regular application of biological or chemical insecticides to water bodies (larviciding) for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission as a supplementary intervention in areas where optimal coverage with ITNs or IRS has been achieved, where aquatic habitats are few, fixed and findable, and where its application is both feasible and cost-effective.

Remark:
Since larviciding only reduces vector density, it does not have the same potential for health impact as ITNs and IRS – both of which reduce vector longevity and provide protection from biting vectors. As a result, larviciding should never be seen as a substitute for ITNs or IRS in areas with significant malaria risk but represents a potential supplementary strategy for malaria control. Larviciding will generally be most effective in areas where larval habitats are few, fixed and findable, and likely less feasible in areas where the aquatic habitats are abundant, scattered and variable.

The following settings are potentially the most suitable for larviciding as a supplementary measure implemented alongside ITNs or IRS:

- urban areas: where breeding sites are relatively few, fixed and findable in relation to houses (which are targeted for ITNs or IRS);
- arid regions: where larval habitats may be few and fixed throughout much of the year.

Larval habitat modification and/or larval habitat manipulation (2021)

No recommendation can be made because the evidence on the effectiveness of a specific larval habitat modification and/or larval habitat manipulation intervention for the prevention and control of malaria was deemed to be insufficient.

Larvivorous fish (2019)

No recommendation can be made because no evidence on the effectiveness of larvivorous fish for the prevention and control of malaria was identified.

Conditional recommendation against , Low certainty evidence

Topical repellents (2019)

WHO conditionally recommends against the deployment of topical repellents for the prevention and control of malaria at the community level in areas with ongoing malaria transmission.

Remark:
Further work is required to investigate the potential public health value of topical repellents to separate out potential effects at the individual and/or community level. Analysis conducted to date indicates that no significant impact on malaria can be achieved when the intervention is deployed at community-level due to the high level of individual compliance needed.

Conditional recommendation against , Low certainty evidence

Insecticide-treated clothing (2019)

WHO conditionally recommends against deployment of insecticide-treated clothing for the prevention and control of malaria at the community level in areas with ongoing malaria transmission; however, insecticide-treated clothing may be beneficial as an intervention to provide personal protection against malaria in specific population groups.

Remark: In the absence of insecticide-treated nets, there is some evidence that insecticide-treated clothing may reduce the risk of malaria infection in specific populations such as refugees and military; it is presently unclear if the results are applicable to the general population.

Spatial/Airborne repellents (2019)

No recommendation can be made because the evidence on the effectiveness of spatial/airborne repellents for the prevention and control of malaria was deemed to be insufficient.

Conditional recommendation against , Very low certainty evidence

Space spraying (2019)

WHO conditionally recommends against using space spraying for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission; IRS or ITNs should be prioritized instead.

Conditional recommendation , Low certainty evidence New

House screening (2021)

WHO conditionally recommends the use of untreated screening of residential houses for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission.

Remark:

This recommendation addresses the use of untreated screening of windows, ceilings, doors and/or eave spaces, and does not cover other ways of blocking entry points in houses.

4.1.4 Other considerations for vector control

4.1.4.1 Special situations

4.1.4.2 Implementation challenges

4.1.4.3 Monitoring and evaluation of vector control

4.1.5 Research needs

4.2 Preventive chemotherapies & Mass drug administration

4.2.1 Intermittent preventive treatment of malaria in pregnancy (IPTp)

Strong recommendation for , High certainty evidence

In malaria-endemic areas in Africa, provide intermittent preventive treatment with SP to all women in their first or second pregnancy (SP-IPTp) as part of antenatal care. Dosing should start in the second trimester and doses should be given at least 1 month apart, with the objective of ensuring that at least three doses are received.

4.2.2 Intermittent preventive treatment of malaria in infants (IPTi)

Strong recommendation for

In areas of moderate-to-high malaria transmission of Africa, where SP is still effective, provide intermittent preventive treatment with SP to infants (< 12 months of age) (SP-IPTi) at the time of the second and third rounds of vaccination against diphtheria, tetanus and pertussis (DTP) and vaccination against measles.

*unGRADEd recommendation, anticipated to be updated in 2022

4.2.3 Seasonal malaria chemoprevention (SMC)

Strong recommendation for , High certainty evidence

In areas with highly seasonal malaria transmission in the Sahel subregion of Africa, provide seasonal malaria chemoprevention (SMC) with monthly amodiaquine + SP for all children aged < 6 years during each transmission season.

4.3 Vaccine

Strong recommendation for , High certainty evidence New

The RTS,S/AS01 malaria vaccine should be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO.

Remark:

- The RTS,S/AS01 malaria vaccine should be provided in a four-dose schedule in children from 5 months of age.
- Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a five-dose strategy, in areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks.
- Countries that choose to introduce the vaccine in a five-dose seasonal strategy are encouraged to document their experiences, including adverse events following immunization.
- RTS,S/AS01 malaria vaccine should be provided as part of a comprehensive malaria control strategy.

5. CASE MANAGEMENT

5.1 Diagnosing malaria (2015)

Good practice statement

All cases of suspected malaria should have a parasitological test (microscopy or RDT) to confirm the diagnosis.

Both microscopy and RDTs should be supported by a quality assurance programme.

5.2 Treating uncomplicated malaria

5.2.1 Artemisinin-based combination therapy

Strong recommendation for , High certainty evidence

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following ACTs:

- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine–pyrimethamine (SP)
- artesunate + pyronaridine (currently unGRADEd, anticipated to be updated in 2022)

Remark:
Artesunate pyronaridine is included in the WHO list of prequalified medicines for malaria, the Model List of Essential Medicines and the Model List of Medicines for Children. The drug has also received a positive scientific opinion from the European Medicines Agency and undergone a positive review by the WHO Advisory Committee on Safety of Medicinal Products. Countries can consider including this medicine in their national treatment guidelines for the treatment of malaria based on WHO's position on the use of this drug pending the formal recommendation anticipated in 2021. WHO's position was published in the information note *The use of artesunate-pyronaridine for the treatment of uncomplicated malaria (122)* which clarifies that artesunate pyronaridine can be considered a safe and efficacious ACT for the treatment of uncomplicated malaria in adults and children weighing 5 kg and over in all malaria-endemic areas.

5.2.2 Duration of treatment

Strong recommendation for , High certainty evidence

Treating uncomplicated *P. falciparum* malaria (2015)
Duration of ACT treatment: ACT regimens should provide 3 days' treatment with an artemisinin derivative.

5.2.3 Dosing of ACTS

Strong recommendation for

Revised dose recommendation for dihydroartemisinin + piperaquine in young children: Children weighing <25kg treated with dihydroartemisinin + piperaquine should receive a minimum of 2.5 mg/kg bw per day of dihydroartemisinin and 20 mg/ kg bw per day of piperaquine daily for 3 days.

*unGRADEd recommendation, anticipated to be updated in 2022

5.2.4 Recurrent falciparum malaria

5.2.5 Reducing the transmissibility of treated P. falciparum infections in areas of low-intensity transmission

Strong recommendation for , Low certainty evidence

Reducing the transmissibility of treated *P. falciparum* infections: In low-transmission areas, give a single dose of 0.25 mg/kg bw primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. G6PD testing is not required.

5.3 Treating special risk groups

5.3.1 Pregnant and lactating women

Strong recommendation for

Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.

*unGRADEd recommendation, anticipated to be updated in 2022

5.3.2 Young children and infants

Strong recommendation for

Infants less than 5kg body weight (2015)
Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with ACT at the same mg/kg bw target dose as for children weighing 5 kg.

*unGRADEd recommendation, anticipated to be updated in 2022

5.3.3 Patients co-infected with HIV

Good practice statement

Patients co-infected with HIV (2015)
Patients co-infected with HIV: In people who have HIV/AIDS and uncomplicated *P. falciparum* malaria, avoid artesunate + SP if they are being treated with co-trimoxazole, and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.

5.3.4 Non-immune travellers

Strong recommendation for , High certainty evidence

Non-immune travellers (2015)
Treat travellers with uncomplicated *P. falciparum* malaria returning to non-endemic settings with ACT.

5.3.5 Uncomplicated hyperparasitaemia

Good practice statement

Hyperparasitaemia (2015)
People with *P. falciparum* hyperparasitaemia are at increased risk for treatment failure, severe malaria and death and should be closely monitored, in addition to receiving ACT.

5.4 Treating uncomplicated malaria caused by P. vivax, P. ovale, P. malariae or P. knowlesi

Good practice statement

Blood stage infection (2015)
If the malaria species is not known with certainty, treat as for uncomplicated.

Strong recommendation for , High certainty evidence

In areas with chloroquine-susceptible infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria with either ACT (except pregnant women in their first trimester) or chloroquine.

In areas with chloroquine-resistant infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria (except pregnant women in their first trimester) with ACT.

Strong recommendation for , Very low certainty evidence

Blood stage infection (2015)
Treat pregnant women in their first trimester who have chloroquine-resistant *P. vivax* malaria with quinine.

Good practice statement

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.

Strong recommendation for , High certainty evidence

To prevent relapse, treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) with a 14-day course of primaquine in all transmission settings.

Conditional recommendation , Very low certainty evidence

In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced haemolysis.

Good practice statement

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)
When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.

Conditional recommendation , Moderate certainty evidence

Pregnant and breastfeeding women: In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.

5.5 Treating severe malaria

5.5.1 Artesunate

Strong recommendation for , High certainty evidence

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT.

Strong recommendation for

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.

*unGRADEd recommendation based on pharmacokinetic modelling, anticipated to be updated in 2022

5.5.2 Parenteral alternatives when artesunate is not available

Conditional recommendation , Low certainty evidence

If artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.

5.5.3 Pre-referral treatment options

Strong recommendation for , Moderate certainty evidence

Where complete treatment of severe malaria is not possible, but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care. Where intramuscular artesunate is not available use intramuscular artemether or, if that is not available, use intramuscular quinine.

Where intramuscular injection of artesunate is not available, treat children < 6 years with a single rectal dose (10mg/kg bw) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults.

5.6 Other considerations in treating malaria

5.6.1 Management of malaria cases in special situations

5.6.2 Quality of antimalarial drugs

Good practice statement

Antimalarial drug quality (2015)
National drug and regulatory authorities should ensure that the antimalarial medicines provided in both the public and the private sectors are of acceptable quality, through regulation, inspection and law enforcement.

5.6.3 Monitoring efficacy and safety of antimalarial drugs and resistance

Good practice statement

All malaria programmes should regularly monitor the therapeutic efficacy of antimalarial drugs using the standard WHO protocols.

5.7 National adaptation and implementation

Good practice statement

The choice of ACTs in a country or region should be based on optimal efficacy, safety and adherence.

Good practice statement

National adaptation and implementation (2015)
Drugs used in IPTp, SMC and IPTi should not be used as a component of first- line treatments in the same country or region.

Good practice statement

National adaptation and implementation (2015)
When possible, use:

- fixed-dose combinations rather than co-blistered or loose, single-agent formulations; and
- for young children and infants, paediatric formulations, with a preference for solid formulations (e.g. dispersible tablets) rather than liquid formulations.

6. ELIMINATION

7. SURVEILLANCE

8. METHODS

9. GLOSSARY

10. CONTRIBUTORS AND INTERESTS

10.1 Guidelines for malaria vector control

10.2 Malaria vaccine recommendation

10.3 Guidelines for the treatment of malaria

1. ABBREVIATIONS

Anti-CS	Anti circumsporozoite antibody
ACT	artemisinin-based combination therapy
AE	Adverse Event
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
ANC	antenatal care
AVPU	Alert, Voice, Pain, Unresponsive
BCC	behaviour change communication
bw	body weight
CI	confidence interval
CIDG	Cochrane Infectious Diseases Group
DALY	disability adjusted life year
DHIS2	District Health Information Software 2
DTP	diphtheria, tetanus and pertussis (vaccine)
EIR	entomological inoculation rate
EPI	Expanded Programme on Immunization
EtD	evidence to decision framework
GDG	Guidelines Development Group
GMP	Global Malaria Programme
GPIRM	*Global plan for insecticide resistance management*
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTS	*Global technical strategy for malaria 2016 - 2030*
G6PD	glucose-6-phosphate dehydrogenase
HBHI	High burden to high impact approach
HRP2	histidine-rich protein 2
ICER	incremental cost-effectiveness ratio
IPTi	intermittent preventive treatment in infants
IPTp	intermittent preventive treatment in pregnancy
IRM	insecticide resistance management
IRS	indoor residual spraying
IOS	International Organization for Standardization
ITN	insecticide-treated net
ITPS	insecticide-treated plastic sheeting
IVB	WHO Department for Immunization, Vaccines and Biologicals
IVM	integrated vector management
LLIN	long-lasting insecticidal net
LSM	larval source management
M&E	monitoring and evaluation
MPAG	Malaria Policy Advisory Group *(previously Malaria Policy Advisory Committee)*
MVIP	WHO Malaria Vaccine Implementation Programme
NAAT	nucleic acid amplification test
NMP	national malaria programme
NSP	national (malaria) strategic plan
PBO	piperonyl butoxide
PCR	polymerase chain reaction
*Pf*HRP2	*Plasmodium falciparum* histidine-rich protein-2
PICO	population, participants or patients; intervention or indicator; comparator or control; outcome
PPC	preferred product characteristic
PQ	prequalification (WHO)
*p*LDH	*parasite*-lactate dehydrogenase
Pvdhfr	*Plasmodium vivax* dihydrofolate reductase gene
PYAR	person-years at risk
QC	quality control
RCT	randomized controlled trial
RDT	rapid diagnostic test
RR	relative risk, or risk ratio
SP	sulfadoxine–pyrimethamine
SP + AQ	sulfadoxine-pyrimethamine + amodiaquine
SMC	seasonal malaria chemoprevention
TES	therapeutic efficacy study
VCAG	Vector Control Advisory Group
VCTEG	Technical Expert Group on Malaria Vector Control
WHO	World Health Organization

2. EXECUTIVE SUMMARY

The consolidated *WHO Guidelines for malaria* present all of the current WHO recommendations for malaria. These are the product of careful evaluation following standardized methods as part of the WHO process for developing guidelines *(1)*. WHO uses strictly defined processes to assess the quality, consistency and completeness of evidence to determine the strength of each recommendation.

WHO malaria recommendations tend to be short, evidence-based statements. They are usually accompanied by supplementary statements which draw attention to contextual and implementation considerations that may influence the appropriateness and impact of a recommendation in different settings. Clearly distinguishing recommendations from their associated contextual considerations provides a degree of flexibility for national policymakers to adopt and adapt the strategies that are most appropriate in their settings.

This online platform and the associated PDF help to distinguish the formal recommendations from the supplementary statements. The Global Malaria Programme (GMP) will use this platform to produce "living guidelines", which can be updated more rapidly than printed documents as new evidence becomes available. The tabs below each recommendation enable users to access the research evidence and evidence-to-decision frameworks (EtD) that informed the recommendation. There is also a feedback tab where users are encouraged to provide input directly related to each intervention. The online platform contains links to other resources including guidance and information on: strategic use of information to drive impact; surveillance, monitoring and evaluation; operational manuals, handbooks and frameworks; and a glossary of terms and definitions.

Scope

The consolidated *WHO Guidelines for malaria* bring together all recommendations for malaria, including prevention using vector control, preventive chemotherapy and the vaccine; diagnosis, treatment and elimination strategies. The Guidelines also provide links to other resources including guidance and information on: strategic use of information to drive impact; surveillance, monitoring and evaluation; operational manuals, handbooks and frameworks; and a glossary of terms and definitions.

The Guidelines provide:

- evidence-based recommendations pertaining to vector control tools, technologies and approaches that are currently available for malaria prevention and control, and for which sufficient evidence on their efficacy is available to support systematic reviews. The Guidelines are intended to provide an underlying framework for the design of effective, evidence-based national vector control strategies and their adaptation to local disease epidemiology and vector bionomics;
- evidence-based recommendations on the use of antimalarial medicines as preventive chemotherapy in people living in malaria-endemic areas who are at risk of malaria morbidity and mortality. These approaches include intermittent preventive treatment (IPT) in pregnancy (IPTp), IPT in infants (IPTi) and seasonal malaria chemoprevention (SMC);
- evidence-based recommendations on the treatment of uncomplicated and severe malaria in all age groups and situations, including in young children and pregnant women; and
- guidance on strategies for elimination settings (recommendations are in development).

No guidance is given on the use of antimalarial agents to prevent malaria in people travelling from non-endemic settings to areas of malaria transmission. This is available in the WHO International travel and health guidance *(2)*.

WHO guidelines, recommendations and good practice statements

A WHO guideline is any document developed by WHO containing recommendations for clinical practice or public health practice or health policy. A recommendation informs the intended end-user what he or she can or should do in specific situations to achieve the best possible health outcomes, individually and/or collectively. It guides the choice among different interventions or measures to ensure a positive impact on health and implications for the use of resources.

In certain situations, good practice statements may be provided. These statements reflect the consensus of the Guidelines Development Group (GDG) that the benefits of adhering to the intervention or course of action are large and unequivocal, and do not need to be supported by a systematic evidence review or could be based on indirect evidence.

The primary purpose of these WHO Guidelines is to support policy-makers in ministries of health and the managers of national malaria control programmes in endemic countries to establish national policies and plans tailored to their local context.

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, including dossier review, consistency testing or performance evaluation and site visits to manufacturers. This information, in conjunction with other procurement criteria, is used by the United Nations (UN) 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 use.

Updating evidence-based guidance

The first edition of these consolidated Guidelines was published in February 2021 as a compilation of the existing recommendations for malaria vector control and treatment.

This current update includes the first ever WHO recommendation

on a malaria vaccine. This was based on a full evidence review of the RTS,S/AS01 malaria vaccine and advice from the Malaria Policy Advisory Group (MPAG) and the Strategic Group of Experts (SAGE) on Immunization following a joint session on 6 October 2021.

Areas currently under review for chemotherapy include recommendations already in the Guidelines for which the evidence was previously not subjected to the GRADE process, along with updates on the use of antimalarial medicines in special risk populations including pregnant women. These updates will be presented to the GRC as they become available in 2022.

Readers should note the dates of individual recommendations. Revisions to this guidance will be communicated via the GMP website and through WHO's standard dissemination channels. These consolidated Guidelines represent the latest and definitive reference for all WHO guidance on malaria.

Dissemination

These consolidated *WHO Guidelines for malaria* are available on the MAGICapp online platform, linked to the WHO malaria website. The original English version has been translated into French and will be translated into two additional languages (Spanish and Arabic). All research evidence and references are available on the web platform and will be available to download, and relevant implementation guidance will be linked to the recommendations. When recommendations are updated, they will be labelled as such and will always display the date of the most recent update. Each time there is an update, an updated PDF version of the Guidelines will be downloadable on the WHO GMP website to facilitate access where the Internet is not reliably available. Users should note that older downloaded PDFs of the Guidelines may be outdated and may not contain the latest recommendations.

WHO Headquarters will work closely with its regional and country offices to ensure the wide dissemination of the Guidelines to all malaria endemic countries. There will also be dissemination through regional, sub-regional and country meetings. Member States will be supported to adapt and implement these Guidelines.

Feedback

GMP welcomes feedback, either via the tab associated with each recommendation or by e-mail to gmpfeedback@who.int, to help identify recommendations in need of update or development.

3. INTRODUCTION

Background

Malaria continues to cause unacceptably high levels of disease and death, as documented in successive editions of the *World malaria report (3)*. According to the latest report, there were an estimated 241 million cases and 627 000 deaths globally in 2020. Malaria is preventable and treatable, and the global priority is to reduce the burden of disease and death while retaining the long-term vision of malaria eradication. Here, we present the *WHO Guidelines for malaria* developed by the WHO Global Malaria Programme (GMP) as a comprehensive and inclusive resource for advice on malaria.

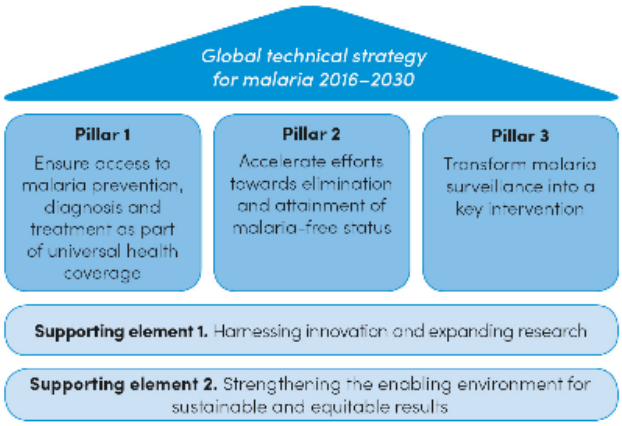
The *Global technical strategy for malaria 2016–2030 (4)* (GTS) provides an overarching framework to guide malaria control and elimination efforts. Adopted by the World Health Assembly in May 2015 and update adopted in May 2020, the Strategy defines goals, milestones and targets on the path to a world free of malaria (Table 1). The goals focus attention on the need to both reduce morbidity and mortality, and to progressively eliminate malaria from countries that had malaria transmission in 2015. The GTS presents a framework through which the goals can be achieved (Table 1).

Table 1. Goals, milestones and targets for the *Global technical strategy for malaria 2016–2030*

GOALS	MILESTONES		TARGETS
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

The GTS *(4)* states that it is essential for malaria programmes to 'ensure access to malaria prevention, diagnosis and treatment as part of universal health coverage' (Fig.1 - Pillar 1). Universal health coverage (UHC) means that 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. For malaria, WHO has recommended a range of interventions namely, vector control, chemoprevention, diagnostic testing and treatment to reduce transmission and prevent morbidity and mortality. A UHC approach means ensuring that individuals and communities are covered by the appropriate mix of these interventions, based on local context, to control and ultimately eliminate malaria.

Fig. 1: Global technical strategy for malaria 2016 - 2030: framework, pillars and supporting elements



The principal objective of national malaria programmes (NMPs) is to combine a selection of these interventions into packages that are tailored to achieve sustainable and equitable impact in a given setting. To decide upon the appropriate intervention package and allocation of resources that will achieve this objective and contribute to UHC, programmes should use a process that combines the analysis of impact and value for money with extensive stakeholder engagement and discussion. The process should be informed by past and current malaria transmission intensity and incidence data; contextual vulnerability related to the human host, parasites, vectors, and past and present intervention coverage; acceptability; and equality of access and use (including analysis of financial barriers and how to address them). When the objective is elimination, a similar process is undertaken although the types of interventions and value for money analysis will be different than in high-burden settings.

Following progressive reductions in malaria burden between 2000 and 2015, progress stalled. By 2017, the world was off track to achieve the malaria morbidity and mortality reduction targets. In response, a revitalization effort called "High burden to high impact (HBHI)" was launched in 2018 *(5)*. This approach focuses attention on how to get back on track: garnering political will to reduce the toll of malaria; using strategic information to drive impact; developing better guidance, policies and strategies; and improving coordination of support for national malaria responses. Although the impetus for articulating these key activities was the need to get back on track to achieve the GTS morbidity and mortality targets, these activities apply equally well to all malaria-endemic countries and to ensure continued progress towards the GTS elimination goals.

Objectives

These consolidated *WHO Guidelines for malaria* aim to provide the latest evidence-based recommendations in one reference to support countries in their efforts to reduce and ultimately eliminate malaria. The objectives of the Guidelines are:

- to provide evidence-based and context-sensitive recommendations on the appropriate choice(s) for malaria prevention (vector control and chemotherapies) and case

management (diagnosis and treatment) across all transmission settings;
- to support the development by WHO Member States of evidence-based national malaria policies for prevention and case management across all transmission settings;
- to encourage the use of local data to inform subnational stratification to maximize the impact of available resources; and
- to inform the research agenda to enable updates to the Guidelines by identifying gaps in evidence that constrain the development of guidance or weaken current recommendations.

Evidence base

These Guidelines are based on the synthesis of the available evidence on the health effects of interventions, and the grading of the certainty of that evidence using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. The synthesized and graded evidence on the health effects of interventions, as well as any evidence on contextual factors, is used to develop an evidence-to-decision (EtD) framework for each recommendation *(6)*. The judgement of the different factors in the EtD framework (including the certainty of evidence) facilitates the determination of the strength and direction of each recommendation.

Expert input is important for the interpretation of the evidence, and the development of guidance may rely on expert opinion, particularly in areas where the evidence is currently weak, scarce or absent. For example, the vector control recommendations presented in the Guidelines are based on a consideration of the evidence gained from randomized controlled trials (RCTs) and other types of trials and studies, as well as the technical knowledge and experience of the GDG and External Review Group involved in the standard guideline development process. Details of how evidence is considered are presented in Section 8: Methods. Details of contributors for specific recommendations are presented in Section 10: Contributors and interests.

Target audience

The primary audience for these guidelines is policy-makers in ministries of health and the managers of NMPs in endemic countries. The Guidelines may also be of interest to health care practitioners, environmental health service professionals, procurement agencies, the private sector, and civil society groups. The Guidelines are also intended for use by international development partners, donors and funding agencies in order to support decision-making on allocation of resources for interventions and procurement of appropriate malaria control products. In addition, the Guidelines are intended to guide researchers, research funders and those interested in the outcomes of research to address the evidence gaps that are constraining the development of guidance or weakening current recommendations.

Etiology

Malaria is a life-threatening disease caused by the infection of red blood cells with protozoan parasites of the genus *Plasmodium* that are transmitted to people through the bites of infected female *Anopheles* mosquitoes. Four species of *Plasmodium* (*P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*) most commonly infect humans. *P. falciparum* and *P. vivax* are the most prevalent species and *P. falciparum* is the most dangerous. A fifth species, *P. knowlesi* (a species of *Plasmodium* that primarily infects non-human primates) is increasingly being reported in humans inhabiting forested regions of some countries of South-East Asia and the Western Pacific regions, and in particular on the island of Borneo.

Malaria transmission, acquisition of immunity, and clinical manifestations of disease

The intensity of transmission depends on factors related to the parasite, the vector, the human host and the environment. Transmission tends to be more intense in places where the mosquito lifespan is longer and where the females prefer to bite humans rather than other animals. The survival and longevity of female mosquitoes is of critical importance in malaria transmission, as the malaria parasite generally requires a period of 7–10 days to develop inside the mosquito into a form that is infective to humans. Female mosquito longevity is dependent on intrinsic, genetic factors, as well as on environmental factors including temperature and humidity. The strong human-biting habit of the African vector species is one of the reasons why approximately 90% of the world's malaria cases occur in Africa.

Transmission intensity is usually assessed as the incidence of cases or the prevalence of infection. Most countries have information on the annual parasite incidence (number of new parasitologically confirmed malaria cases per 1000 population per year) from routine surveillance and/or on the parasite prevalence from surveys, often conducted during or just after periods of peak transmission *(7)*.

The following categories of transmission intensity are indicative and meant to provide an adaptable framework in which each country can conduct a stratification exercise to classify geographical units according to local malaria transmission.

- Areas of high transmission are characterized by an annual parasite incidence of about 450 or more cases per 1000 population and a *P. falciparum* prevalence rate of ≥35%.
- Moderate transmission areas have an annual parasite incidence of 250–450 cases per 1000 population and a prevalence of *P. falciparum*/*P. vivax* malaria of 10–35%.
- Areas of low transmission have an annual parasite incidence of 100–250 cases per 1000 population and a prevalence of *P. falciparum*/*P. vivax* of 1–10%. It should be noted that the incidence of cases or infections is a more useful measure in geographical units in which the prevalence is low, given the difficulty of measuring prevalence accurately at low levels *(8)*.
- Very low transmission areas have an annual parasite incidence of < 100 cases per 1000 population and a prevalence of *P. falciparum*/*P. vivax* malaria that is > 0 but < 1%.

The relation between parasite incidence, parasite prevalence and the number of cases presenting to health facilities per week can be estimated using models *(9)*. Differences in transmission from one area to another may be due to geographical characteristics, such as altitude, temperature, humidity, rainfall patterns, proximity

to water bodies, land use, vector species and distribution, socio-demographic characteristics, access to antimalarial treatment, and coverage with vector control. In most endemic areas, seasonal patterns of transmission are observed, with high transmission during part of the year. Both the intensity and timing of transmission are important considerations in designing elimination strategies.

The manifestation of clinical disease depends strongly on the background level of acquired protective immunity, which is a consequence of the pattern and intensity of malaria transmission in the area of residence. In areas of moderate to high transmission, partial immunity to clinical disease and a reduced risk of developing severe malaria are acquired in early childhood. The pattern of acquired immunity is similar across the Sahel subregion, where malaria transmission is intense only during the three- or four-month rainy season and low at other times. In both these situations, clinical disease is confined mainly to young children, who may develop high parasite densities that can progress rapidly to severe malaria. By contrast, in these settings, adolescents and adults are partially immune and suffer clinical disease much less frequently, although they are often infected with low blood-parasite densities. Immunity is modified in pregnancy and gradually lost, at least partially, when individuals move out of the endemic areas for prolonged periods (e.g., a year or more).

In areas of low and very low transmission, as found in much of Asia, Latin America and other malaria-endemic areas, the transmission fluctuates widely by season, year, and over relatively small distances. *P. vivax* is an important cause of malaria in these regions. This generally low transmission delays acquisition of immunity, so that adults and children alike suffer from acute clinical malaria, with a significant risk for progression to severe malaria if left untreated. Epidemics may occur in these low or very low transmission areas when the inoculation rate increases rapidly because of a sudden increase in vectorial capacity. Epidemics may result in a very high incidence across all age groups, which can overwhelm health services.

In moderate and high transmission areas with sustained high coverage of vector control and access to treatment, reduced exposure to malaria infection may change the population structure of acquired immunity to reflect that found in low or very low transmission areas, resulting in a corresponding change in the clinical epidemiology of malaria and an increasing risk of epidemics if control measures are not sustained.

Recommendations and supporting implementation guidance

Evidence-informed recommendations are a critical component to support the development of national malaria strategic plans; they are intended to communicate “what to do”. A second critical element is the strategic use of local data. This informs an understanding of the contextual diversity within each malaria-endemic country. Local data provide an understanding of the different types of settings – or strata – within each country. This is an essential prerequisite to identify the optimal mix of interventions and the best means to deliver them in the different subnational strata.

GMP is working with countries to strengthen the generation and use of local information for stratification, the definition of optimal mixes of interventions, and the rational, safe and ethical prioritization of resources to maximize impact. Local data are also essential to understand the impact of the strategies deployed, providing opportunities to further refine sub-national strategies and inform global knowledge.

WHO also develops implementation guidance such as operational and field manuals to support the “how” aspect of delivering the recommended tools and strategies. Operational manuals and other guidance hold practical information for increasing the target population's access to interventions. These documents are referenced and linked to these Guidelines. GMP is working to align this implementation guidance with the recommendations in the *WHO Guidelines for malaria*. However, where there are inconsistencies, the Guidelines should be the default resource for national decisions. Countries may use the implementation guidance to define ways in which a recommendation can be implemented effectively – for example, intermittent preventive treatment for malaria in pregnancy could be implemented through antenatal care and/or community distribution. The intention of the guidance is to enable delivery, not to prescribe exactly how it should be done.

Strategic information to tailor programmatic response and selection of interventions

As malaria control improves, malaria transmission and risk become increasingly heterogeneous, both between and within countries. Thus, a “one-size-fits all” approach to programme decisions on intervention selection becomes inefficient. The situation requires stratification of the country at subnational levels according to past, present and future malaria risk, the structure and function of the health system, and other contextual factors. Stratification provides a rational basis to identify context-specific packages of interventions to target specific populations in the different subnational strata. Local data are essential to complete stratification and to inform the selection of the optimal mixes of interventions to maximize impact. Given that resource constraints usually limit the implementation of all desirable interventions in all areas of malaria risk, a prioritization exercise must also be conducted to ensure that resource allocation also optimizes intervention mixes and resultant impact. Guidance on these activities is available in Section 7: Surveillance.

The choice of interventions in each stratum should be informed by WHO’s recommendations. However, given the complexities of malaria, with heterogeneity of risk and the unique contexts that every programme has to consider, global guidance is not intended and should not be used to provide prescriptive guidance on what should be done in every situation. These Guidelines signal a paradigm shift towards a problem-solving approach using local data to identify recommendations that are relevant at a country level and based on local context, defining stratum-specific packages of interventions that optimize impact and are prioritized for resource allocation. This shift moves away from overly prescriptive recommendations and will clearly distinguish evidence-informed recommendations from contextual considerations. The contextual considerations at national and subnational levels will inform how recommendations should be

applied and strategies that may increase access for the target population.

Accurate stratification of malaria transmission intensity is essential for effective targeting of interventions. As countries progress towards elimination, finer scale mapping is required, and stratification should be more specific, ideally at the level of localities or health facility catchment areas *(10)(11)*. As transmission intensity is progressively reduced, stratification needs to include vulnerability and receptivity to malaria, i.e., the risk for importation of malaria cases and the inherent potential of the vector-human ecosystem to transmit malaria.

Conclusion

These Guidelines therefore provide a framework within which NMPs and their implementing partners may adopt and adapt the recommendations for use. Good quality surveillance data can also feed into this process by providing the granular local information needed to inform and evaluate national programme decisions (see Section 7: Surveillance). Where the boundaries of current knowledge are pushed, it is particularly important to ensure adequate attention to monitoring and evaluation. The information generated can then feed into updated guidance.

4. PREVENTION

Nearly half of the world's population is at risk of malaria. In areas with high malaria transmission, young children and pregnant women are particularly vulnerable to malaria infection and death. Since 2000, expanded access to WHO-recommended malaria prevention tools and strategies – including effective vector control and the use of preventive chemotherapies – has had a major impact in reducing the global burden of this disease.

4.1 Vector control

Background

The Guidelines commence by providing general recommendations on malaria vector control, followed by more specific recommendations on individual interventions and good practice statements on their deployment. The interventions are divided into categories of those recommended for large-scale deployment and those recommended as supplementary. Interventions that are recommended for large-scale deployment are those that have demonstrated public health value, i.e., have proven protective efficacy to reduce or prevent infection and/or disease in humans at the community level, and - in the case of insecticide treated nets (ITNs) - at the individual level, and that are broadly applicable for populations at risk of malaria in most epidemiological and ecological settings. Supplementary interventions are those with conditional recommendations that may be applicable for specific populations, situations or settings. These include personal protection measures that have a primary use-pattern of protecting individual users, although they may have some as yet unproven impact when deployed at the community level.

Vectors, their behaviour and distribution

Malaria is transmitted through the bites of infective female *Anopheles* mosquitoes. There are more than 400 different species of *Anopheles* mosquitoes, of which around 40 are malaria vectors of major importance. *Anopheles* mosquitoes lay their eggs in water. The eggs hatch to produce larvae, which undergo several moults before emerging from the pupal stage as adult mosquitoes. Different species of *Anopheles* mosquito have their own preferred aquatic habitats; for example, some prefer small, shallow collections of fresh water such as puddles and animal hoof prints, whereas others prefer large, open water bodies including lakes, swamps and rice fields.

Immediately after emerging from the pupal stage, mosquitoes rest on the water surface until their wings have fully expanded and hardened. After taking an initial meal of plant nectar, female mosquitoes seek a blood meal, as they require protein to develop their eggs. In the majority of species of *Anopheles*, the females feed on warm-blooded animals, usually mammals. Different mosquito species demonstrate preferences for feeding on animals (zoophily) or on humans (anthropophily); however, these preferences are not absolute, and females may take a blood meal from a non-preferred host when these are present in the area. Blood-feeding can take place inside human habitations (endophagy) or outdoors (exophagy), depending on the mosquito species. Several factors have been implicated in the attraction of female mosquitoes to a host, including exhaled carbon dioxide, lactic acid, host odours, warmth and moisture. Different host individuals may be more or less attractive to mosquitoes than other individuals of the same species.

Female *Anopheles* mosquitoes feed predominantly at night, although some species may bite during the day in heavily shaded conditions, and some exhibit a peak in biting activity in the early evening or early morning. The interplay between the peak biting time of the *Anopheles* vector and the activity and sleeping patterns of the human host has important consequences for malaria transmission and the choice of appropriate vector control interventions.

After blood-feeding, female mosquitoes rest in order to digest the blood meal and mature their eggs. Female mosquitoes may rest indoors (endophily) or outdoors (exophily), and this depends on innate species preferences as well as the availability of suitable resting sites in the local environment. The mosquitoes' choice of post-feeding resting site also has major implications for the selection of control interventions.

It is important to note that while an individual species of *Anopheles* will characteristically exhibit certain biting and resting behaviours, these are not absolute; subpopulations and individuals may exhibit different behaviours depending on a combination of intrinsic genetic factors, availability of preferred hosts and availability of suitable resting sites. Environmental and climatic factors, including rainfall, moonlight, wind speed, etc., as well as the deployment of vector control interventions can all influence biting and resting behaviours. For example, the highly efficient African malaria vector *Anopheles gambiae s.s.* is generally considered to be human-biting, indoor-biting and indoor-resting, but it can also exhibit more zoophilic and exophagic tendencies. *Anopheles arabiensis* is a species that generally exhibits an outdoor biting and resting habit, but may exhibit indoor biting and resting tendencies, depending on the availability of alternative hosts.

Accurate species identification is crucial for all studies and surveillance activities on field populations of vectors. Many of the vectors belong to species complexes and require advanced molecular analyses for species identification, necessitating appropriate laboratory resources. Without accurate species identification, the data collected on behaviour, distribution and infection rates will have limited use for decision-making by control programmes.

Background and rationale for vector control

The role of arthropods in the transmission of diseases to humans

was first elucidated in the late 19th and early 20th centuries. Since effective vaccines or drugs were not always available for the prevention or treatment of these diseases, control of transmission often had to rely principally on control of the vector. Early control activities included the screening of houses, the use of mosquito nets, the drainage or filling of swamps and other water bodies used by insects for breeding, and the application of oil or Paris green to breeding places. Following the discovery of the insecticidal properties of dichlorodiphenyltrichloroethane (DDT) in the 1940s and subsequent discovery of other insecticides, the focus of malaria vector control shifted to the deployment of insecticides to target both the larval and adult stages of mosquito vectors.

Nowadays, it is well established that effective vector control programmes can make a major contribution to advancing human and economic development. Aside from direct health benefits, reductions in vector-borne diseases enable greater productivity and growth, reduce household poverty, increase equity and women's empowerment, and strengthen health systems *(12)*. Despite the clear evidence in broad support of vector control efforts, the major vector-borne diseases combined still account for around 17% of the estimated global burden of communicable diseases, claiming more than 700 000 lives every year *(13)*. Recognizing the great potential to enhance efforts in this area, WHO led the development of the *Global vector control response 2017–2030 (13)*, which is outlined in the subsequent section.

The control of malaria, unlike that of most other vector-borne diseases, saw a major increase in financial resources from 2000 to about 2010, leading to a significant reduction in the global burden. However, since 2010, total malaria funding has largely stagnated. Moreover, the funding gap between the amount invested and the resources needed has continued to widen significantly in recent years, largely as a result of population growth and the need to switch to more expensive tools. This gap increased from US$ 1.3 billion in 2017 to US$ 2.3 billion in 2018, and to US$ 2.6 billion in 2019 *(3)*.

Between 2000 and 2015, the infection prevalence of *Plasmodium falciparum* in endemic Africa was halved and the incidence of clinical disease fell by 40% *(14)*. Malaria control interventions averted an estimated 663 million (credible interval (CI) 542–753 million) clinical cases in Africa, with ITNs making the largest contribution (68% of cases averted). Indoor residual spraying (IRS) contributed an estimated 13% (11–16%), with a larger proportional contribution where intervention coverage was high *(14)*.

Global vector control response 2017–2030

The vision of WHO and the broader infectious diseases community is a world free of human suffering from vector-borne diseases. In 2017, the World Health Assembly welcomed the *Global vector control response 2017–2030 (13)* (GVCR) and adopted a resolution to promote an integrated approach to the control of vector-borne diseases. The approach builds on the concept of integrated vector management (IVM), but with renewed focus on improved human capacity, strengthening infrastructure and systems, improved surveillance, and better coordination and integrated action across sectors and diseases.

The ultimate aim of the GVCR is to reduce the burden and threat of vector-borne diseases through effective, locally adapted, sustainable vector control in full alignment with Sustainable Development Goal 3.3: to end epidemics of malaria by 2030. The 2030 targets are: to reduce mortality due to vector-borne diseases globally by at least 75% (relative to 2016); to reduce case incidence due to vector-borne diseases globally by at least 60% (relative to 2016); and to prevent epidemics of vector-borne diseases in all countries. Detailed national and regional priority activities and associated interim targets for 2017–2022 have also been defined.

Priority activities set out in the GVCR fall within four pillars that are underpinned by two foundational elements:

Pillars of action:

- Strengthen inter- and intra-sectoral action and collaboration.
- Engage and mobilize communities.
- Enhance vector surveillance, monitoring and evaluation of interventions.
- Scale up and integrate tools and approaches.

Foundations:

- Enhance vector control capacity and capability.
- Increase basic and applied research, and innovation.

Effective and sustainable vector control is achievable only with sufficient human resources, an enabling infrastructure and a functional health system. National programmes should lead a vector control needs assessment across the relevant sectors *(15)* to help appraise current capacity, define the requisite capacity to conduct proposed activities, identify opportunities for improved efficiency in vector control delivery, and guide resource mobilization to implement the national strategic plan.

In some settings, vector control interventions have the potential to reduce transmission and disease burden of more than one disease. Examples include the deployment of ITNs against malaria and lymphatic filariasis (in settings where *Anopheles* mosquitoes are the principal vector), against malaria and leishmaniasis in India, and larval control for malaria and dengue vectors in cities with particular vector habitats. With the recently documented invasion of *Anopheles stephensi* in the Horn of Africa, the integrated surveillance and control of this vector alongside *Aedes* provides a clear opportunity for GVCR implementation. More approaches effective against *Aedes* spp. mosquitoes generally have the potential to impact dengue, chikungunya, Zika virus disease and possibly yellow fever where their vectors and distributions overlap.

Prevention, mitigation and management of insecticide resistance

Widespread and increasing insecticide resistance poses a threat to effective malaria vector control. Failure to mitigate and manage insecticide resistance is likely to result in an increased burden of disease, potentially reversing some of the substantial gains made in controlling malaria over the last decade.

WHO maintains a global insecticide resistance database and an online mapping tool that consolidate information on the status of the insecticide susceptibility of *Anopheles* mosquitoes in malaria-endemic countries *(16)*. The latest data revealed that almost 90% of the malaria-endemic countries reporting insecticide resistance have detected resistance of their vectors to at least one insecticide class. Globally, resistance to pyrethroids is widespread, having been detected in at least one malaria vector in 70% of the sites for which data were available. Resistance to organochlorines was reported in 63% of the sites. Resistance to carbamates and organophosphates was less prevalent, detected in 32% and 35% of the sites that reported monitoring data, respectively *(3)*.

To date, there is no evidence of operational failure of vector control programmes as a direct result of increasing frequency of pyrethroid resistance *(17)(18)*. Based on past experience, however, it is likely that operational failure will eventually occur if effective insecticide resistance management (IRM) strategies are not designed and implemented. Ideally, such strategies should be implemented early to prevent spread and increase in the intensity of resistance. The overarching concepts of such resistance management strategies were outlined in the *Global plan for insecticide resistance management in malaria vectors* (GPIRM) in 2012 *(19)*.

Guidance on monitoring of insecticide resistance, interpretation of test results interpretations and implications for decision-making are given in the WHO Test procedures for monitoring insecticide resistance in malaria vector mosquitoes *(20)* and in the Framework for a national plan for monitoring and the management of insecticide resistance in malaria vectors *(21)*. When deciding whether adjustments to the national malaria strategic plan are required in a given area, at least the following must be considered for that locality:

- current and past transmission levels;
- current and past interventions deployed, including the coverage, usage and duration of efficacy;
- the insecticide resistance profile of the main vector species (including resistance intensity and resistance mechanisms); and
- other entomological information including vector species distribution, abundance, and other bionomic data.

The susceptibility of mosquitoes to insecticides and determination of the species-specific presence, intensity and mechanisms of resistance in vector populations can be used to guide the selection of the most appropriate insecticidal products to deploy. Generally, if mosquitoes are found to be resistant to an insecticide, insecticides with a different mode of action should be deployed. However, there are reports of mosquitoes having differential susceptibility to insecticides within the same class, and questions have been raised about the level of cross-resistance between pyrethroid products *(19)*. The Global Fund recently commissioned a review of the interpretation of insecticide resistance assays when selecting insecticidal products *(22)*. The review aimed to answer the question: in areas where pyrethroid resistance exists, but mosquitoes of the same population differ in their susceptibility to different pyrethroids, should programmes consider selecting one pyrethroid over another in order to manage insecticide resistance? Based on a review of evidence from molecular, laboratory and field data, the authors concluded that differences between adult mosquito mortalities in pyrethroid insecticide resistance assays are not indicative of a true or operationally relevant difference in the potential performance of pyrethroids currently in common use (deltamethrin, permethrin, α-cypermethrin and λ-cyhalothrin). Consequently, switching between pyrethroid insecticides (to improve intervention efficacy) should not be used as a means of managing insecticide resistance. This finding supports WHO's past and present position. Given that pyrethroid resistance in mosquitoes is widespread, WHO encourages the development and continued evaluation of nets treated with alternative insecticides *(23)*.

Key technical principles for addressing insecticide resistance are as follows:

- Insecticides should be deployed with care and deliberation in order to reduce unnecessary selection pressure and maximize impact on disease. National malaria programmes should consider whether they are using insecticides judiciously, carefully and with discrimination, and if there is a clear epidemiological benefit.
- Vector control programmes should avoid using a single class of insecticide everywhere and over consecutive years. Whenever possible, vector control programmes should diversify from pyrethroids to preserve their effectiveness. Although pyrethroids will continue to be used for ITNs in the near term, they should not generally be deployed for IRS in areas with pyrethroid ITNs, whether alone or combined with insecticides from a different class.
- IRM principles and methods should be incorporated into all vector control programmes, not as an option, but as a core component of programme design.
- National malaria programmes should engage with the agricultural sector to coordinate insecticide use, with the aim of avoiding use of the same classes of insecticide for both crop protection and public health within the same geographical area.
- Routine monitoring of insecticide resistance is essential to inform the selection and deployment of insecticides.
- The additional costs of deploying new vector control tools as part of a comprehensive IRM response should be balanced against the potential long-term public health impact. Where feasible formal economic evaluation is encouraged to investigate the likely incremental costs and effectiveness of potential IRM approaches, relative to feasible alternatives, for a given context.

Approaches

Historically, the most common way insecticides have been deployed to control malaria vectors has been through "sequential use". In essence, this is when a single insecticide class is used continuously or repeatedly until resistance has rendered it less effective or ineffective, after which a switch is made to an insecticide with a different mode of action to which there is no (or less) resistance. In theory, this may allow for an eventual switch back to the original insecticide class if resistance decreases to the point that it is no longer detectable by means of bioassays.

The agricultural industry has had some success in managing resistance by using different insecticides over space and time. Similar approaches have been proposed with the aim of preventing or delaying the spread and increase of resistance by removing selection pressure or by killing resistant mosquitoes. However, there is no empirical evidence of the success of these strategies for malaria vector control, which is likely to depend on mosquito genetics, behaviour and population dynamics, and the chemical nature of the insecticides and their formulation. These strategies include mixtures of insecticides, mosaic spraying, rotations of insecticides and deployment of multiple interventions in combination.

- Mixtures are co-formulations that combine two or more insecticides with different modes of action. Mixtures are widely used as drug treatments in co-formulated combination therapy. Effective deployment of a mixture requires the presence of resistance to all insecticides in the mixture to be rare, so that any individual mosquito that survives exposure to one insecticide is highly likely to be killed by the other insecticide or insecticides. Ideally, all insecticides in a mixture should have a similar residual life and remain bioavailable over time; in practice, this is difficult to achieve, particularly for vector control products that are meant to last for a number of years, such as long-lasting insecticide-treated nets (LLINs). An ITN product containing a pyrethroid and a pyrrole insecticide and another containing a pyrethroid and a juvenile hormone mimic have been developed and prequalified by WHO *(24)*. WHO will require data on the epidemiological impact of these products to enable assessment of their public health value and to develop a WHO recommendation. A mixture of a pyrethroid and a neonicotinoid insecticide for IRS was recently prequalified by WHO.
- Rotations involve switching between insecticides with different modes of action at pre-set time intervals, irrespective of resistance frequencies. The theory is that resistance frequencies will decline (or at least not increase) during the period of non-deployment of insecticides with a specific mode of action.
- Mosaics involve the deployment of insecticides with different modes of action in neighbouring geographical areas. The optimal spatial scale (size of areas) for mosaics has yet to be determined, and rotations are generally considered to be more practical and feasible.
- Combinations expose the vector population to two classes of insecticides with differing modes of action through the co-deployment of different interventions in the same place. For instance, pyrethroid-only LLINs combined with a non-pyrethroid IRS (where both are at high coverage) is a potential approach to IRM, although there is little evidence to indicate that such a combination of interventions would lead to additional epidemiological impact relative to one intervention deployed at high coverage (see recommendation under section 4.1.2).

For vector control, there is still little evidence and no consensus on the best IRM approach or approaches to apply in a given situation. A 2013 review of experimental and modelling studies on insecticide, pesticide and drug resistance concluded that mixtures generally lead to the slowest evolution of resistance *(25)*. However, more recently, an exploration of overlaps between agriculture and public health found that – owing to caveats and case specificity – there is only weak evidence of one IRM approach being better than another, and that the standard practice of using insecticides until resistance emerges before switching to an alternative (i.e., sequential use) may be equally effective under certain circumstances. More research is needed to compare resistance management approaches in the field *(26)* and to improve understanding of the biological mechanisms that are likely to favour different approaches in different situations *(27)(28)*.

Evidence-based planning

Given the heavy reliance on insecticidal interventions – primarily ITNs and IRS – insecticide resistance of local vectors is a key consideration in vector control planning and implementation. Ideally, IRM practices should be implemented as part of routine operations, rather than waiting for resistance to spread or increase and for control failure to be suspected or confirmed. A pragmatic approach must be taken that seeks to select appropriate vector control interventions based on the insecticide resistance profile of the major malaria vectors in the target area. To outline how resistance will be monitored and managed, national malaria programmes should develop and implement national plans in accordance with the WHO *Framework for a national plan for monitoring and management of insecticide resistance in malaria vectors (21)*. Detailed information on insecticide resistance monitoring methods and on how to use the data to inform the selection of appropriate interventions will be provided in the revised WHO *Test procedures of monitoring insecticide resistance in malaria vectors* anticipated to be published in 2021.

IRM plans should be revisited regularly to consider new information, and to integrate new interventions once they have been supported by WHO recommendations and prequalified. Further information on insecticide resistance monitoring and, more broadly, on entomological surveillance is included in the WHO reference manual on malaria surveillance, monitoring and evaluation, which outlines priority data across different transmission settings *(29)*.

Vector control across different malaria transmission settings

Understanding the degree of risk of malaria transmission in a given geographic area provides the foundation for the design of cost-effective intervention programmes to decrease malaria burden, eliminate transmission and prevent re-establishment of

malaria. The risk of malaria transmission is the product of receptivity, importation risk and infectivity of imported parasites, and is referred to as the malariogenic potential. The receptivity of an ecosystem to malaria transmission is determined by the presence of competent vectors, a suitable climate and a susceptible human population. Importation risk, sometimes referred to as vulnerability, refers to the probability of influx of infected individuals and/or infective anopheline mosquitoes. Infectivity depends on the ability of a given *Plasmodium* strain to establish an infection in an *Anopheles* mosquito species and undergo development until the mosquito has sporozoites in its salivary glands.

National malaria programmes should undertake stratification by malariogenic potential in order to: differentiate receptive from non-receptive areas; identify receptive areas in which malaria transmission has already been curtailed by current interventions; distinguish between areas with widespread transmission and those in which transmission occurs only in discrete foci; and determine geographical variations and population characteristics that are associated with importation risk *(7)*.

Specific packages of interventions may be designed for implementation in the various strata identified. These may include:

- enhancement and optimization of vector control;
- further strengthening of timely detection, high-quality diagnosis (confirmation), and management and tracking of cases;
- strategies to accelerate clearance of parasites or vectors in order to reduce transmission rapidly when possible;
- information, detection and response systems to identify, investigate and clear remaining malaria foci.

Access to effective vector control interventions will need to be maintained in the majority of countries and locations where malaria control has been effective. This includes settings with ongoing malaria transmission, as well as those in which transmission has been interrupted but in which some level of receptivity and vulnerability remains. Malaria elimination is defined as the interruption of local transmission (reduction to zero incidence of indigenous cases) of a specified malaria parasite species in a defined geographical area as a result of deliberate intervention activities. Following elimination, continued measures to prevent re-establishment of transmission are usually required *(29)*. Interventions are no longer required once eradication has been achieved. Malaria eradication is defined as the permanent reduction to zero of the worldwide incidence of infection caused by all human malaria parasite species as a result of deliberate activities.

A comprehensive review of historical evidence and mathematical simulation modelling undertaken for WHO in 2015 indicated that the scale-back of malaria vector control was associated with a high probability of malaria resurgence, including for most scenarios in areas where malaria transmission was very low or had been interrupted. Both the historical review and the simulation modelling clearly indicated that the risk of resurgence was significantly greater at higher entomological inoculation rates (EIRs) and case importation rates, and lower coverage of active case detection and case management *(30)*.

Once transmission has been reduced to very low levels approaching eliminations, ensuring access to vector control for at-risk populations remains a priority, even though the size and specific identity of the at-risk populations may change as malaria transmission is reduced.

As malaria incidence falls and elimination is approached, increasing heterogeneity in transmission will result in foci with ongoing transmission in which vector control should be enhanced. Such foci may be due to particularly intense vectorial capacity, lapsed prevention and treatment services, changes in vectors or parasites that make the current strategies less effective, or reintroduction of malaria parasites by the movement of infected people or, more rarely, infected mosquitoes. Guidance on entomological surveillance across the continuum from control to elimination is provided elsewhere *(29)*.

Once elimination has been achieved, vector control may need to be continued by targeting defined at-risk populations to prevent reintroduction or resumption of local transmission.

It is acknowledged that malaria transmission can persist following the implementation of a widely effective malaria programme. The sources and risks of residual transmission may vary by location, time and the existing components of the current malaria programme. This variation is potentially due to a combination of both mosquito and human behaviours, such as when people live in or visit forest areas or do not sleep in protected houses, or when local mosquito vector species bite and/or rest outdoors and thereby avoid contact with IRS or ITNs.

Supplementary interventions may be used in addition to ITNs or IRS in specific settings and circumstances. Recommendations on larviciding with chemical or biological insecticides are outlined in a subsequent chapter. Implementation of supplementary interventions should be in accordance with the principles outlined in the *Global vector control response 2017–2030* *(13)*.

Once elimination has been achieved, vector control coverage should be maintained in receptive areas where there is a substantial risk for reintroduction.

There is a critical need for all countries with ongoing malaria transmission, and in particular those approaching elimination, to build and maintain strong capacity in disease and entomological surveillance and health systems. The capacity to detect and respond to possible resurgences with appropriate vector control relies on having the necessary entomological information (i.e., susceptibility status of vectors to insecticides, as well as their biting and resting preferences). Such capacity is also required for the detailed assessment of malariogenic potential, which is a pre-condition for determining whether vector control can be scaled back (or focalized).

Summary of recommendations

Vector control is a vital component of malaria prevention, control and elimination strategies. Development of WHO recommendations for vector control interventions relies on evidence from well-designed and well-conducted trials and studies with epidemiological endpoints that demonstrate the public health value of the intervention *(31)*. The consolidated Guidelines incorporate: i) recommendations based on systematic reviews of the available evidence on the effectiveness of vector control interventions; and ii) existing WHO recommendations developed previously. Evidence profiles reporting impact on malaria outcomes, as published in the systematic reviews are provided for each intervention. Evaluation and reviews of additional vector control interventions are ongoing, and recommendations based on this evidence will be added to the Guidelines. In cases where readers observe inconsistencies with earlier WHO publications, the Guidelines should be considered to supersede prior guidance.

The Guidelines cover interventions that are recommended for large-scale deployment and those that are recommended as supplementary interventions. Malaria vector control interventions recommended for large-scale deployment are applicable for all populations at risk of malaria in most epidemiological and ecological settings, namely: i) deployment of ITNs that are prequalified by WHO, which in many settings continue to be long-lasting insecticidal nets (LLINs); and ii) IRS with a product prequalified by WHO. Once optimal coverage with one of these interventions has been achieved, supplementary interventions may be considered for deployment depending on the specifics of the settings.

4.1.1 Interventions recommended for large-scale deployment

Interventions that are recommended for large-scale deployment in terms of malaria vector control are those that have proven protective efficacy to reduce or prevent infection and/or disease in humans and are broadly applicable for populations at risk of malaria in most epidemiological and ecological settings.

Vector control interventions applicable for all populations at risk of malaria in most epidemiological and ecological settings are: i) deployment of ITNs that are prequalified by WHO, and ii) IRS with a product prequalified by WHO. The exception to this is DDT, which has not been prequalified. This insecticide may be used for IRS if no equally effective and efficient alternative is available, and if it is used in line with the Stockholm Convention on Persistent Organic Pollutants *(32)*. Between 2000 and 2015, 78% of the clinical malaria cases averted was attributed to insecticidal vector control, namely through the widespread scale-up of ITNs and IRS *(14)*.

Programmatic targets against malaria, as detailed within national strategic plans, should be used to guide the decision-making process to assemble context-appropriate intervention packages. Decision-making around the intervention mix to deploy and the coverage level of each intervention needs to consider available local data to guide the stratification of interventions, the available funding, the relative cost-effectiveness of available intervention options, the resources required to provide access within the broader context of UHC, the feasibility of deploying the intervention(s) at the desired coverage level, and the country's strategic goal. The resulting optimal coverage of the components of an intervention package for a given geographical area will also depend on other site-specific factors such as past and present transmission intensity, past and present intervention coverage, acceptability, and equity of access/use.

For malaria vector control interventions recommended for large-scale deployment namely, ITNs and IRS, optimal coverage refers to providing populations at risk of malaria with access to ITNs coupled with health promotion to maximize use, and ensuring timely replacement; or providing these populations with regular application of IRS. Either intervention should be deployed at a level that provides the best value for money while reflecting programmatic realities. In practice, this often means quantifying of commodities to provide full access by the population at risk while realizing that this will not result in 100% coverage or 100% access due to various system inefficiencies. Being cognizant of such constraints, decision-making should then consider other alternatives as part of the intervention package, ranging from chemoprevention to supplementary vector control, instead of pursuing the idealistic goal of providing full population coverage.

Insecticide-treated nets

WHO recommends ITNs – which in many settings are pyrethroid-only LLINs – for use in protecting populations at risk of malaria, including in areas where malaria has been eliminated but the risk of reintroduction remains. An ITN repels, disables and/or kills mosquitoes that come into contact with the insecticide on the netting material in addition to providing a physical barrier, thereby protecting the individual user. In addition, some studies have indicated that ITNs produce a “community effect”, which means that when enough ITNs are being used in a community, the survival of the mosquito population as a whole is affected; this effect increases the protection against malaria for ITN users and extends protection to members of the community who do not sleep under an ITN *(33)(34)(35)(36)(37)*. However, such a community effect has not been observed in all settings *(38)(39)(40)*. WHO GMP commissioned a review to examine the evidence for a community effect and to investigate the biological mechanisms by which ITNs provide both personal- and community-level protection against malaria. The review also investigated what factors may determine the presence of a community effect and moderate its intensity (Paintain & Lines, unpublished findings).

The review concluded that a community effect does occur in

the majority of settings, and that its extent is driven by a number of contextual factors. These factors include vector behaviour (particularly the extent of anthropophily, i.e., the propensity to feed on people, and endophagy, i.e., the tendency of mosquitoes to blood-feed indoors); the relative availability of human and non-human hosts in the locality; the level of ITN coverage and use in a community; the insecticide used (its residual insecticidal activity and repellency); and the resistance of the local malaria vectors, both physiological and behavioural, to the insecticide on the net.

The ITN coverage threshold for when the community effect becomes apparent depends on a large number of contextual factors. Regardless of the context-dependent starting threshold, the extent of the community-level protection increases as ITN coverage and net use in a given community increases. Because ITNs kill insecticide-susceptible mosquitoes that come into contact with the insecticide on the netting material, more mosquitoes will be killed as ITN coverage increases. This killing effect reduces both mosquito population density and mosquito longevity, resulting in fewer malaria vectors overall and a lower infectivity rate as fewer mosquitoes will survive the time it takes for the malaria parasite to develop in the mosquito. Consequently, the reduced density, age and proportion of the local mosquito population that is infective offer an additional level of protection to the community as a whole beyond the individual protection provided by ITNs.

Large-scale field trials *(37)(41)* and transmission models *(42)(43)* originally suggested that community coverage (i.e., the proportion of human population using an ITN with effective insecticide treatments each night) of ≥ 50% is expected to result in some level of community-wide protection. The WHO-commissioned review indicated that this area-wide protection may start to occur at lower coverage levels (Paintain & Lines, unpublished findings). The review modelled the short-term effect of increasing ITN coverage on the EIR (infectious bites per person per year) in an area with high malaria transmission and an insecticide susceptible, anthropophilic vector, assuming fixed human infectiousness. In the coverage range of 15% to 85%, an additional 20% increase in coverage of the human population at risk was shown to result in a reduction in malaria transmission intensity of approximately 50% (these findings are taken from the report submitted to WHO; findings may be revised if indicated by peer review). Additional ITN coverage is always beneficial in terms of providing more protection to individuals – both users and non-users of ITNs – and, conversely, any reduction in coverage may result in increased malaria transmission. However, there may be diminishing marginal returns to increasing coverage at higher levels. In terms of absolute cases of malaria averted, a reduction in malaria transmission when increasing ITN coverage from 80% to 100% may not generate the same impact as a 20% increase in coverage at lower levels of coverage; the marginal costs required to increase coverage at high levels (>80%) will also increase due to growing system inefficiencies. At the country level, these diminishing returns must be balanced against potential investments in other cost-effective malaria prevention and control activities by means of a well-informed prioritization process.

Three main ITN classes are recognized by WHO as given below. These classes are formally established once public health value by a first-in-class product has been demonstrated:

- ITNs designed to kill host-seeking insecticide-susceptible mosquito populations that have demonstrated public health value compared to untreated nets and whose entomological effects consist of killing and reducing the blood-feeding of insecticide-susceptible mosquito vectors. This intervention class covers pyrethroid-only nets prequalified by WHO and conventionally treated nets that rely on periodic re-treatment with a WHO prequalified self-treatment kit. Public health value has been demonstrated for products within this class and WHO recommends use of pyrethroid-only nets prequalified by WHO for large scale deployment.
- ITNs designed to kill host-seeking insecticide-resistant mosquitoes and for which a first-in-class product demonstrates public health value compared to the epidemiological impact of pyrethroid-only nets. This class includes nets that are treated with a pyrethroid insecticide and a synergist such as piperonyl butoxide (PBO) and is thought to also include nets treated with insecticides other than pyrethroid-based formulations. Public health value has been demonstrated for this class and WHO has issued a recommendation for the use of pyrethroid-PBO nets. Public health value has not been demonstrated for a first-in-class net treated with non-pyrethroid formulations and no recommendation is in place for such nets.
- ITNs designed to sterilize and/or reduce the fecundity of host-seeking insecticide-resistant mosquitoes for which a first-in-class product demonstrates public health value compared to the epidemiological impact of pyrethroid-only nets. Public health value of products in this class has yet to be demonstrated. This class is thought to includes nets treated with pyrethroid + pyriproxyfen (an insect growth regulator). This class will be created once the public health value of a first-in-class ITN product containing an insect growth regulator has been demonstrated. No recommendation is in place for such nets.

ITNs are most effective where the principal malaria vector(s) mosquitoes bite predominantly at night after people have retired under their nets. ITNs can be used both indoors and outdoors, wherever they can be suitably hung (although hanging nets in direct sunlight should be avoided, as sunlight can affect insecticidal activity).

Indoor residual spraying

IRS is the application of a residual insecticide to potential malaria vector resting surfaces, such as internal walls, eaves and ceilings of houses or structures (including domestic animal shelters), where such vectors might come into contact with the insecticide. IRS with a product that has been prequalified by

WHO PQ is recommended for large-scale deployment in most malaria-endemic locations. DDT, which has not been prequalified, may be used for IRS if no equally effective and efficient alternative is available, and if it is used in line with the Stockholm Convention on Persistent Organic Pollutants.

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.

Strong recommendation for , High certainty evidence

Pyrethroid-only nets (2019)

WHO recommends pyrethroid-only long-lasting insecticidal nets (LLINs) that have been prequalified by WHO for deployment for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission.

WHO recommends ITNs that have been prequalified by WHO for use in protecting populations at risk of malaria, including in areas where malaria has been eliminated or transmission interrupted but the risk of reintroduction remains.

ITNs are most effective where the principal malaria vector(s) bite predominantly at night after people have retired under their nets. ITNs can be used both indoors and outdoors, wherever they can be suitably hung (though hanging nets in direct sunlight should be avoided, as sunlight can affect insecticidal activity).

Practical Info

The current WHO policy recommendation for ITNs applies only to those mosquito nets that have been prequalified by WHO and that contain only an insecticide of the pyrethroid class (categorized as 'pyrethroid-only LLINs') *(24)*. For ITNs that currently do not have a policy recommendation, including nets treated with another class of insecticide either alone or in addition to a pyrethroid insecticide, WHO will determine the data requirements for assessing their public health value based on technical advice from the Vector Control Advisory Group (VCAG).

Evidence To Decision

Benefits and harms

- ITNs significantly reduce all-cause child mortality, malaria mortality, incidence of *P. falciparum* malaria and prevalence of *P. falciparum*, and incidence of severe malaria disease compared to no nets.
- No undesirable effects were identified in systematic review. However, ITNs may play an as yet undetermined role in insecticide resistance development in *Anopheles* vectors; some users complain that they are too hot to sleep under; brand new nets recently removed from packaging may cause slight, transitory irritation to skin, eyes, nose, etc.

Certainty of the Evidence

High

The systematic review determined that there is HIGH certainty evidence that ITNs generate significant desirable effects in terms of reducing malaria deaths, clinical disease and infections compared to no nets and when compared to untreated nets.

Preference and values

Resources and other considerations

The table below, compiled by the Guidelines Development Group, lists resources that should be considered for the deployment of ITNs. Note that this table does not include resource needs for product selection or assessment of impact of the intervention.

Line Item (Resource)	Resource Description
Staff	• Competent, trained, supervised and adequately remunerated enumerators • Transport logisticians and drivers • Stock managers • Distribution team staff (including those trained in behaviour-change communication [BCC]) • Teachers/health facility staff, where appropriate, trained for distribution channel • Entomologists for quality control (QC) assessments • Environmental assessment support staff
Training	• Training in enumeration, distribution, logistics management, BCC, monitoring and evaluation (M&E) and quality assurance assessments.
Transport	• Shipping of ITNs may require large trucks for transport of containerized nets from port of entry to centralized warehouses and onward to the district or other level. • Vehicles to provide transport of ITNs and potentially distributors to the community (last mile) to enumerate persons/households, provide BCC and distribute ITNs. • Vehicle maintenance costs • Fuel
Supplies	• ITNs • Inventory management forms • Recipient lists, distribution forms, including recipient sign-off sheets, daily distribution reports, inventory status reports, recipient status reports, and BCC materials (e.g. flip charts, posters, banners, staff clothing) • M&E data collection forms • ITN quality/durability assessment materials – e.g., cone bioassay material
Equipment	• Computer and communication equipment
Infrastructure	• Appropriate national and regional storage • Adequate lower level storage for ITNs at the district/school/health facility • Office space for management
Communication	• Communication with other ministries and sectors e.g. environment, transport • Communication with the general public, e.g., through the education sector and advertising on local media to encourage uptake and appropriate use and care of ITNs • Communication with the community/local leaders
Governance/programme management	• Distribution supervisors • BCC supervision • M&E survey support for assessing coverage and use • QC supervision

Other considerations:

- Optimal coverage should be achieved and maintained in endemic settings
- Improved post-distribution monitoring of nets is needed: durability, usage, coverage

Justification

The systematic review *(44)* followed the original 2003 analysis, which included insecticide-treated curtains and

ITNs together and included two studies solely evaluating insecticide-treated curtains and one study evaluating both ITNs and insecticide-treated curtains. There was no obvious heterogeneity that would lead to a subgroup analysis to examine whether the effects were different, and the results from studies evaluating insecticide-treated curtains were consistent with the results of those evaluating ITNs. The GDG drew on the analysis to make recommendations related to ITNs only.

The systematic review *(44)* produced high-certainty evidence that, compared to no nets, ITNs are effective at reducing the rate of all-cause child mortality, the rate of uncomplicated episodes of *P. falciparum*, the incidence rate of severe malaria episodes, and the prevalence of *P. falciparum*. ITNs may also reduce the prevalence of *P. vivax*, but here the evidence of an effect is less certain.

Compared to untreated nets, there is high certainty evidence that ITNs reduce the rate of uncomplicated episodes of *P. falciparum* and reduce the prevalence of *P. falciparum*. There is moderate certainty evidence that ITNs also reduce all-cause child mortality compared to untreated nets. The effects on the incidence of uncomplicated *P. vivax* episodes and *P. vivax* prevalence are less clear.

The systematic review did not identify any undesirable effects of pyrethroid ITNs.

Research needs:

- Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection), as well as potential harms and/or unintended consequences of new types of nets and insecticides in areas where resistance to pyrethroids is high.
- Determine the comparative effectiveness and durability of different net types.
- Determine the effectiveness of nets in situations of residual/outdoor transmission.
- Determine the impact of ITNs in transmission 'hotspots' and elimination settings.

Conditional recommendation , Moderate certainty evidence

Pyrethroid-PBO nets (2019)

WHO conditionally recommends pyrethroid-PBO nets prequalified by WHO for deployment instead of pyrethroid-only ITNs for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission where the principal malaria vector(s) exhibit pyrethroid resistance that is: a) confirmed, b) of intermediate level, and c) conferred (at least in part) by a monooxygenase-based resistance mechanism, as determined by standard procedures.

Practical Info

Mosquito nets that include both a pyrethroid insecticide and the synergist PBO have become available. PBO acts by inhibiting certain metabolic enzymes (e.g., mixed-function oxidases) within the mosquito that detoxify or sequester insecticides before they can have a toxic effect on the mosquito. Therefore, compared to a pyrethroid-only net, a pyrethroid-PBO net should, in theory, have an increased killing effect on malaria vectors that express such resistance mechanisms. However, the entomological and epidemiological impact of pyrethroid-PBO nets may vary depending on the bioavailability and retention of PBO in the net, and on the design of the net (i.e. whether only some or all of the panels are treated with PBO). At present, it is unknown how these differences in the design/composition of pyrethroid-PBO nets affect their relative efficacy. A non-inferiority design for experimental hut studies with entomological endpoints is being explored by WHO as a means to provide clarity in this respect.

Evidence To Decision

Benefits and harms

- Prevalence of malaria may be decreased with pyrethroid-PBO nets compared to standard pyrethroid-only LLINs in areas of high insecticide resistance.
- No undesirable effects were identified in systematic review. However, like pyrethroid- only ITNs, pyrethroid-PBO nets may play an as yet undetermined role in insecticide resistance development in *Anopheles* vectors; some users complain that they are too hot to sleep under; brand new nets recently removed from packaging may cause slight, transitory irritation to skin, eyes, nose, etc.

Certainty of the Evidence

Moderate

The systematic review determined that the evidence for the effect of pyrethroid-PBO nets on malaria infection

prevalence in an area with highly pyrethroid-resistant mosquitoes was MODERATE.

Preference and values

Resources and other considerations

Similar resources are needed for the deployment of pyrethroid-PBO nets as those listed for pyrethroid-only ITNs. (See table provided under 'Resources and other considerations' for pyrethroid-only ITNs.)

Other considerations:

- Determination of insecticide resistance status in primary vectors and mechanisms of resistance is required.
- Improved post-distribution monitoring of nets is needed: durability, usage, coverage.

Justification

Pyrethroid-PBO nets combine pyrethroids and a synergist. The synergist inhibits certain metabolic enzymes within the mosquito that would otherwise provide a protective effect against the insecticide. Therefore, compared to a pyrethroid-only net, a pyrethroid-PBO net should have an increased killing effect on malaria vectors that express such resistance mechanisms.

The systematic review *(45)* identified one cluster RCT in the United Republic of Tanzania with epidemiological data *(46)*. The study indicated that a pyrethroid-PBO net product had additional public health value compared to a pyrethroid-only LLIN product in an area where the principal malaria vector(s) had confirmed pyrethroid resistance (results from CDC bottle bioassays indicated that <30% of mosquitoes were killed following exposure to pyrethroids). Resistance was conferred (at least in part) by monooxygenase-based resistance mechanisms, as determined by standard procedures. Mathematical modelling work, drawing on mosquito mortality data obtained from WHO test kit assays, CDC bottle bioassays and experimental hut trials, indicated that the added benefit of pyrethroid-PBO nets compared to pyrethroid-only LLINs is expected to be greatest where pyrethroid resistance is at “intermediate levels”, which was defined as a range of 10% to 80% mosquito mortality after exposure to a pyrethroid insecticide in WHO test kits or CDC bottle bioassays *(47)*.

Based on the above evidence, WHO concluded and recommended the following in 2017:

- Based on the epidemiological findings and the need to deploy products that are effective against pyrethroid-resistant mosquitoes, pyrethroid-PBO nets were given a conditional endorsement as a new WHO class of vector control products.
- National malaria control programmes and their partners should consider the deployment of pyrethroid-PBO nets in areas where the principal malaria vector(s) have pyrethroid resistance that is: a) confirmed, b) of an intermediate level (as defined above by the mathematical modelling studies), and c) conferred (at least in part) by a monooxygenase-based resistance mechanism, as determined by standard procedures. Deployment of pyrethroid-PBO nets must only be considered in situations where coverage with effective vector control (primarily ITNs or IRS) will not be reduced. The primary goal must be to ensure continued access and use of ITNs at levels that ensure optimal coverage for all people at risk of malaria as part of an intervention package.
- Pyrethroid-PBO nets should not be considered a tool that can alone effectively manage insecticide resistance in malaria vectors. It is an urgent task to develop and evaluate ITNs treated with non-pyrethroid insecticides and other innovative vector control interventions for deployment across all settings, in order to provide alternatives for use in a comprehensive IRM strategy.

The conditional recommendation will be reviewed and potentially revised once the 2018 systematic review *(45)* has been updated to include data from a second trial on pyrethroid-PBO nets which was completed in Uganda in 2020.

Research needs:

- Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection), as well as potential harms and/or unintended consequences of pyrethroid-PBO nets.

Good practice statement

Achieving and maintaining optimal coverage with ITNs for malaria prevention and control (2019)

To achieve and maintain optimal ITN coverage, WHO recommends that countries apply mass free net distribution through campaigns, combined with other locally appropriate delivery mechanisms such as continuous distribution using antenatal care (ANC) clinics and the Expanded Programme on Immunization (EPI).

Recipients of ITNs should be advised (through appropriate communication strategies) to continue using their nets beyond the three-year expected lifespan of the net, irrespective of the condition and age of the net, until a replacement net is available.

Practical Info

To achieve and maintain optimal ITN coverage, countries should apply a combination of mass free net distribution through campaigns and continuous distribution through multiple channels, in particular through ANC clinics and the EPI. Mass campaigns are the only proven cost-effective way to rapidly achieve high and equitable coverage. Complementary continuous distribution channels are also required because coverage gaps can start to appear almost immediately post-campaign due to net deterioration, loss of nets, and population growth.

Mass campaigns should distribute one ITN for every two persons at risk of malaria. However, for procurement purposes, the calculation to determine the number of ITNs required needs to be adjusted at the population level, since many households have an odd number of members. Therefore, a ratio of one ITN for every 1.8 persons in the target population should be used to estimate ITN requirements, unless data to inform a different quantification ratio are available. In places where the most recent population census is more than five years old, countries can consider including a buffer (e.g. adding 10% after the 1.8 ratio has been applied) or using data from previous ITN campaigns to justify an alternative buffer amount. Campaigns should also normally be repeated every three years, unless available empirical evidence justifies the use of a longer or shorter interval between campaigns. In addition to these data-driven decisions, a shorter distribution interval may be justified during humanitarian emergencies, as the resulting increase in population movement may leave populations uncovered by vector control and potentially increasing their risk of infection as well as the risk of epidemics.

Continuous distribution through ANC and EPI channels should remain functional before, during and after mass distribution campaigns. In determining the optimal mix of ITN delivery mechanisms to ensure optimal coverage and maximized efficiency, consideration should be given to the required number of nets, the cost per net distributed and coverage over time. For example, during mass distribution campaign years, other delivery schemes may need to be altered to avoid-over supply of ITNs.

'Top-up' campaigns (i.e., ITN distributions that take into account existing nets in households and provide each household only with the additional number of nets needed to bring it up to the target number) are not recommended. Substantial field experience has shown that accurate quantification for such campaigns is generally not feasible and the cost of accounting for existing nets outweighs the benefits.

There should be a single national ITN plan and policy that includes both continuous and campaign distribution strategies. This should be developed and implemented under the leadership of the national malaria control programme, based on an analysis of local opportunities and constraints, and identification of a combination of distribution channels with which to achieve optimal coverage and minimize gaps. This unified plan should include a comprehensive net quantification and gap analysis for all public sector ITN distribution channels. As much as possible, the plan should include major ITN contributions by the private sector.

Therefore, in addition to mass campaigns, the distribution strategy could include:

- ANC, EPI and other child health clinics: These should be considered high-priority continuous ITN distribution channels in countries where these services are used by a large proportion of the population at risk of malaria, as occurs in much of sub-Saharan Africa.
- Schools, faith- and community-based networks, and agricultural and food-security support schemes: These can also be explored as channels for ITN distribution in countries where such approaches are feasible and equitable. Investigating the potential use of these distribution channels in complex emergencies is particularly important.
- Occupation-related distribution channels: In some settings, particularly in Asia, the risk of malaria may be strongly associated with specific occupations (e.g., plantation and farm workers and their families, miners, soldiers and forest workers). In these settings, opportunities for distribution through channels such as private sector employers, workplace programmes and farmers' organizations may be explored.
- Private or commercial sector channels: These can be

important channels for supplementing free ITN distribution through public sector channels. Access to ITNs can also be expanded by facilitating the exchange of vouchers or coupons provided through public sector channels for a free or subsidized ITN at participating retail outlets. ITN products distributed through the private sector should be regulated by the national registrar of pesticides in order to ensure that product quality is in line with WHO recommendations.

The procurement of ITNs with attributes that are more costly (e.g., nets of conical shape) is not recommended for countries in sub-Saharan Africa, unless nationally representative data clearly show that the use of ITNs with particular attributes increases significantly among populations at risk of malaria. To build an evidence base to support the purchase of more costly nets, investigation into the preferences and into whether meeting preferences translates into increased use of ITNs may also be warranted, particularly in situations where standard nets are unlikely to suit the lifestyle of specific population groups at risk of malaria, such as may be the case for nomadic populations.

The lifespans of ITNs can vary widely among individual nets used within a single household or community, as well as among nets used in different settings. This makes it difficult to plan the rate or frequency at which replacement nets need to be procured and delivered. All malaria programmes that have undertaken medium- to large-scale ITN distributions should conduct ITN durability monitoring in line with available guidance to inform appropriate replacement intervals. Where there is evidence that ITNs are not being adequately cared for or used, programmes should design and implement BCC activities aimed at improving these behaviours.

In countries where untreated nets are widely available, national malaria control programmes should promote access to ITNs. Strategies for treating untreated nets can also be considered, for example, by supporting access to insecticide treatment kits.

As national malaria control programmes implement different mixes of distribution methods in different geographic areas, there will be a need to accurately track ITN coverage at subnational levels. Subnational responses should be triggered if coverage falls below programmatic targets. Tracking should differentiate among the contributions of various delivery channels to overall ITN coverage.

Countries should generate data on defined standard indicators of coverage and access rates in order to ascertain whether optimal coverage has been achieved and maintained. The data should also inform changes in implementation in order to improve performance and progress towards the achievement of programmatic targets. Currently, the three basic survey indicators are: i) the proportion of households with at least one ITN; ii) the proportion of the population with access to an ITN within their household; and iii) the proportion of the population reporting having slept under an ITN the previous night (by age [<5 years; 5–14 years; 15+ years], gender and access to ITN).

Justification

In December 2017, WHO published updated recommendations on Achieving and maintaining universal coverage with LLINs for malaria control *(48)*. These recommendations were developed and revised based on expert opinion through broad consultation, including multiple rounds of reviews by the Malaria Policy Advisory Group (MPAG). Under the section on 'practical information', these recommendations have been summarized and slightly revised to clarify that these recommendations are not specific to LLINs, but apply to ITNs in general.

Good practice statement

Management of old ITNs (2019)

WHO recommends that old ITNs should only be collected where there is assurance that: i) communities are not left without nets, i.e., new ITNs are distributed to replace old ones; and ii) there is a suitable and sustainable plan in place for safe disposal of the collected material.

If ITNs and their packaging (bags and baling materials) are collected, the best option for disposal is high-temperature incineration. They should not be burned in the open air. In the absence of appropriate facilities, they should be buried away from water sources and preferably in non-permeable soil.

WHO recommends that recipients of ITNs be advised (through appropriate communication strategies) not to dispose of their nets in any water body, as the residual insecticide on the net can be toxic to aquatic organisms (especially fish).

Practical Info

It is important to determine whether the environmental benefits outweigh the costs when identifying the best disposal option for old ITNs and their packaging. For malaria programmes in most endemic countries, there are limited

options for dealing with ITN collection. Recycling is not currently a practical option in most malaria-endemic countries (with some exceptions for countries with a well-developed plastics industry). High-temperature incineration is likely to be logistically difficult and expensive in most settings. In practice, when malaria programmes have retained or collected packaging material in the process of distributing ITNs, it has mostly been burned in the open air. This method of disposal may lead to the release of dioxins, which are harmful to human health.

If such plastic material (with packaging an issue at the point of distribution and old ITNs an intermittent issue at household level when the net is no longer in use) is left in the community, it is likely to be re-used in a variety of ways. While the insecticide exposure entailed by this kind of re-use has yet to be fully studied, the expected negative health and environmental impacts of leaving the waste in the community are considered to be less than amassing it in one location and/or burning it in the open air.

Since the material from nets represents only a small proportion of total plastic consumption, it will often be more efficient for old ITNs to be dealt with as part of larger and more general solid-waste programmes. National environment management authorities have an obligation to consider and plan for what happens to old ITNs and packing materials in the environment in collaboration with other relevant partners.

Justification

Currently, ITNs and the vast majority of their packaging (bags and baling materials) are made of non-biodegradable plastics *(49)*.The large-scale deployment of ITNs has given rise to questions as to the most appropriate and cost-effective way to deal with the resulting plastic waste, particularly given that most endemic countries do not currently have the resources to manage ITN collection and waste disposal programmes.

A pilot study was conducted to examine patterns of ITN usage and disposal in three African countries (Kenya, Madagascar and United Republic of Tanzania). Findings of this pilot study, along with other background information were used to generate recommendations through the WHO Vector Control Technical Working Group (VCTEG) and MPAG on best practices with respect to managing waste.

The following are the main findings from the pilot study and other background material:

- ITNs entering domestic use in Africa each year contribute approximately 100 000 tonnes of plastic and represent a per capita rate of plastic consumption of 200 grams per year. This is substantial in absolute terms; however, it constitutes only approximately 1% to 5% of the total plastic consumption in Africa and thus is small compared to other sources of plastic and other forms of plastic consumption.
- The plastic from ITNs is treated with a small amount of pyrethroid insecticide (less than 1% per unit mass for most products), and plastic packaging is therefore considered a pesticide product/container.
- Old ITNs and other nets may be used for a variety of alternative purposes, usually due to the perceived ineffectiveness of the net, loss of net physical integrity or presence of another net.
- ITNs that no longer serve a purpose are generally disposed of at the community level along with other household waste by discarding them in the environment, burning them in the open, or placing them into pits.
- ITN collection was not implemented on a large scale or sustained in any of the pilot study countries. It may be feasible to recycle ITNs, but it is not practical or cost-effective at this point, as there would need to be specialized adaptation and upgrading of recycling facilities before insecticide-contaminated materials could be included in this process.
- Two important and potentially hazardous practices are: i) routinely removing ITNs from bags at the point of distribution and burning discarded bags and old ITNs, which can produce highly toxic fumes including dioxins, and ii) discarding old ITNs and their packaging in water, as they may contain high concentrations of residual insecticides that are toxic to aquatic organisms, particularly fish.
- Insecticide-treated plastics can be incinerated safely in high-temperature furnaces, but suitable facilities are lacking in most countries. Burial away from water sources and preferably in non-permeable soil is an appropriate method to dispose of net bags and old ITNs in the absence of a suitable high-temperature incinerator.
- In most countries, ministries of environment (national environment management authorities) are responsible for setting up and enforcing laws/regulations to manage plastic waste broadly. Although some countries have established procedures for dealing with pesticide-contaminated plastics, it is unrealistic to expect national malaria control and elimination programmes to single-handedly address the problem of managing waste from ITNs. Environmental regulations; leadership and guidance from national environmental authorities; and oversight from international agencies, such as the United Nations Environment Programme, are all necessary.

Strong recommendation for , Low certainty evidence

Indoor residual spraying (2019)

WHO recommends IRS using a product prequalified by WHO for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission

DDT, which has not been prequalified, may be used for IRS if no equally effective and efficient alternative is available, and if it is used in line with the Stockholm Convention on Persistent Organic Pollutants.

IRS is considered an appropriate intervention where:

- *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 malaria transmission pattern is such that the population can be protected by one or two rounds of IRS per year;*
- *the majority of structures are suitable for spraying; and*
- *structures are not scattered over a wide area, resulting in high transportation and other logistical costs.*

Practical Info

Insecticide formulations currently used for IRS *(24)* fall into five major insecticide classes with three modes of action, based on their primary target site in the vector. These are listed below, where applicable with examples of the active ingredients contained in IRS products that have been prequalified by WHO:

Sodium channel modulators

- Pyrethroids: alphacypermethrin, deltamethrin, lambda-cyhalothrin, etofenprox, bifenthrin
- Organochlorines: No prequalified product available

Acetylcholinesterase inhibitors

- Organophosphates: malathion, fenitrothion, pirimiphos-methyl
- Carbamates: bendiocarb, propoxur

Nicotinic acetylcholine receptor competitive modulators

- Neonicotinoids: clothianidin

IRS products using four of these insecticide classes have been prequalified by WHO; as of August 2020, there were no organochlorine IRS formulations prequalified *(24)*, but DDT continues to be used in a few countries. The prequalified products have been assessed for their safety, quality and entomological efficacy, which includes evaluation of their mortality effect on mosquitoes when applied to a range of interior surfaces of dwellings found in malaria-endemic areas. Residual efficacy needs to continue for at least three months after the application of the insecticide to the substrate, usually cement, mud or wood *(51)*. Insecticides are available in various formulations to increase their longevity on different surfaces.

IRS is considered an appropriate intervention where:

- 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 malaria transmission pattern is such that the population can be protected by one or two rounds of IRS per year;
- the majority of structures are suitable for spraying; and
- structures are not scattered over a wide area, resulting in high transportation and other logistical costs.

Indoor residual spraying: an operational manual for IRS for malaria transmission, control and elimination
IRS is a vector control intervention that can rapidly reduce malaria transmission. It involves the application of a residual insecticide to internal walls and ceilings of housing structures where malaria vectors may come into contact with the insecticide. This operational manual *(52)* aims to assist malaria programme managers, entomologists and public health officers in designing, implementing and sustaining high-quality IRS programmes.

Evidence To Decision

Benefits and harms

- IRS significantly reduces all-cause child mortality, malaria mortality, *P. falciparum* incidence and prevalence, and incidence of severe disease compared to no IRS.
- No undesirable effects were identified in systematic review. However, IRS may play an as yet undetermined role in insecticide resistance development in *Anopheles* vectors; IRS requires householders to grant permission for spray teams to enter the house; IRS requires householders to remove personal items from houses prior to spraying (e.g., foodstuffs); some insecticide formulations leave unsightly residue on sprayed surfaces.

Certainty of the Evidence

Low

The certainty of the evidence identified in the systematic review is graded LOW. The Guidelines Development Group considers that despite the LOW certainty of the evidence included in the systematic review, a strong recommendation for the intervention is warranted based on the fact that there is a considerable body of evidence stretching back several decades pertaining to implementation trials and programmatic data. The Guidelines Development Group considers that this body of evidence, when viewed as a whole, provides strong evidence of the effectiveness of IRS as a malaria prevention and control intervention. ITNs are considered to be an equally effective alternative intervention.

Preference and values

Resources and other considerations

The table below compiled by the GDG lists resources that should be considered for the deployment of IRS. Note that this table does not include resource needs for product selection or assessment of impact of the intervention.

Line Item (Resource)	Resource Description
Staff	• Competent, trained, supervised and adequately remunerated enumerators • Transport logisticians, drivers • Stock managers • Spray personnel • Entomologists for quality check assessments (QC) • Environmental assessment support staff
Training	• Training in enumeration, logistics management, spray technique, environmental safety, personal protective equipment (PPE) use and maintenance, spray pump operation and maintenance, insecticide mixing and clean-up, entomological quality assessments, BCC and M&E
Transport	• Movement of insecticide requires environmentally compliant vehicles and ground transport plans. Spray team movement typically requires significant numbers of small vehicles capable of movement across challenging roads/terrain. Individual spray personnel may in some cases also require bicycles • Transportation of pesticide-contaminated spray pumps and clothing to clean-up sites typically using spray team transportation • Insecticide-contaminated residues and packaging must be transported from remote clean-up sites under an environmentally compliant transport plan often using small trucks • Vehicles to provide transport for staff that provide BCC and entomological staff and associated supplies for QC wall cone bioassays • Vehicle maintenance costs

	• Fuel
Supplies	• PPE • Spray pump repair parts • Insecticide and packaging (including return/clean packaging) • Soap/bathing materials • Inventory management forms • Documentation paperwork/forms or electronic devices • Entomological supplies for wall cone bioassays and maintenance of adult mosquitoes • M&E data collection forms
Equipment	• Computer and communication equipment • Spray pumps appropriate for the specific insecticide • Collection tanks/wash buckets and cleaning supplies (varies with insecticide)
Infrastructure	• Appropriate national and regional/provincial storage • Temporary insecticide storage depots at the local level • Office space for management • Clean-up sites (soak pits/evaporation pools) • Training facilities with spray practice capacity • Insectary to maintain mosquitoes exposed in QC wall cone bioassays
Communication	• Communication with other ministries and sectors, e.g., environment, transport • Communication with the general public, e.g., through the education sector and advertising on local media to encourage uptake • Communication with the community/local leaders
Governance/programme management	• Spray team supervisors / district or higher-level supervisors / clean-up site managers • BCC supervision • M&E support for QC • Entomology supervisors for QC testing

Other considerations include:

- Decisions on selection of insecticide to be used will depend on the resistance profile of the local vector population.
- Optimal coverage should be maintained in endemic settings.
- The primary vector(s) should be endophilic.
- Implementation of the intervention should take place prior to the onset of the peak transmission season.
- It is important to monitor the residual activity of the insecticide(s).

Justification

When carried out correctly, IRS has historically been shown to be a powerful intervention to reduce adult mosquito vector density and longevity and, therefore, to reduce malaria transmission. However, despite its long tradition and the large body of associated operational experience, few RCTs have been conducted on IRS and so the availability of data suitable for use in a meta-analysis is limited *(50)*. The GDG determined that the data from these randomized trials, as well as the large body of evidence generated from other studies, warranted the continued recommendation of IRS for malaria prevention and control. An updated systematic review of data on IRS interventions from recent studies, RCTs and other designs is needed to further underpin this recommendation or modify it as appropriate.

Research needs:

- Further evidence is needed of the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of IRS.

- Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as harms and/or unintended consequences of IRS in urbanized areas with changing housing designs.
- Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of IRS using new insecticides in areas where mosquitoes are resistant to currently deployed insecticides.
- Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) of IRS in areas with different mosquito behaviours (such as in areas with outdoor transmission).
- Given the relatively high cost of implementing IRS, especially in the context of growing insecticide resistance, and when delivering IRS in more remote areas, there is a need to investigate new approaches to delivering IRS to increase the cost-effectiveness of this intervention.

Good practice statement

Access to ITNs or IRS at optimal coverage levels (2019)

WHO recommends ensuring access to effective vector control using ITNs or IRS at optimal coverage levels for all populations at risk of malaria in most epidemiological and ecological settings.

Evidence To Decision

Benefits and harms

- In areas of intense malaria transmission, those receiving IRS had lower incidence of malaria compared to those who received ITNs. However, there may be little or no difference between IRS and ITNs in terms of parasite prevalence. In areas of unstable malaria, ITNs were associated with lower malaria incidence and parasite prevalence.
- No undesirable effects were identified in the systematic review. However, as stated under the evidence-to-decision table for ITNs, ITNs may play an as yet undetermined role in insecticide resistance development in *Anopheles* vectors; some users complain that they are too hot to sleep under; and brand-new nets recently removed from packaging may cause slight, transitory irritation to skin, eyes, nose, etc. Similarly, IRS may play an as yet undetermined role in insecticide resistance development in *Anopheles* vectors; it requires householders to grant permission for spray teams to enter the house; householders are required to remove personal items from houses prior to spraying (e.g., foodstuffs); and some insecticide formulations leave unsightly residue on sprayed surfaces.

Certainty of the Evidence

The certainty of the evidence subjected to systematic review is graded LOW or VERY LOW. The Guidelines Development Group considers that despite the LOW certainty of the evidence included in the systematic review, a strong recommendation for either intervention is warranted based on the fact that there is a considerable body of evidence stretching back several decades pertaining to implementation trials and programmatic data of IRS. The GDG considers this body of evidence, when viewed as a whole, provides strong evidence of the effectiveness of IRS as a malaria prevention and control intervention and that ITNs are considered to be an equally effective alternative intervention.

Preference and values

Resources and other considerations

Similar resources and other considerations apply as to those for IRS and ITNs

Justification

In terms of the relative effectiveness of IRS compared to ITNs, the systematic review published in 2010 *(50)* reported was only low certainty evidence available for areas of intense transmission and for areas with unstable transmission. It was therefore not possible to arrive at a definitive conclusion on their comparative effectiveness. WHO therefore currently

views these two interventions as being of equal effectiveness, and there is no general recommendation to guide the selection of one over the other. Preferences of national malaria programmes, beneficiaries or donors are usually based on operational factors, such as perceived or actual implementation challenges (see Section 4.1.6.2) and the requirement for insecticide resistance prevention, mitigation and management (see Section 4.1). Financial considerations such as cost and cost-effectiveness are also major drivers of decision-making, and selection of malaria vector control interventions should thus be embedded in a prioritization process that considers the cost and effectiveness of all available malaria interventions and aims at achieving maximum impact with the available resources. Evaluations of the relative cost and cost-effectiveness of ITNs and IRS are ongoing to inform revision of the Guidelines.

4.1.2 Combining ITNs and IRS

Conditional recommendation against , Moderate certainty evidence

Prioritize optimal coverage with either ITNs or IRS over combination (2019)

WHO recommends against combining ITNs and IRS and that priority be given to delivering either ITNs or IRS at optimal coverage and to a high standard, rather than introducing the second intervention as a means to compensate for deficiencies in the implementation of the first intervention.

In settings where optimal ITN coverage, as specified in the strategic plan, has been achieved and where ITNs remain effective, additionally implementing IRS may have limited utility in reducing malaria morbidity and mortality. Given the resource constraints across malaria-endemic countries, it is recommended that effort be focused on good-quality implementation of either ITNs or IRS, rather than deploying both in the same area. However, the combination of these interventions may be considered for resistance prevention, mitigation or management should sufficient resources be available.

Practical Info

Given the resource constraints across malaria-endemic countries, the deployment of a second vector control intervention on top of optimal coverage with an existing one should only be considered as part of a broader prioritization analysis aimed at achieving maximum impact with the available resources. In many settings, a switch from ITNs to IRS or vice versa, rather than their combination, is likely to be the only financially feasible option.

Evidence To Decision

Benefits and harms

- No benefit of adding IRS to areas where pyrethroid-only ITNs are being used was identified in systematic review.
- In areas of confirmed pyrethroid resistance, IRS with a non-pyrethroid insecticide may increase effectiveness against malaria.
- No undesirable effects were identified in systematic review. However, the cost of combining two interventions will significantly increase commodity and operational costs.

Certainty of the Evidence

Moderate

The evidence identified in the systematic reviews showing no benefit of adding IRS in situations where ITNs are already being used is graded as MODERATE.

Preference and values

Resources and other considerations

- The degree of pyrethroid resistance and its impact on the effectiveness of pyrethroid-only ITNs should be considered.
- Status of vector resistance to the proposed IRS active ingredient needs to be known.
- In resource-constrained situations, it is unlikely to be financially feasible to deploy both ITNs and IRS.
- It is important to monitor:
  - vector population densities, EIRs and behaviour
  - insecticide resistance status and investigations of cross-resistance
  - quality control of the IRS and ITNs
  - coverage (access and use) of ITNs
  - coverage of IRS.

Justification

The systematic review published in 2019 *(53)* on the deployment of IRS in combination with ITNs (specifically pyrethroid-only LLINs) provided evidence that, in settings where there is optimal coverage with ITNs and where these remain effective, IRS may have limited utility in reducing malaria morbidity and mortality. WHO guidance was developed accordingly to emphasize the need for good-quality implementation of either ITNs or IRS, rather than deploying both in the same area *(54)*. However, the combination of these interventions may be considered for resistance prevention, mitigation or management should sufficient resources be available

Insecticide resistance threatens the effectiveness of insecticidal interventions and hence is a key consideration in determining which vector control interventions to select to ensure impact of is maximized. One approach to the prevention, mitigation and management of vector insecticide resistance is the co-deployment (or combination) of interventions with different insecticides (see Section 4.1 on 'Prevention, mitigation and management of insecticide resistance'). Therefore, WHO guidance developed based on systematic review *(53)* differentiated between the effect of combined interventions on malaria morbidity and mortality versus the utility of this approach in a resistance management strategy *(54)*.

A summary of the conclusions (with slight updates for clarity) used to develop the above recommendations is as follows:

- In settings with high ITN coverage where ITNs remain effective, IRS may have limited utility in reducing malaria morbidity and mortality. However, IRS may be implemented as part of an IRM strategy in areas where there are ITNs *(19)*.
- Malaria control and elimination programmes should prioritize the delivery of ITNs or IRS at optimal coverage and to a high standard, rather than introducing the second intervention as a means to compensate for deficiencies in the implementation of the first intervention.
- If ITNs and IRS are to be deployed together in the same geographical location, IRS should be conducted with a non-pyrethroid insecticide.
- Evidence is needed to determine the effectiveness of combining IRS and ITNs in malaria transmission foci, including in low transmission settings. Evidence is also needed from different eco-epidemiological settings outside of Africa.
- All programmes in any transmission setting that decide to prioritize the combined deployment of ITNs and IRS over other potential use of their financial resources should include a rigorous programme of M&E (e.g., a stepped wedge introduction of the combination) in order to confirm whether the additional inputs are having the desired impact. Countries that are already using both interventions should similarly undertake an evaluation of the effectiveness of the combination versus either ITNs or IRS alone.
- The approach of combining interventions for resistance management was developed largely based on experience with agricultural pest management, and the evidence base from public health remains weak.

These findings and conclusions were substantiated by a systematic review of the evidence published in 2019 *(53)*. The review is currently being updated with evidence from further trials that have been conducted since. Once published, the evidence will be reviewed by WHO.

Research needs:

- Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of combining non-pyrethroid IRS with ITNs vs ITNs only in areas with insecticide resistant mosquito populations.
- Determine whether there are comparative benefits (incidence of malaria [infection or clinical] and/or prevalence of malaria infection), as well as potential harms and/or unintended consequences of combining non-pyrethroid IRS with ITNs vs IRS only in areas with insecticide-resistant mosquito populations.
- Determine the acceptability of combining IRS and ITNs among householders and communities.
- Evaluate new tools for monitoring the quality of IRS and

ITN interventions.

Good practice statement

No scale-back in areas with ongoing local malaria transmission (2019)

In areas with ongoing local malaria transmission (irrespective of both the pre-intervention and current level of transmission), WHO recommends that vector control interventions should not be scaled back. Ensuring access to effective malaria vector control at optimal levels for all inhabitants of such areas should be pursued and maintained.

Practical Info

Access to effective vector control interventions will need to be maintained in the majority of countries and locations where malaria control has been effective. This includes settings with ongoing malaria transmission, as well as those in which transmission has been interrupted but in which some level of receptivity and importation risk remains. Malaria elimination is defined as the interruption of local transmission (reduction to zero incidence of indigenous cases) of a specified malaria parasite species in a defined geographical area as a result of deliberate intervention activities. Following elimination, continued measures to prevent re-establishment of transmission are usually required *(29)*. Interventions are no longer required once eradication has been achieved. Malaria eradication is defined as the permanent reduction to zero of the worldwide incidence of infection caused by all human malaria parasite species as a result of deliberate activities.

There is a critical need for all countries with ongoing malaria transmission, and in particular those approaching elimination, to build and maintain strong capacity in disease and entomological surveillance and health systems. The capacity to detect and respond to possible resurgences with appropriate vector control relies on having the necessary entomological information (i.e., susceptibility status of vectors to insecticides, as well as their biting and resting preferences). Such capacity is also required for the detailed assessment of malariogenic potential, which is a pre-condition for determining whether vector control can be scaled back (or focalized).

If areas where transmission has been interrupted are identified, the decision to scale-back vector control should be based on a detailed analysis that includes assessment of the receptivity and importation risk of the area, as well as an assessment of the active disease surveillance system, and capacity for case management and vector control response.

Justification

A comprehensive review of historical evidence and mathematical simulation modelling undertaken for WHO in 2015 indicated that the scale-back of malaria vector control was associated with a high probability of malaria resurgence, including for most scenarios in areas where malaria transmission was very low or had been interrupted *(30)*. Both the historical review and the simulation modelling clearly indicated that the risk of resurgence was significantly greater at higher EIRs and case importation rates, and lower coverage of active case detection and case management.

Once transmission has been reduced to very low levels approaching elimination, ensuring optimal access to vector control for at-risk populations remains a priority, even though the size and demographics of the at-risk populations may change as malaria transmission is reduced.

As malaria incidence falls and elimination is approached, increasing heterogeneity in transmission will result in foci with ongoing transmission in which vector control may need to be optimized and enhanced. Such foci may be the result of particularly high vectorial capacity, lapsed prevention and treatment services, changes in parasites that make the current strategies less effective, or reintroduction of malaria parasites by the movement of infected people or infected mosquitoes. Monitoring the coverage, quality and impact of vector control interventions is essential to maintain the effectiveness of control. Guidance on entomological surveillance across the continuum from control to elimination is provided elsewhere *(29)*.

Once elimination has been achieved, vector control may need to be continued by targeting defined at-risk populations to prevent reintroduction or re-establishment of local transmission.

It is acknowledged that malaria transmission can persist following the implementation of a widely effective malaria programme. The sources and risks of residual transmission may vary by location, time and the existing components of the current malaria programme. This variation is potentially due to a combination of both mosquito and human behaviours, such as when people live in or visit forest areas or do not sleep in protected houses, or when local mosquito vector species bite and/or rest outdoors and thereby avoid contact with IRS or ITNs/LLINs.

Once elimination has been achieved, optimal vector control coverage should be maintained in receptive areas where there is a substantial risk for reintroduction.

4.1.3 Supplementary interventions

Larval source management (LSM)
LSM in the context of malaria control is the management of water bodies that are potential larval habitats for mosquitoes. Such management of water bodies is conducted to prevent the development of the immature stages (eggs, larvae and pupae) and hence the production of adult mosquitoes, with the overall aim of preventing or controlling transmission of malaria. There are four types of LSM:

- habitat modification: a permanent alteration to the environment, e.g. land reclamation, filling of water bodies;
- habitat manipulation: a recurrent activity, e.g. flushing of streams, drain clearance;
- larviciding: the regular application of biological or chemical insecticides to water bodies; and
- biological control: the introduction of natural predators into water bodies.

Topical repellents, insecticide-treated clothing and spatial/ airborne repellents
Topical repellents, insecticide-treated clothing and spatial/ airborne repellents have all been proposed as potential methods for preventing malaria in areas where the mosquito vectors bite or rest outdoors, or bite in the early evening or early morning when people are not within housing structures. These methods have also been proposed for specific population groups, such as those who live or work away from permanent housing structures (e.g., migrants, refugees, internally displaced persons, military personnel) or those who work outdoors at night. In these situations, the effectiveness of ITNs or IRS may be reduced. Repellents have also been proposed for use in high-risk groups, such as pregnant mothers. Despite the potential to provide individual protection against bites from malaria vectors, the deployment of the above personal protection methods in large-scale public health campaigns has been limited, at least partially due to the scarcity of evidence of their public health value. Daily compliance and appropriate use of repellents seem to be major obstacles to achieving such potential impact *(56)*. Individuals' use of the intervention to achieve personal protection faces the same obstacles.

Space spraying
Space spraying refers to the release of fast-acting insecticides into the air as smoke or as fine droplets as a method to reduce the numbers of adult mosquitoes in dwellings and also outdoors. Application methods include thermal fogging; cold aerosol distribution by handheld or backpack sprayers, ground vehicles or aerial means; and repetitious spraying by two or more sprays in quick succession. Space spraying is most often deployed in response to epidemics or outbreaks of mosquito-borne disease, such as dengue.

Housing modifications
In the context of malaria control, housing modifications are defined as any structural changes, pre- or post-construction, of a house that prevents the entry of mosquitoes and/or decreases exposure of inhabitants to vectors with the aim of preventing or reducing the transmission of malaria. Housing modifications may encompass a wide range of interventions – from those made at the outset in the structural design of the house and the choice of materials used, to modifications made to existing homes, such as the screening or closure of gaps. In 2018, the WHO Department of Public Health, Environmental and Social Determinants of Health published the *WHO Housing and health guidelines (56)*. This document brings together the most recent evidence to provide practical recommendations for reducing the health burden due to unsafe and substandard housing. The review concluded that improved housing conditions have the potential to save lives, prevent disease, increase quality of life, reduce poverty, and help mitigate climate change. It was, however, noted that further evidence was needed on the impact of improved housing in preventing vector-borne diseases.

Available evidence indicates that poor-quality housing and neglected peri-domestic environments are risk factors for the transmission of a number of vector-borne diseases such as malaria, arboviral diseases (e.g. dengue, yellow fever, chikungunya and Zika virus disease), Chagas disease and leishmaniasis *(57)*. Together with metal roofs, ceilings, and finished interior walls, the closing of open eaves, screening doors and windows with fly screens or mosquito netting, and filling holes and cracks in walls and roofs may reduce the mosquitoes' entry points into houses and potentially reduce transmission of malaria and other vector-borne diseases. A recent review indicated that housing quality is an important risk factor for malaria infection across the spectrum of malaria endemicity in sub-Saharan Africa *(58)*.

Structural housing interventions that may reduce exposure of inhabitants to mosquitoes fall largely into two categories:

1. Primary house construction:

- house designs, such as elevating houses (e.g., using stilts) and using fewer or smaller windows;
- construction materials, such as cement or brick walls, corrugated iron roofing, door designs with fewer openings, and closure of eaves that minimize entry holes for mosquitoes.

2. Modifications to existing house designs:

- non-insecticidal interventions which include screening and covering of potential entry points, filling eaves with mud, sand, rubble or cement, installing ceilings and conducting wall maintenance to fill in any cracks;
- insecticidal interventions which include insecticidal screening of mosquito entry points, particularly eaves, and the installation of lethal house lures.

Housing modifications are likely to be most effective against

mosquitoes that display endophilic and/or endophagic behaviours (i.e., indoor resting and feeding, respectively).

Conditional recommendation , Low certainty evidence

Larviciding (2019)

WHO conditionally recommends the regular application of biological or chemical insecticides to water bodies (larviciding) for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission as a supplementary intervention in areas where optimal coverage with ITNs or IRS has been achieved, where aquatic habitats are few, fixed and findable, and where its application is both feasible and cost-effective.

Since larviciding only reduces vector density, it does not have the same potential for health impact as ITNs and IRS – both of which reduce vector longevity and provide protection from biting vectors. As a result, larviciding should never be seen as a substitute for ITNs or IRS in areas with significant malaria risk but represents a potential supplementary strategy for malaria control. Larviciding will generally be most effective in areas where larval habitats are few, fixed and findable, and likely less feasible in areas where the aquatic habitats are abundant, scattered and variable.

The following settings are potentially the most suitable for larviciding as a supplementary measure implemented alongside ITNs or IRS:

- *urban areas: where breeding sites are relatively few, fixed and findable in relation to houses (which are targeted for ITNs or IRS);*
- *arid regions: where larval habitats may be few and fixed throughout much of the year.*

Practical Info

Larviciding is most likely to be cost-effective in urban areas where the appropriate conditions are more likely to be present. Larviciding is not generally recommended in rural settings, unless there are particular circumstances limiting the larval habitats and specific evidence confirming that such measures can reduce malaria incidence in the local setting.

WHO's 2013 *Operational manual on larval source management (60)* concluded that ITNs and IRS remain the backbone of malaria vector control, but LSM represents an additional (supplementary) strategy for malaria control in Africa. Larviciding will generally be most effective in areas where larval habitats are few, fixed and findable, and likely less feasible in areas where the aquatic habitats are abundant, scattered and variable. Determination of whether or not specific habitats are suitable for larviciding should be based on assessment by an entomologist. The WHO operational manual focuses on sub-Saharan Africa, but the principles espoused are likely to hold for other geographic regions that fit the same criteria. The following settings are potentially the most suitable for larviciding as a supplementary measure implemented alongside ITNs or IRS:

- urban areas: where breeding sites are relatively few, fixed and findable in relation to houses (which are targeted for ITNs or IRS);
- arid regions: where larval habitats may be few and fixed throughout much of the year.

Evidence To Decision

Benefits and harms

- Larviciding for non-extensive larval habitats less than 1 km^2 may have an effect in reducing malaria incidence and parasite prevalence compared to no larviciding. However, it is not known if there is an effect in large-scale aquatic habitats.
- No undesirable effects were identified in systematic review. However, larviciding may affect non-target fauna; communities may not accept its application to sources of drinking water or water used for other domestic purposes.

Certainty of the Evidence

Low

For larval habitats less than 1 km^2, the systematic review assessed that the evidence that larviciding reduces malaria incidence is MODERATE. The certainty of evidence that larviciding in small-scale habitats reduces parasite prevalence is

graded as LOW. In larger habitats, the evidence for impact on incidence or prevalence is graded as VERY LOW.

Preference and values

Resources and other considerations

The table below compiled by the Guidelines Development Group lists resources that should be considered for implementing larviciding. Note that, this table does not include resource needs for product selection or assessment of impact of the intervention.

Line Item (Resource)	Resource Description
Staff	• Competent, trained, supervised and adequately remunerated larvicide operators and skilled entomological technicians, divided into separate teams for surveillance and application of larvicide • Transport logisticians and drivers • Stock managers • Mapping technicians and assistants • Environmental assessment support staff
Training	• *Anopheles* larval habitat identification and classification • Larvicide application and safety • Entomological sampling and identification of *Anopheles* mosquitoes - larvae, pupae and adults • Training for awareness campaigns and to encourage acceptability
Transport	• Appropriate vehicles to provide transport of larvicide, equipment, entomological sampling materials and workers to the community • Vehicle maintenance costs • Fuel
Supplies	• Larvicide • PPE • Entomological supplies for larval monitoring and rearing/maintenance of adult mosquitoes
Equipment	• Larvicide application equipment • Larvae, pupae and adult monitoring equipment • Mosquito identification equipment, e.g. microscopes • Computer/communication equipment
Infrastructure	• Appropriate storage facilities for larvicide and equipment • Office space for management • Insectary for collected larvae and to rear/maintain mosquitoes
Communication	• Communication with other ministries and sectors e.g., environment, transport, ministry of works/other infrastructure sectors and city/local councils • Communication with the general public e.g. through the education sector and media for awareness of campaigns and to encourage acceptability • Communication with the community/local leaders

Governance/programme management	• Supervision of mapping and application • Supervision of standard monitoring of larval, pupal and adult populations to assess entomological impact • Environmental impact assessment supervision

Other considerations include:

- Determining whether or not specific habitats have immature *Anopheles* larvae and are suitable for larviciding is essential and should be based on expert technical opinion and knowledge.

Justification

Larviciding is deployed for malaria control in several countries, including Somalia and Sudan. However, the systematic review on larviciding conducted in 2019 *(59)* assessed that the certainty of evidence of impact on malaria incidence or parasite prevalence was moderate or low in non-extensive habitats. Since larviciding only reduces vector density, it does not have the same potential for health impact as ITNs and IRS – both of which reduce vector longevity (a key determinant of transmission intensity) and provide protection from biting vectors. As a result, larviciding should never be seen as a substitute for ITNs or IRS in areas with significant malaria risk.

Larval habitat modification and/or larval habitat manipulation (2021)

No recommendation can be made because the evidence on the effectiveness of a specific larval habitat modification and/or larval habitat manipulation intervention for the prevention and control of malaria was deemed to be insufficient.

Practical Info

Although the available evidence which met the inclusion criteria for the systematic review was considered insufficient to develop specific recommendations, national programmes may decide to use environmental management (habitat modification and/or manipulation) to avoid the creation, and reduce the availability of, larval habitats, where deemed appropriate, based on expert guidance and local knowledge. If such strategies are employed, the selection of the specific intervention(s) should be highly contextual, i.e., it should take into account the specific environment the type of intervention(s) that are relevant to that environment, the resources needed and their availability, the feasibility of the intervention(s), their acceptability by local stakeholders and how they might impact equity. The selection should also take into account previous experience either gained locally or from other areas of similar ecological and epidemiological characteristics where such intervention(s) have been implemented. Additionally, the selection of the comparator should consider other interventions that are known to be cost-effective, for example, larviciding. Where the decision is taken to invest resources into larval habitat modification and/or larval habitat manipulation, the intervention(s) should be designed and conducted with the explicit aim of generating data to demonstrate effective malaria control and preferably, supported with environmental and entomological data as secondary end-points.

When assessing the impact of environmental management against malaria, it is important that the testing of the intervention(s) being investigated is/are specifically conducted for the purpose of preventing or controlling malaria by reducing the availability and productivity of larval habitats. For example, dams are generally constructed for water management, irrigation or power production purposes, not for malaria control. In fact, in some cases, their construction may result in increased larval production due to the creation of standing water bodies. The controlled release of water from the impoundment of a dam, however, is considered an example of habitat manipulation, a recurrent activity which potentially controls mosquito larvae by increasing the flow rate of downstream water with the aim of preventing mosquito development and so controlling malaria transmission. This is one example of the multitude of interventions that fall under the broad category of habitat modification and/or manipulation. To be able to generate evidence on the efficacy of larval habitat modification and/or manipulation in preventing malaria, and to facilitate the interpretation of the evidence once generated, it is important to well define the interventions that are being evaluated and, importantly, compare how the water conditions of larval habitats at the intervention and control sites are affected. For example, if the intervention aimed to increase the water flow of downstream areas, the evaluation should include an assessment of whether this was achieved, as well as to what extent this impacted the development of the immature and adult stages of the mosquito and, ultimately, whether there was an epidemiological impact on against malaria in the intervention arms compared to control areas. This information will then support the evolution of WHO guidance in this area and, ultimately, guide the choice and

implementation of efficacious interventions.

Evidence To Decision

Benefits and harms

The systematic review identified two studies that provided low or very low certainty evidence that the controlled release of water from flood gates of dams or spillways (overflow channels) across streams to flush downstream areas with water may reduce malaria incidence and parasite prevalence. Both studies were conducted in very specific settings.

No undesirable effects were identified in the systematic review.

Certainty of the Evidence

The certainty of evidence that release of water using flood gates in dams or spillways on streams reduces malaria incidence or parasite prevalence is graded as LOW or VERY LOW.

Preference and values

No research was identified to determine preference and values

Resources and other considerations

No research was identified that assessed cost effectiveness or resource needs.

Justification

The systematic review to inform WHO recommendations in this area identified only two controlled before-and-after studies meeting the inclusion criteria with epidemiological outcomes that investigated the impact of larval habitat manipulation/modification alone. Two other identified studies combined habitat manipulation with larviciding and so the effect of the two could not be separated. The two eligible studies investigated the impact of larval habitat manipulation against malaria (Martello, E., Yogeswaran, G. & Leonardi-Bee, J. unpublished findings). One study was conducted in an urban area of the Philippines in 1960 and the other in a forested area of India in 2008 where annual IRS was also conducted. The studies provided low or very low certainty evidence that the controlled release of water from flood gates of dams to discharge excess water or using spillways (overflow channels) across streams to automatically flush downstream areas with water (continually or intermittently) reduced clinical malaria incidence or parasite prevalence. The evidence was downgraded due to the lack of appropriate randomization or poor statistical reporting. The studies examined very specific interventions, each studied in a single site, which limited their generalizability. The systematic review reported a number of other studies with only entomological outcomes investigating a wide range of highly heterogeneous interventions falling under the broad term of larval habitat manipulation and/or modification, some of which may only be appropriate in specific ecologies. Given the broad range of interventions and settings in which larval habitat manipulation and/or modification may be applied, the potential impact, feasibility, acceptability and resource needs for each intervention is likely to be highly variable.

Although it is acknowledged that there is a wealth of historical research on environmental management of malaria, unfortunately this literature was insufficiently robust to be included in this systematic review. Therefore, there remains a continued need to robustly demonstrate the epidemiological impact environmental management (habitat modification and/or manipulation) through measurement of malaria incidence or prevalence through further well-designed intervention studies.

Research needs:
The GDG encourages funding of high-quality research on the impact of habitat manipulation and/or modification on malaria transmission to inform the development of specific WHO recommendations in this area. A number of evidence gaps and associated requirements were identified:

- Determine the impact (incidence of clinical malaria and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of the different interventions.
- Epidemiological evidence is required on the efficacy against malaria of the same intervention implemented in different settings (where vector species may differ).

- Detailed descriptions of the interventions deployed, as well as larval habitat types and vector species targeted. The impact of the intervention on the water conditions of the larval habitats should be assessed, i.e. properties of the habitat that the intervention aims to modify such as water flow, volume, sunlight penetration, salinity or other physical conditions.
- Evidence on contextual factors, (i.e., acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences) related to larval habitat modification and/or manipulation is needed.

Larvivorous fish (2019)

No recommendation can be made because no evidence on the effectiveness of larvivorous fish for the prevention and control of malaria was identified.

Evidence To Decision

Benefits and harms

- No desirable effects were identified in the systematic review. However, fish can serve as an additional source of nutrition.
- No undesirable effects were identified in the systematic review.

The GDG recognizes that there are specific settings in which the intervention is currently implemented, and in these specific settings programme staff consider it to be effective.

Certainty of the Evidence

The systematic review did not identify any eligible studies demonstrating the effect of larvivorous fish on malaria transmission or disease outcomes.

Preference and values

Resources and other considerations

- There is evidence that this intervention would require mosquito aquatic habitats to be large, permanent and few.
- Local capacity for breeding fish, maintaining fish and monitoring aquatic habitats would be needed.
- The characteristics of settings in which this intervention might be applicable would be needed.

Justification

The systematic review conducted in 2017 on use of larvivorous fish *(61)* did not identify any studies demonstrating impact on malaria and so there is insufficient evidence to support a recommendation. The GDG recognizes that there are specific settings in which the intervention is currently implemented, and in these specific settings programme staff consider it to be effective. In some of the settings where larvivorous fish are being deployed, programmatic evidence exists; however, this was not determined appropriate for inclusion in the systematic review due to unsuitable study design or other concerns. The GDG acknowledges that there may be data at country/ programme level that it is not aware of.

Research needs:

- Determine the impact (incidence of malaria (infection or clinical) and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of the use of larvivorous fish.

Conditional recommendation against , Low certainty evidence

Topical repellents (2019)

WHO conditionally recommends against the deployment of topical repellents for the prevention and control of malaria at the community level in areas with ongoing malaria transmission.

Further work is required to investigate the potential public health value of topical repellents to separate out potential effects at the individual and/or community level. Analysis conducted to date indicates that no significant impact on malaria can be achieved when the intervention is deployed at community-level due to the high level of individual compliance needed.

Evidence To Decision

Benefits and harms

- No desirable effects were identified in systematic review. Based on expert opinion and in line with current WHO recommendations, topical repellents may still be useful in providing personal protection against malaria.
- No undesirable effects were identified in the systematic review.

Certainty of the Evidence

Low

The systematic review assessed that the evidence of a benefit from the deployment of topical repellents as a malaria prevention tool in a public health setting is of LOW certainty.

Preference and values

Resources and other considerations

Adherence to daily compliance remains a major limitation

Justification

The evidence from the RCTs included in the systematic review conducted in 2018 *(62)* provided low certainty evidence of a possible effect of topical repellents on malaria parasitaemia (*P. falciparum* and *P. vivax*). The evidence is insufficiently robust to determine whether topical repellents have an effect on clinical malaria.

Research needs:

- Determine the impact (incidence of malaria (infection or clinical) and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of topical repellents for individuals in specific settings and target populations.

Conditional recommendation against , Low certainty evidence

Insecticide-treated clothing (2019)

WHO conditionally recommends against deployment of insecticide-treated clothing for the prevention and control of malaria at the community level in areas with ongoing malaria transmission; however, insecticide-treated clothing may be beneficial as an intervention to provide personal protection against malaria in specific population groups.

In the absence of insecticide-treated nets, there is some evidence that insecticide-treated clothing may reduce the risk of malaria infection in specific populations such as refugees and military; it is presently unclear if the results are applicable to the general population.

Evidence To Decision

Benefits and harms

- There is some evidence of the use of insecticide -treated clothing on clinical *P. falciparum* and *P. vivax* malaria in refugee camps or other disaster settings in the absence of ITNs
- No evidence was available on epidemiological effects in the general at-risk population.
- No undesirable effects were identified in the systematic review.

Certainty of the Evidence

Low

The systematic review assessed that the evidence of a benefit from the use of insecticide-treated clothing in specific populations as a malaria prevention tool is of LOW certainty.

Preference and values

Resources and other considerations

Such clothing may be beneficial as a tool to provide personal protection against malaria in specific population groups (refugees, military).

Justification

The systematic review carried out in 2018 *(62)* provided low certainty evidence that insecticide-treated clothing may have protective efficacy against *P. falciparum* and *P. vivax* cases, at least in certain specific populations (refugees, military personnel and others engaged in occupations that place them at high risk) and where ITNs were not in use. There was no evidence available on epidemiological effects in the general at-risk population.

Research needs:

- Determine the impact (incidence of malaria (infection or clinical) and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of insecticide-treated clothing in the general population.
- Identification of approaches to enhance acceptability/ desirability and increase uptake and adherence is needed.
- Development of formulations that improve the durability of insecticidal efficacy is needed.

Spatial/Airborne repellents (2019)

No recommendation can be made because the evidence on the effectiveness of spatial/airborne repellents for the prevention and control of malaria was deemed to be insufficient.

Evidence To Decision

Benefits and harms

- No desirable effects were identified in systematic review. The meta-analysis showed that spatial repellents had no impact on *Plasmodium* species' parasitaemia.
- No undesirable effects were identified in the systematic review.

Certainty of the Evidence

The systematic review assessed that the evidence that spatial/airborne repellents has an impact on malaria is of VERY LOW certainty.

Preference and values

Justification

The systematic review published in 2018 *(62)* concluded that there is very low certainty evidence that spatial or airborne repellents may have a protective efficacy against malaria parasitaemia. Therefore, no recommendation on the use of spatial/airborne repellents in the prevention and control of malaria can be made until more studies assessing malaria epidemiological outcomes have been conducted.

- Determine the impact (incidence of malaria (infection or clinical) and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of spatial/airborne repellents.
- Development of spatial repellent insecticide formulations that provide a long-lasting effect is required.

Research needs:

Conditional recommendation against , Very low certainty evidence

Space spraying (2019)

WHO conditionally recommends against using space spraying for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission; IRS or ITNs should be prioritized instead.

Evidence To Decision

Benefits and harms

- No desirable effects were identified by systematic review. Anticipated desirable effects of space spraying are likely to be small, as insecticide formulations used are short-lived. *Anopheles* mosquitoes are generally considered to be less susceptible to space spraying than *Culex* or *Aedes*.
- No undesirable effects were identified by systematic review.

Certainty of the Evidence

Very low

The systematic review identified only observational studies reporting number of malaria cases per month. These are graded as VERY LOW certainty evidence.

Preference and values

Resources and other considerations

- The costs are anticipated to be high and cost-effectiveness to be limited of this intervention
- Specialist technical equipment required

Justification

Only observational studies were identified by the systematic review and the certainty of the evidence was graded as very low *(63)*. The lack of data from RCTs, other trial designs or quasi-experimental studies has therefore hampered a comprehensive assessment of this intervention and the review concluded that it is unknown whether space spraying causes a reduction in incidence of malaria. Anticipated desirable effects of space spraying are likely to be small, as insecticide formulations used are short-lived. *Anopheles* mosquitoes are generally considered to be less susceptible to space spraying than *Culex* or *Aedes*. Space spraying is frequently applied when cases are at their peak, which is followed by a decline in cases, whether or not control measures are applied. Nevertheless, space spraying is often deployed in response to outbreaks of mosquito-borne disease. Due to the high visibility of this intervention, the decision to use this approach is usually made to demonstrate that the authorities are taking action in response to the

outbreak. This practice should be strongly discouraged given the limited evidence of the intervention's effectiveness, the high cost and the potential for wastage of resources. The GDG therefore felt it necessary to develop a clear recommendation against space spraying for malaria control.

Research needs:

- Determine the impact (incidence of malaria (infection or clinical) and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of space spraying, particularly in emergency situations.

Conditional recommendation , Low certainty evidence

New

House screening (2021)

WHO conditionally recommends the use of untreated screening of residential houses for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission.

This recommendation addresses the use of untreated screening of windows, ceilings, doors and/or eave spaces, and does not cover other ways of blocking entry points in houses.

Practical Info

If house screening is being considered as a means to prevent malaria, it is important to identify who the end-user will be and how the intervention will be implemented, i.e. whether this would be a tool that the program promotes for individuals or communities to implement at their own cost, or if screening of houses is undertaken as a programmatic initiative. Depending on the approach, the resources needed, feasibility, up-take and impact on equity may vary and would need to be considered.

Screening of houses may be done post-construction or could be a standard feature for new homes. Intersectoral collaboration, for example between health, housing and environmental sectors, is crucial in the implementation of house screening. It is also important to consider what standards and criteria, if any, need to be set for screening materials and designs as they are for buildings.

Screening of residential houses should be part of an integrated vector management (IVM) approach as promoted under the Global Vector Control Response *(13)* and deployment of interventions recommended for large-scale deployment (such as ITN or IRS) should be maintained.

In settings where national or local government authorities are not able to provide screening of residential houses as a public health strategy (e.g., due to feasibility/ resource challenges), they should promote its use amongst affected communities.

If house screening is deployed or adopted by communities to prevent malaria, post-distribution monitoring of the intervention is needed to assess material durability, usage, and coverage. This information should guide how regularly screens require replacement or repair and provide information on the sustainability of the intervention.

Evidence To Decision

Benefits and harms

The systematic review *(64)* concluded that screening may reduce clinical malaria and parasite prevalence of infection, and probably reduces anaemia and entomological inoculation rates.

The systematic review noted the following unintended consequences of the intervention:

- Pooled analysis of the two trials showed that individuals living in fully screened houses (covered eaves, windows and doors) were around 16% less likely to sleep under a bed net (RR 0.84 95% CI 0.65 to 1.09; 2 trials, 203 participants).
- In one study from the Gambia, individuals living in houses with screened ceilings were around 31% less likely to sleep under a bed net (RR 0.69 95% CI 0.50 to 0.95; 1 trial; 135 participants).
- None of the other pre-specified outcomes (all-cause mortality; other disease incidence; adverse effects; unintended effects other than bed net usage) were reported in the included studies.

The GDG noted some other potential undesirable effects, that were judged to be small :

- Inhabitants of screened houses may not use other effective interventions such as ITNs
- Screening may reduce airflow and result in increased indoor temperatures and reduced ventilation. As a result, occupants may open doors and windows
- Reduced airflow and ventilation may result in increased respiratory problems and infections, and increased indoor air pollution

Certainty of the Evidence

Low

The systematic review assessed that the evidence of an impact of house screening on clinical malaria incidence, malaria parasite prevalence and EIR is of LOW certainty. The certainty of evidence for reductions in anaemia was graded as MODERATE.

Preference and values

No research was identified regarding preferences and values.

Resources and other considerations

Resources needed for the screening of houses may depend on whether the intervention is deployed by the programme or implemented by the community. The table below compiled by the GDG lists resources that should be considered. Note that this table does not include resource needs for product selection or assessment of impact of the intervention.

Line Item (Resource)	Resource Description
Staff	• Competent, trained, supervised and adequately remunerated skilled carpenters/ construction workers/community members • Behavioural change communication (BCC) staff • Transport logisticians and drivers • Demonstrators/teachers • Monitoring and evaluation (M & E) staff
Training	• Training in appropriate construction/modification and or installation techniques. • Training for awareness campaigns and to encourage uptake
Transport	• Vehicles to provide transport of material and workers to the community to support installation and maintenance of the intervention and provide BCC • Vehicle maintenance costs • Fuel
Supplies	• Adequate construction material for screening (including but not limited to wood/ screen, fasteners). • BCC materials (e.g. flip charts, posters, banners, staff clothing) • M & E data collection forms
Equipment	• Construction tools / equipment • Computer/communication equipment
Infrastructure	• Storage space for construction materials

	• Office space for management
Communication	• Communication with other ministries and sectors e.g. environment, transport, housing, city/local councils and large infrastructure projects, as well as coordination with local building regulators • Communication with the community/local leaders • Communication with the general public e.g. through the education sector and media for awareness and to encourage uptake
Governance/ programme management	• Construction/installation supervisors • BCC supervision • M & E survey support for coverage

Equity

National programs considering the adoption of screening of residential houses as a public health strategy should assess how the implementation of a screening program would affect health equity in the community. Depending on how the intervention is deployed, the effect on equity may vary. For example, if individuals are encouraged to screen houses themselves, equity may be reduced. If the intervention is deployed at the programme level, it may be increased. The impact on equity may also depend on house structure and conditions, as some features may not allow for screening.

Acceptability

The studies included in the systematic review used in-depth interviews and focus group discussions to assess community acceptance of the interventions. In both studies, participants reported that the intervention reduced the number of indoor mosquitoes and house flies. Most participants in both trials chose to have screening after the duration of the trial. Additionally, participants in the study from The Gambia reported a reduction in entry of other animals, such as bats, cockroaches, earwigs, geckos, mice, rats, snakes, and toads. In both trials, participants expressed concern that screening would be damaged by domestic animals and children, or that it would become dirty. In the Ethiopian study, some participants reported that they made further efforts to reduce mosquito entry after screening installation, such as filling in wall openings with mud.

Feasibility

National programs considering the adoption of screening of residential houses as a public health strategy should assess:

- Whether the structure and condition of residential houses in respective communities allow for the installation of screening and are accessible.
- Whether adequate resources are available, particularly if houses require screening to be made bespoke and if there is a need to renovate some houses to allow screening
- The level of community buy-in (acceptability and/or willingness to implement the intervention)
- The feasibility of implementation if it is on a large scale, including the impact on resource use and potential changes in cost-effectiveness of the program, but also taking into account values, preferences and cultural norms of the main stakeholders.
- How the intervention will be delivered and maintained

Justification

The systematic review to inform WHO guidance in this area identified only two eligible published studies assessing epidemiological outcomes *(64)*. Both studies investigated the impact of house screening (screening of windows, ceilings, doors and/or eaves) with untreated materials against malaria. The evidence for the assessed outcomes was rated as low to moderate certainty due to risk of bias and imprecision. In the trials included in the systematic review, research teams deployed screening at the community level and as a result, currently there is no evidence as to the benefits and harms

of individuals or communities deploying screens themselves. The review identified several studies that were yet to be published on the efficacy of insecticide-treated screening, eave tubes or other forms of housing interventions but the data were not yet available for inclusion in the review. The panel concluded that untreated screening of residential houses may prevent malaria and reduce malaria transmission. The panel judged that policy makers considering house screening should assess the feasibility, acceptability, impact on equity and resources needed for screening houses in their contexts.

Research needs:

WHO encourages funding of high-quality research on the impact of interventions under the broad category of 'housing modifications' to further inform the development of specific WHO recommendations. Four trial results awaiting publication are likely to enrich the current evidence-base on housing modifications for preventing malaria and controlling malaria transmission, and publication of these studies is strongly encouraged.

A number of specific evidence gaps and associated requirements were identified:

- Further evidence is required on the impact (incidence of malaria (infection or clinical) and/or prevalence of malaria infection) and potential harms/unintended consequences of house screening, as well as other house modification interventions deployed singly or in combination.
- Epidemiological evidence is required on the efficacy against malaria of the same intervention implemented in different settings (where vector species may differ).
- Evidence on contextual factors (i.e., acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences) related to house screening, as well as other house modification interventions is needed.
- Resources needed, costs and cost-effectiveness, for various deployment options (at the programme-, community-, individual-level) of house screening need to be identified.
- Deployment mechanisms and community buy-in for house screening as well as other house modification interventions.

4.1.4 Other considerations for vector control

4.1.4.1 Special situations

Residual transmission

WHO acknowledges that even full implementation of ITNs or IRS will not be sufficient to completely halt malaria parasite transmission across all settings *(65)*. Some residual malaria parasite transmission will occur, even with optimal access to and usage of ITNs or in areas with high IRS coverage. Residual transmission occurs as a result of a combination of human and vector behaviours, for example, when people reside in or visit forest areas or do not sleep in protected houses, or when local mosquito vector species exhibit one or more behaviours that allow them to avoid ITNs or IRS, such as biting outside early in the evening before people have retired indoors and/or resting outdoors.

There is an urgent need for greatly improved knowledge of the bionomics of the different sibling species within malaria vector species complexes, and new interventions and strategies in order to effectively address residual transmission. While this knowledge is being gained and interventions are being developed, national malaria control programmes must prioritize the effective implementation of current interventions to reduce transmission to the lowest level possible. At the same time, they should collaborate with academic or research institutions to generate local evidence on the magnitude of the problem of residual transmission of malaria, including information on human and vector behaviours, and the effectiveness of existing and novel interventions.

Residual transmission is difficult to measure, as is the specific impact of supplementary tools on this component of ongoing transmission. Standardized methods for quantifying and characterizing this component of transmission are required in order to evaluate the effectiveness of single or combined interventions in addressing this biological challenge to malaria prevention and control and elimination.

Epidemics and humanitarian emergencies

In the acute phase of a humanitarian emergency, the first priorities for malaria control are prompt and effective diagnosis and treatment. Vector control also has the potential to play an important role in reducing transmission. However, the evidence base on the effectiveness of vector control interventions deployed in these settings is weak *(66)*.

During the acute phase, decisions on vector control and prevention will depend on:

- Malaria infection risk;
- Behaviour of the human population (e.g. mobility, where they are sleeping or being exposed to vector mosquitoes);
- Behaviour of the local vector population (e.g. indoor resting, indoor biting, early evening or night biting);
- The type of shelter available (e.g. ad-hoc refuse materials, plastic sheeting, tents, more permanent housing).

Effective case management can be supplemented with distribution of ITNs, first targeting population groups most susceptible to developing severe malaria, but with the ultimate goal of achieving and maintaining optimal coverage. IRS can also be applied in well-organized settings, such as transit camps, but is generally unsuitable where dwellings are scattered widely, of a temporary nature (less than three months) or constructed with surfaces that are unsuitable for spraying. IRS is best suited for protecting larger populations in more compact settings, where shelters are more permanent and solid.

Some vector control interventions and personal protection measures have been specifically designed for deployment in acute emergency situations. Plastic sheeting is sometimes provided in the early stages of humanitarian emergencies to enable affected communities to construct temporary shelters. In these new settlements, where shelter is very basic, use of insecticide-treated plastic sheeting (ITPS) to construct shelters may be a practical, acceptable and feasible approach. Laminated polyethylene tarpaulins that are impregnated with a pyrethroid during manufacture are suitable for constructing such shelters. As with IRS, ITPS is only effective against indoor resting mosquitoes, but the degree to which it impacts transmission has yet to be confirmed. Moreover, pyrethroid-treated plastic sheeting should not be deployed in areas where the local malaria vectors are resistant to pyrethroids.

Another intervention with potential for deployment in emergency situations is the long-lasting insecticide impregnated blanket or topsheet. Blankets or lightweight topsheets are often included in emergency relief kits. One advantage of blankets and topsheets is that they can be used anywhere people sleep (e.g. indoors, outdoors, any type of shelter). However, as with ITPS, the evidence base regarding the effectiveness of this approach is currently limited. Data from community RCTs of long-lasting pyrethroid-treated wash-resistant blankets and topsheets would be required to determine public health value and develop specific policy recommendations for such interventions.

In the post-acute phase, optimal coverage with ITNs or IRS may be feasible. Deployment of insecticide-treated plastic sheeting for shelter construction may be more practical in situations where ITN use or the application of IRS is not possible, although currently there is no WHO policy recommendation for this intervention.

Migrant populations and populations engaged in high-risk activities

As noted above, topical repellents and insecticide-treated clothing may be practical interventions for providing personal protection to specific populations at risk of malaria due to occupational exposure, e.g. military personnel, night-shift workers, forestry workers. However, the available evidence does not support the large-scale deployment of such interventions for reducing or preventing infection and/or disease in humans when assessed at the population level and few studies have reported disease outcomes at the individual level. Data demonstrating epidemiological impact would be required to determine their public health value for these populations.

4.1.4.2 Implementation challenges

Vector control plays a vital role in reducing the transmission and burden of vector-borne disease, complementing the public health gains achieved through disease management. Unfortunately, at present, the potential benefits of vector control are far from being fully realized. WHO identifies the following reasons for this shortfall *(67)*:

- The skills to implement vector control programmes remain scarce, particularly in the resource-poor countries in most need of effective vector-borne disease control. In some cases, this has led to control measures being implemented that are unsuitable, poorly targeted or deployed at insufficient coverage. In turn, this has led to suboptimal resource use and sometimes avoidable insecticide contamination of the environment;
- Insecticide application in agriculture and poor management of insecticides in public health programmes have contributed to resistance in disease vectors; and
- Development programmes, including irrigated agriculture, hydroelectric dam construction, road building, forest clearance, housing development and industrial expansion, all influence vector-borne diseases, yet opportunities for intersectoral collaboration and for adoption of strategies other than those based on insecticides are seldom realized.

Acceptability, participation and ethical considerations

Acceptability and end-user suitability of the vector control interventions included in the Guidelines were considered when developing the Evidence-to-Decision Frameworks, as part of the GRADE process.

ITNs are generally acceptable to most communities. In many malaria-endemic countries, untreated nets were in use for many years prior to the introduction of ITNs and, even where there is not a long history of their use, they have become familiar tools for preventing mosquito bites. Individuals often appreciate the extra privacy afforded by a net, as well as its effectiveness in controlling other nuisance insects. In very hot climates, ITNs may be less acceptable, as they are perceived to reduce air flow, making it too hot to allow for a comfortable sleep. In areas where mosquito densities are low or where malaria transmission is low, individuals and communities may perceive less benefit in

using nets.

Community acceptance of IRS is critical to the programme's success, particularly as it involves disruption to the household, requiring householders to remove certain articles and allow spray teams to enter all rooms of the house. Repeated, frequent spraying of houses over extended periods can lead to refusal by householders. Reduced acceptance has been an impediment to effective IRS implementation in various parts of the world *(68)*.

Larviciding for malaria vector control is currently not deployed at the scale of ITNs or IRS, and many communities are therefore unfamiliar with it. Larviciding is likely to be more acceptable in communities that have a good understanding of the lifecycle of mosquitoes and the link with the transmission of malaria or other diseases. Community members may have concerns about larvicides being applied to drinking water or other domestic water sources. A well-designed community sensitization programme is required to ensure that communities fully understand the intervention and that any concerns about health and safety aspects are addressed.

Community participation in the implementation of vector control interventions is often in the form of "instruction" and "information", with decisions about the need for interventions being made at international and national levels. Taking into account communities' views on the recommended interventions may promote acceptance and adherence to the intervention. Increased levels of participation (e.g. consultation, inclusion and shared decision-making) should ideally be included in the future development of improved and new vector control interventions, from inception through to the planning and implementation stages.

WHO acknowledges that appropriate policy-making often requires explicit consideration of ethical matters in addition to scientific evidence. However, the ethical issues relevant to vector-borne disease control and research have not previously received the analysis necessary to further improve public health programmes. Moreover, WHO Member States lack specific guidance in this area. The Seventieth World Health Assembly *(69)* requested the Director-General "to continue to develop and disseminate normative guidance, policy advice and implementation guidance that provides support to Member States to reduce the burden and threat of vector-borne diseases, including to strengthen human-resource capacity and capability for effective, locally adapted, sustainable and ethically sensitive vector control; to review and provide technical guidance on the ethical aspects and issues associated with the implementation of new vector control approaches in order to develop mitigating strategies and solutions; and to undertake a review of the ethical aspects and related issues associated with vector control implementation that include social determinants of health, in order to develop mitigating strategies and solutions to tackle health inequities." As a first step towards developing appropriate guidelines within the next two years, a scoping meeting was convened by WHO to identify the ethical issues associated with vector-borne diseases *(70)*. Further work has been undertaken to develop guidance. Once available, it will be reflected in the Guidelines.

Unique ethical issues associated with vector control that were identified at the February 2017 scoping meeting include the ethics of coercive or mandated vector control, the deployment of insecticides (and growing vector resistance to insecticides), and research on and/or deployment of new vector control technologies. Genetically modified mosquitoes are one such innovation that presents potential challenges, including how to prevent their spread beyond the intended geographical target areas and limit potential effects on the local fauna. WHO has established a robust evaluation process for new vector control interventions *(31)* in order to ensure that these are fully and properly assessed prior to any WHO recommendation for their deployment.

Equity, gender and human rights

The aim of all of the work of WHO is to improve population health and decrease health inequities. Sustained improvements to physical, mental and social well-being require actions in which careful attention is paid to equity, human rights principles, gender and other social determinants of health. A heightened focus on equity, human rights, gender and social determinants is expressed in the WHO Thirteenth General Programme of Work.

In pursuit of this outcome, WHO is committed to providing guidance on the integration of sustainable approaches that advance health equity, promote and protect human rights, are gender-responsive and address social determinants into WHO programmes and institutional mechanisms; promoting disaggregated data analysis and health inequality monitoring; and providing guidance on the integration of sustainable approaches that advance health equity, promote and protect human rights, are gender-responsive and address social determinants into WHO's support at country level *(71)*.

WHO advocates for optimal coverage with recommended vector control interventions. As such, malaria vector control is expected to be implemented without discrimination on the basis of age, sex, ethnicity, religion or other characteristics. In some cases, special effort is required to reach populations that are geographically isolated or adopt a nomadic lifestyle.

In contrast to the situation observed with HIV and TB, malaria has not been associated with systematic discrimination against individuals or groups assumed to be at a high risk of infection. However, malaria disproportionately affects the most vulnerable populations, including the rural poor, pregnant women, children, migrants, refugees, prisoners and indigenous populations. For these populations, social inequality and political marginalization may impede access to health services, and there may be additional barriers created by language, culture, poor sanitation, lack of

access to health information, lack of informed consent in testing and treatment, and inability to pay user fees for medical services. National malaria control programmes are increasingly encouraged to identify vulnerable groups and situations of inequitable access to services and to design approaches, strategies and specific activities to remove human rights and gender-related inequities.

Resource implications and prioritization

In this edition of the Guidelines, resource implications and the cost-effectiveness of vector control interventions were largely addressed by drawing on expert opinion within the GDG due to limited data to inform discussions. Although it is recognized that resource considerations should ideally be based on evidence, there was insufficient clarity on how to collate and present such data to the GDG and how to reflect this within the Guidelines at the time of writing. For future revisions of the Guidelines, it is envisaged that this area will be expanded upon for both new and existing recommendations.

The most recent systematic review of the cost and cost-effectiveness of vector control interventions was published in 2011, drawing on studies published between 1990 and 2010 *(72)*. The body of evidence collated was based on the use of ITNs/LLINs and IRS in a few sites in sub-Saharan Africa. The authors found large variations in the costs of intervention delivery, which reflected not only the different contexts but also the various types of costing methodologies employed; these studies were rarely undertaken alongside clinical and epidemiological evaluations. The review reported that, while ITNs/LLINs and IRS were consistently found to be cost-effective across studies, evidence to determine their comparative cost-effectiveness was insufficient. WHO GMP is working with partners to update the evidence review on the cost and cost-effectiveness evidence of the vector control interventions as part of an ongoing broader systematic review on the cost and cost-effectiveness of malaria control interventions and this review will be drawn upon in future GDG discussions. WHO GMP is also working with partners to ensure that the internal database on the cost and cost-effectiveness evidence of malaria control interventions is maintained, to support future GDG deliberations. It is also planned that systematic reviews commissioned in future will include a search of the literature on both the cost and cost-effectiveness of interventions under consideration. This information will be collated in advance of the GDG meetings to be considered as part of the evidence to decision framework alongside other evidence for an intervention, such as its epidemiological impact, acceptability, feasibility, and impact on equity. Furthermore, it is envisaged that the gaps in the economic evidence for the previously approved recommendations will be gradually closed by means of systematic searches of the literature for studies adding to the evidence in this area.

Given that resource considerations are highly context-specific and that the guideline content will not be sufficient to inform resource prioritization at (sub-)national levels, GMP is conducting further work to support country-level decision-making as part of the High burden to high impact initiative, and will expand on this work with a particular focus on informing deployment of an increasing number of interventions across different settings.

Human resources and entomological capacity

The *Global vector control response 2017–2030* *(13)* notes that effective and sustainable vector control is achievable only with sufficient human resources, an enabling infrastructure and a functional health system. A vector control needs assessment *(15)* will help to appraise current capacity, define what is needed to conduct proposed activities, identify opportunities for improved efficiencies in vector control, and guide resource mobilization.

Formulating an inventory of existing human, infrastructural (functioning insectary and entomological laboratory for species identification and resistance testing, vehicles, spray equipment, etc.), institutional and financial resources available, and making an appraisal of existing organizational structures for vector control are essential first steps. The inventory should cover all resources available at national and subnational levels, including districts. A broader appraisal of relevant resources available outside of the vector-borne disease programme, including in municipal governments, non-health ministries, research institutions and implementing partners, should be conducted. An evaluation of career structures within national and subnational programmes is also important. A comprehensive plan for developing the necessary human, infrastructural and institutional capacity within programmes should be formulated. The plan should identify any additional resources and associated costs involved in achieving the desired objectives and set out clear terms of reference for the different staffing positions required.

Capacity-building priorities for established staff should be defined through a comprehensive training needs assessment led by the ministry of health and aligned with available WHO guidance *(73)*.

4.1.4.3 Monitoring and evaluation of vector control

Monitoring involves routine data collection and reporting to determine progress made in the implementation of a programme or strategy. Evaluation involves rigorous assessment and attribution of impacts to a programme or strategy. The combination of monitoring and evaluation facilitates understanding of the cause-and-effect relationship between implementation and impact and is used to guide planning and implementation, to assess effectiveness, to

identify areas for improvement, and to account for resources used.

Monitoring and evaluation of vector control interventions is covered in detail in the WHO reference manual on malaria surveillance, monitoring and evaluation *(29)*. In addition, a brief synopsis of quality assurance is provided below.

Quality assurance of vector control interventions
Quality assurance is the implementation of systematic and well-planned activities to prevent substandard services or products.

Lower than expected effectiveness may be due to a variety of factors related to implementation. These can include incorrect application of the intervention, inadequate procurement planning, poor quality of deployed products and failure to achieve optimal coverage. Quality assurance efforts should be continuous, systematic and independent. Continuous monitoring and supervision are required to ensure that staff are adequately trained and follow technical guidelines for pesticide application and personal safety. Vector control programmes must include a quality assurance programme designed to monitor the effectiveness of the control activities. A quality assurance programme should monitor applicator performance and control outcomes.

The WHO Model Quality Assurance System for Procurement Agencies *(74)* details the quality assurance steps and processes involved in procuring pharmaceutical products and diagnostics, but the principles are equally applicable to vector control products.

For vector control products, the key elements of quality assurance are:

- Sourcing only products prequalified by WHO for deployment against malaria vectors;
- Requesting the supplier/manufacturer to provide a Certificate of Analysis for each batch of the product actually being supplied;
- Pre-shipment inspection and sampling according to WHO guidance and/or International Organization for Standardization (ISO) standards, performed by an independent sampling agent;
- Pre-shipment testing conducted by an independent quality control laboratory (WHO prequalified, or ISO 17025 or Good Laboratory Practice accredited) to determine that the product conforms to approved specifications according to the WHO/CIPAC test methods;
- Testing on receipt in country (post-shipment quality control testing) should only be conducted if specific risks related to transport have been identified or specific concerns over potential product performance justify this additional expense;
- Tender conditions should include provisions for free-of-cost replacement of shipments that fail quality control checks and disposal of failed lots;
- Post-marketing surveillance may be required, depending on the product and context, to monitor performance over time in order to ensure that products continue to conform to their specifications and/or recommended performance as set by WHO. For ITNs, this may require testing both physical durability and insecticidal efficacy. For IRS products, bioefficacy on sprayed surfaces of a different nature (e.g. mud, brick), as applicable, should be periodically tested according to WHO procedures when an insecticide is first introduced into a country. Subsequent measurement of insecticide decay on sprayed surfaces should be done only if necessary, as it will incur additional expense. Countries can make post-marketing surveillance a priority in cases where there are no country-specific data on certain ITNs or IRS products, or where anecdotal data on poor performance of certain products may exist. Agreement on the need and scope of the proposed activities should be reached by all in-country stakeholders, including the national regulatory authority. All evaluations should follow WHO guidance.

Quality assurance of the field application of vector control interventions should form an integral part of the national programme's strategy and should include:

- High-quality training for all staff engaged in field implementation of vector control interventions;
- Regular supervision, monitoring and follow-up of field operations;
- Periodic testing of the quality of IRS operations through WHO cone bioassay of sprayed surfaces;
- Periodic testing of the insecticide concentration on ITNs using WHO cone bioassay and/or chemical analysis.

The WHO cone bioassay (preferably using fully susceptible anophelines obtained from insectaries) is currently the only tool available for assessing the bioefficacy of ITNs and the quality of the application of IRS insecticides to walls and other internal surfaces. Colorimetric assays are under development that aim to rapidly quantify the amount of insecticide on a sprayed surface in the field without the need for a bioassay on live mosquitoes. These colorimetric assays, when available, should enable programmes to increase the speed and ease of quality assurance testing of IRS applications.

4.1.5 Research needs

WHO's guideline development process for new vector control interventions relies on evidence from at least two well-

designed and well-conducted studies with epidemiological endpoints to demonstrate the public health value of the intervention. If the initial two studies generate contradictory or inconsistent results or suffer from design limitations that preclude comprehensive assessment of an intervention's potential public health value, further trials with epidemiological endpoints may be required. As such, WHO encourages the use of appropriate study designs, including the generation of baseline data and appropriate follow-up times that consider the characteristics of the intervention and its intended deployment, expected durability/residual efficacy and replacement intervals, and the epidemiology (e.g., pathogen transmission intensity) of the selected study site. WHO encourages studies to be conducted for durations that maximize the likelihood that the study objectives and targeted statistical power will be robustly achieved so as to strengthen the evidence used to inform deliberations by a GDG regarding a potential WHO recommendation. Detailed descriptions of the setting, interventions deployed, and vector species targeted are required. Investigators are encouraged to share their study design and methodology with WHO prior to commencing the study in order to enable the VCAG to validate whether the data generated are likely to provide quality evidence to inform the development of a WHO recommendation. High research standards should be employed in conducting, analysing and reporting studies, ensuring that studies are adequately powered, and appropriate randomization methods and statistical analyses are used. WHO requires studies to be conducted in compliance with international ethical standards and good clinical and laboratory practices. Further information on evaluation standard for vector control interventions can be found in *Norms, standards and processes underpinning WHO vector control policy development (31)*.

Intervention	Research needs
Pyrethroid-only ITNs	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) as well as potential harms and/or unintended consequences* of new types of nets and insecticides in areas where resistance to pyrethroids is high.
	Determine the comparative effectiveness and durability of different net types.
	Determine the effectiveness of nets in situations of residual/ outdoor transmission.
	Determine the impact of ITNs in transmission 'hotspots' and elimination settings.
Pyrethroid-PBO nets	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences on pyrethroid-PBO nets.
Indoor residual spraying (IRS)	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of IRS.
	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) as well as harms and/or unintended consequences of IRS in urbanized areas with changing housing designs.
	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) as well as potential harms and/or unintended consequences of IRS using new insecticides in areas where mosquitoes are resistant to currently deployed insecticides.
	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) of IRS in areas with different mosquito behaviours (such as in areas with outdoor transmission).
	Given the relatively high cost of implementing IRS, especially in the context of growing insecticide resistance, and when delivering IRS in remote areas, there is a need to investigate new approaches to the implementation of IRS to increase cost-effectiveness.
Combining IRS and ITNs	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or

	unintended consequences of combining non-pyrethroid IRS with ITNs vs ITNs only in areas with insecticide resistant mosquito populations.
	Determine whether there are comparative benefits (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of combining non-pyrethroid IRS with ITNs vs IRS only in areas with insecticide resistant mosquito populations.
	Determine the acceptability of combining IRS and ITNs among householders and communities.
	Evaluation of new tools for monitoring the quality of IRS and ITN interventions is needed.
Larviciding	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of larviciding.
	Evaluation of new technologies for identifying aquatic habitats is needed.
Larval habitat manipulation/ modification	Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of the different interventions. Epidemiological evidence is required on the efficacy against malaria of the same intervention implemented in different settings (where vector species may differ).
	Detailed descriptions of the interventions deployed, as well as larval habitat types and vector species targeted are needed. The impact of the intervention on the water conditions of the larval habitats should be assessed, i.e. properties of the habitat that the intervention aims to modify such as water flow, volume, sunlight penetration, salinity or other physical conditions.
	Evidence is needed on contextual factors, (i.e., acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences) related to larval habitat modification and/or manipulation.
Larvivorous fish	Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of the use of larvivorous fish.
Topical repellents	Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of topical repellents for individuals in specific settings and target populations.
Insecticide-treated clothing	Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of insecticide-treated clothing in the general population.
	Identify approaches to enhance acceptability/desirability and increase uptake and adherence.
	Develop formulations that improve the durability of insecticidal efficacy.
Spatial/airborne repellents	Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms and/or unintended consequences of spatial/airborne repellents.
	Develop spatial repellent

	insecticide formulations that provide a long-lasting effect.
Repellents in general	Generate epidemiological and/or entomological evidence of whether repellents cause diversion of malaria mosquitoes from a treated area to a neighbouring untreated area.
Space spraying	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) as well as potential harms and/or unintended consequences of space spraying, particularly in emergency situations.
House modifications	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) as well as potential harms/ unintended consequences of house screening, and other housing modification interventions deployed singly or in combination.
	Epidemiological evidence is required on the efficacy against malaria of the same intervention implemented in different settings (where vector species may differ).
	Evidence is needed on contextual factors (i.e., acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences) related to house screening, and other housing modification interventions.
	Determine the resources needs, costs and cost-effectiveness, for various deployment options (at the programme-, community-, individual-level) for house screening.
	Develop deployment mechanisms and community buy-in for house screening and other housing modification interventions.
Insecticide resistance management	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) of different strategies for insecticide resistance management such as using rotations of insecticides, mosaics, etc.
	Determine the impact of insecticide resistance on key outcomes (malaria mortality, clinical disease and prevalence of infection).

* Harms/unintended consequences may include undesirable effects on individuals, the community, mosquito bionomics and the environment.

Other research needs and evidence gaps required to further update guidance were identified as follows:

- evidence on the linkage or correlation between the epidemiological and entomological endpoints used to demonstrate impact;
- evidence on contextual factors (i.e., structural challenges and opportunities, acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences in various settings) related to different vector control interventions;
- evidence to support the resources listed and other considerations for resource use provided under each recommended intervention in order to aid guidance on prioritization of interventions (wherever possible, following examples provided in other WHO guidance and guidelines); and
- evidence of the benefits (incidence of clinical malaria and/ or or prevalence of malaria infection) as well as harms/ unintended consequences of deployment of interventions in special situations. For example, a) interventions designed to control outdoor transmission of malaria, and b) protecting specific populations with high occupational exposure to malaria.

4.2 Preventive chemotherapies & Mass drug administration

Chemoprevention is the use of antimalarial medicines for prophylaxis and for preventive treatment. The use of medicines for chemoprophylaxis is not addressed in detail in the current guidelines, beyond the following short description of general conditions of use.

Malaria may be prevented by taking drugs that inhibit liver-stage (pre-erythrocytic) development (causal prophylaxis) or drugs that kill asexual blood stages (suppressive prophylaxis). Causal prophylactics (atovaquone + proguanil, primaquine) can be stopped soon after leaving an endemic area, whereas suppressive prophylactics must be taken for at least 4 weeks after leaving the area in order to eliminate asexual parasites emerging from the liver weeks after exposure. For travellers, chemoprophylaxis is started before entering the endemic area to assess tolerability and for slowly eliminated drugs to build up therapeutic concentrations.

Preventive treatments prevent malarial illness by achieving therapeutic drug levels in the blood throughout the period of greatest risk. Current WHO-recommended malaria chemopreventive therapies include the intermittent preventive treatment of malaria in pregnancy (IPTp), intermittent preventive treatment of malaria in infants (IPTi) and seasonal malaria chemoprevention (SMC).

Mass Drug Administration to reduce morbidity and mortality
Mass antimalarial drug administration (MDA) has been used extensively in various forms over the past 80 years. The objective is to provide therapeutic concentrations of antimalarial drugs to as large a proportion of the target population as possible in order to cure any asymptomatic infections and also to prevent reinfection during the period of post-treatment prophylaxis *(76)*. Mass drug administration rapidly reduces the prevalence and incidence of malaria in the short term, but more studies are required to assess its longer-term impact, the barriers to community uptake, and its potential contribution to the development of drug resistance *(77)*.

The aim of MDA has generally been to reduce malaria transmission (see section 6) but, in recent years, time-limited MDA has also been used to reduce malaria morbidity and mortality for epidemic control as part of the initial response, along with the urgent introduction of other interventions. Use of time-limited MDA has also been used to reduce malaria morbidity and mortality in complex emergencies, during exceptional circumstances when the health system is overwhelmed and unable to serve the affected communities.

During mass campaigns, every individual in a defined population or geographical area is requested to take antimalarial treatment at approximately the same time and at repeated intervals in a coordinated manner. This requires extensive community engagement to achieve a high level of community acceptance and participation. Informed, enthusiastic community participation and comprehensive support structures are needed.

The optimum timing depends of the elimination kinetics of the antimalarial (e.g. using dihydroartemisinin + piperaquine, the drug is given monthly for 3 months at treatment doses, as the residual piperaquine levels suppress reinfections for 1 month). Depending on the contraindications for the medicines used, pregnant women, young infants and other population groups may need to be excluded from the campaign. Thus, the drugs used, the number of treatment rounds, the optimum intervals and the support structures necessary are all context-specific and the subject of active research.

Medicines used for MDA should be of proven efficacy in the implementation area and preferably have a long half-life. WHO recommends that a medicine different from that used for first line treatment be used for MDA. Programmes should include monitoring of efficacy, safety and the potential emergence of resistance to the antimalarial medicines deployed for MDA *(78)*.

WHO supports the need for more research on the optimum methods of implementing MDA programmes, promoting community participation and compliance with treatment, and evaluating their effectiveness. Modelling can help guide the optimum method of administering MDA in different epidemiological circumstances and predict its likely impact.

The evidence for MDA use to reduce malaria disease burden will be reviewed in 2021 and guidance developed accordingly. In the absence of sufficient evidence, WHO does not recommend the use of MDA in situations other than for areas approaching elimination, epidemics, and complex emergencies *(79)*.

Please refer to the WHO Mass drug administration for falciparum malaria: a practical field manual *(80)*.

4.2.1 Intermittent preventive treatment of malaria in pregnancy (IPTp)

Strong recommendation for , High certainty evidence

In malaria-endemic areas in Africa, provide intermittent preventive treatment with SP to all women in their first or second pregnancy (SP-IPTp) as part of antenatal care. Dosing should start in the second trimester and doses should be given at least 1 month apart, with the objective of ensuring that at least three doses are received.

Practical Info

Malaria infection during pregnancy is a major public health problem, with substantial risks for the mother, her fetus and the newborn. WHO recommends a package of interventions for preventing and controlling malaria during pregnancy, which includes promotion and use of insecticide-treated nets, indoor residual spraying, appropriate case management

with prompt, effective treatment and, in areas with moderate to high transmission of *P. falciparum*, administration of IPTp-SP.

In the systematic review *(81)*, the reduction in risk for low birth weight was consistent for a wide range of levels of resistance to SP. The group that received three or more doses also had less placental malaria. There were no differences in serious adverse events between the two groups. On the basis of these results, WHO now encourages that, in areas of moderate-to-high malaria transmission of Africa, IPTp-SP be given to all pregnant women at each scheduled antenatal care visit, starting as early as possible in the second trimester, provided that the doses of SP are given at least 1 month apart. The objective is to ensure that at least three doses are received.

In several countries in Africa, some *P. falciparum* parasites carry quintuple mutations (triple *Pfdhfr* and double *Pfdhps*), which are associated with therapeutic failure of SP treatment. IPTp-SP remains effective in preventing the adverse consequences of malaria on maternal and fetal outcomes in areas where a high proportion (> 90%) of *P. falciparum* parasites carry these quintuple mutations. Therefore, IPTp-SP should still be administered to women in these areas. In areas where *P. falciparum* carrying six mutations (either *Pfdhfr* 164 or *Pfdhps* 581) are prevalent, the efficacy of IPTp-SP may be compromised. It is unclear by how much.

There are currently insufficient data to define the level of *P. falciparum* transmission at which IPTp-SP may cease to be cost-effective from a public health point of view. Furthermore, the natural fluctuations in malaria incidence from year to year, the low cost of the intervention and the challenges of IPTp re-introduction after withdrawal indicate that caution must be exercised in discontinuing IPTp-SP because of recent reductions in transmission. More data will be needed to allow the formulation of more specific guidelines.

Please refer to the *WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP) (82)*.

Evidence To Decision

Benefits and harms

Desirable effects

- Three or more doses of sulfadoxine–pyrimethamine during pregnancy increase mean birth weight and reduce the number of low-birth-weight infants to a greater extent than two doses (high-quality evidence).

Undesirable effects

- No adverse effects have been reported.

Certainty of the Evidence

High

Overall certainty of evidence for all critical outcomes: high.

Preference and values

Justification

GRADE

In a systematic review of IPTp, seven trials involving direct comparison of two doses of SP with three or more doses monthly were evaluated *(81)*. The trials were conducted in Burkina Faso, Kenya, Malawi, Mali and Zambia between 1996 and 2008.

In comparison with two doses of SP, three or more doses:

- increased the mean birth weight by about 56 g (95% CI, 29–83; seven trials, 2190 participants, high-quality evidence);
- reduced the number of low-birth-weight infants by about 20% (RR, 0.80; 95% CI, 0.69–0.94; seven trials, 2190 participants, high-quality evidence);
- reduced placental parasitaemia by about 50% (RR, 0.51; 95% CI, 0.38– 0.68; six trials, 1436 participants, high-quality evidence); and
- reduced maternal parasitaemia by about 33% (RR, 0.68; 95% CI, 0.52– 0.89; seven trials, 2096 participants, high-quality evidence).

The trials conducted to date have not been large enough to detect or exclude effects on spontaneous miscarriage, stillbirth or neonatal mortality (very low- quality evidence).

Other considerations
The guideline development group noted that the beneficial effects were obvious in women in their first and second pregnancies. There was less information on women in their third or later pregnancy, but the available information was consistent with benefit.

Rationale for the recommendation
The Guideline Development Group noted that effects were seen in women in their first and second pregnancy. Less information was available on women in their third or later pregnancy, but this information was consistent with benefit.

4.2.2 Intermittent preventive treatment of malaria in infants (IPTi)

Strong recommendation for

In areas of moderate-to-high malaria transmission of Africa, where SP is still effective, provide intermittent preventive treatment with SP to infants (< 12 months of age) (SP-IPTi) at the time of the second and third rounds of vaccination against diphtheria, tetanus and pertussis (DTP) and vaccination against measles.

*unGRADEd recommendation, anticipated to be updated in 2022

Practical Info

The vast majority of malaria cases and deaths in Africa occur in young children. The key interventions recommended to prevent and control malaria in this vulnerable group include use of insecticide-treated nets or indoor residual spraying, prompt access to diagnosis and treatment and, in areas of Africa with moderate to high transmission of *P. falciparum*, administration of IPTi. This consists of co-administration of a full therapeutic course of SP with the second and third vaccinations against DTP and vaccination against measles delivered routinely in the Expanded Programme on Immunization —usually at 10 weeks, 14 weeks and about 9 months of age, respectively—to infants at risk for malaria *(84)*.

WHO encourages co-administration of SP-IPTi in areas with moderate-to-high malaria transmission (>250 cases per 1000 population and a prevalence of *P. falciparum/P. vivax* ≥10%) of Africa. IPTi has been shown to be efficacious where parasite resistance to SP, defined as a prevalence of the Pfdhps 540 mutation is ≤ 50%.

The studies showed no evidence of any adverse effects of SP-IPTi on infants' serological responses to vaccines (DTP, polio, hepatitis B, *Haemophilus influenzae* B, yellow fever or measles). A rebound effect in terms of greater susceptibility to malaria after termination of SP-IPTi, although reported in some studies, was not found in the pooled analysis.

SP-IPTi should not be given to infants receiving a sulfa-based medication for treatment or prophylaxis, including co-trimoxazole (trimethoprim–sulfamethoxazole), which is widely used as prophylaxis against opportunistic infections in HIV-infected infants.

Surveillance of molecular markers of SP resistance should accompany SP-IPTi, in particular the distribution and prevalence of *Pfdhps* 540 mutations, which is a surrogate measure of SP efficacy.

Please refer to the *Intermittent preventive treatment for infants using sulfadoxine-pyrimethamine (IPTi-SP) for malaria control in Africa: implementation field guide (84)*.

Justification

Evidence supporting the recommendation
The recommendation is based on a pooled analysis of 6 randomized placebo-controlled studies on SP-IPTi conducted in areas of moderate to high transmission of malaria *(83)*:

SP-IPTi delivered through EPI provides an overall protection in the first year of life against clinical malaria [30.3% (95% CI: 19.8%–39.4%)], anaemia [21.3% (95% CI: 8.3%–32.5%)], hospital admissions associated with malaria parasitaemia [38.1% (95% CI 12.5%–56.2%)], and all-cause hospital admissions [22.9% (95% CI: 10.0%–34.0%)]. SP-IPTi offers a personal protection against clinical malaria for a period of approximately 35 days following the administration of each dose.

Other considerations
The recommendation was formulated at the fourth consultative meeting of the Technical Expert Group of Preventive Chemotherapy, GMP, WHO, April 2009 which reviewed all evidence available at the time. The quality of evidence has not been formally assessed.

Remarks
The recommendation is based on a pooled analysis of 6 randomized placebo-controlled studies on SP-IPTi conducted in areas of moderate to high transmission of malaria: SP-IPTi delivered through EPI provides an overall protection in the first year of life against clinical malaria [30.3% (95% CI:

19.8%–39.4%)], anaemia [21.3% (95% CI: 8.3%–32.5%)], hospital admissions associated with malaria parasitaemia [38.1% (95% CI 12.5%–56.2%)], and all-cause hospital admissions [22.9% (95% CI: 10.0%–34.0%)]. SP-IPTi offers a personal protection against clinical malaria for a period of approximately 35 days following the administration of each dose.

Rationale for the recommendation
The recommendation was formulated at the fourth consultative meeting of the Technical Expert Group (TEG) of Preventive Chemotherapy, GMP, WHO, April 2009 which reviewed all evidence available at the time. The evidence was not re-evaluated during this guideline process and therefore the quality of evidence has not been formally assessed.

4.2.3 Seasonal malaria chemoprevention (SMC)

Strong recommendation for , High certainty evidence

In areas with highly seasonal malaria transmission in the Sahel subregion of Africa, provide seasonal malaria chemoprevention (SMC) with monthly amodiaquine + SP for all children aged < 6 years during each transmission season.

Practical Info

Throughout the Sahel subregion, most mortality and morbidity from malaria among children occurs during the rainy season, which is generally short. The interventions currently recommended by WHO for the control of malaria are insecticide-treated nets or indoor residual spraying for vector control, prompt access to diagnostic testing of suspected malaria and treatment of confirmed cases. SMC is defined as the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent illness, with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest risk.

SMC is therefore recommended in areas of highly seasonal malaria transmission throughout the Sahel subregion. A complete treatment course of amodiaquine + SP should be given to children aged 3–59 months at monthly intervals, beginning at the start of the transmission season, and continuing until its end (usually three or four months), provided the drugs retain sufficient antimalarial efficacy when used as SMC.

The results of clinical trials indicate that a high level of protection against uncomplicated clinical malaria is likely to be maintained for 4 weeks after administration of each course of amodiaquine + SP; thereafter, protection appears to decay rapidly.

Treatment of breakthrough *P. falciparum* infections during the period of SMC should not include either amodiaquine or SP, and, in areas where SMC is implemented, alternative antimalarial combinations containing neither amodiaquine nor SP must be made available for the treatment of clinical malaria in the target age group.

IPTi and SMC should not be administered concomitantly; therefore, IPTi should not be used in target areas for SMC. SMC should not be given to children with severe acute illness or who are unable to take oral medication, or to HIV-positive children receiving co-trimoxazole, or children who have received a dose of either amodiaquine or SP during the past month or children with allergy to either drug.

Please refer to the *Seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine in children: A field guide (86)*.

Evidence To Decision

Benefits and harms

Desirable effects

- SMC prevents up to three quarters of malaria episodes (high-quality evidence).
- SMC prevents up to three quarters of severe malaria episodes (high-quality evidence).
- SMC may cause a small reduction in mortality (moderate-quality evidence).

Undesirable effects

- The current regimen of amodiaquine + sulfadoxine–pyrimethamine causes vomiting in some children (high-quality

evidence).

Certainty of the Evidence

High

Overall certainty of evidence for all critical outcomes: high.

Preference and values

Justification

GRADE

In a systematic review *(85)*, SMC was directly compared with no prophylaxis in seven trials with a total of 12 589 children. All the trials were conducted in West Africa, and six of seven trials were restricted to children < 5 years.

In comparison with no chemoprophylaxis, SMC:

- prevented up to 75% of malaria episodes (rate ratio, 0.26; 95% CI, 0.17–0.38; six trials, 9321 participants, high-quality evidence);
- prevented up to 75% of severe malaria episodes (rate ratio, 0.27; 95% CI, 0.10–0.76; two trials, 5964 participants, high-quality evidence); and
- may be associated with a reduction in mortality (risk ratio, 0.66; 95% CI, 0.31–1.39; six trials, 9533 participants, moderate-quality evidence).

These effects remained even when use of insecticide-treated nets was high (two trials, 5964 participants, high-quality evidence).

The current regimen (amodiaquine + SP) caused vomiting after the first dose in some children (high-quality evidence).

Remarks

The target areas for implementation are those where:

- malaria transmission and most clinical malaria cases occur during a short period of about 4 months;
- the clinical attack rate of malaria is > 0.1 episode per child during the transmission season; and
- amodiaquine + sulfadoxine–pyrimethamine remains efficacious (> 90% efficacy).

SMC should not be given to children with severe current illness, who are already taking co-trimoxazole or with a known allergy to amodiaquine or sulfadoxine–pyrimethamine.

Rationale for the recommendation

The Guideline Development Group endorsed the previous recommendation for SMC made by the WHO Technical Expert Group on Preventive Chemotherapy in May 2011, subsequently reviewed and endorsed by the WHO Malaria Policy Advisory Committee in January 2012.

4.3 Vaccine

The use of vaccines for the prevention of malaria

Immunization is a success story for global health and development, saving millions of lives every year. Between 2010 and 2018, 23 million deaths were averted with the measles vaccine alone. The number of infants vaccinated annually – more than 116 million, or 86% of all infants born – has reached the highest level ever reported. More than 20 life-threatening diseases can now be prevented through immunization. Since 2010, 116 countries have introduced vaccines that they did not previously use, including those against major killers such as pneumococcal pneumonia, diarrhoea, cervical cancer, typhoid, cholera and meningitis *(87)*.

A vaccine has the potential to increase the proportion of children with access to one or more approaches to malaria prevention tools (e.g. ITNs). Introduction of the RTS,S/AS01 vaccine in the Malaria Vaccine Implementation Programme extended the reach of malaria prevention tools; across the three pilot countries more than two thirds of children who reportedly did not sleep under an ITN received at least the first dose of RTS,S/AS01. Overall, vaccine introduction increased to over 90% the proportion of children in each of the three countries with access to one or more malaria prevention tool (ITN or RTS,S/AS01). Vaccine uptake was equitable by sex and socioeconomic status and had no negative effects on the uptake of other childhood vaccinations, ITN use, or health-seeking behaviour for febrile illness *(88)*.

Malaria vaccine pipeline

The RTS,S/AS01 vaccine is the first and currently the only

malaria vaccine to be recommended for use by WHO. RTS,S/AS01 is the result of decades of public–private scientific partnership, with origins dating back to 1983. Although there are a handful of *P. falciparum* malaria vaccine candidates in the clinical stages of evaluation, RTS,S/AS01 is the first vaccine to have completed Phase 3 evaluations *(89)* and the first to be provided to children through routine immunization services as part of phased pilot introductions. In 2015, RTS,S/AS01 received a positive scientific opinion from the European Medicines Agency *(90)* and in 2019, it received national regulatory authorization for use in the pilot areas of Ghana, Kenya and Malawi for the Malaria Vaccine Implementation Programme. A separate trial of RTS,S/AS01 took advantage of the vaccine's high initial efficacy by administering a primary series of three doses at monthly intervals and subsequent annual single doses just prior to the intense, 4–5 month-long high transmission season. The vaccine was non-inferior to seasonal malaria chemoprevention (SMC); the combination of the vaccine and SMC was significantly better than either SMC alone or RTS,S/AS01 alone *(91)*.

Two vaccine candidates are approaching late-stage clinical evaluation: the R21/MatrixM vaccine candidate targeting *PfCSP* protein *(92)* and the attenuated whole sporozoite vaccine *Pf*SPZ *(93)*. Additional candidates targeting other malaria life-cycle stages include the Rh5 blood-stage vaccine candidate *(94)* and *Pfs*25 and *Pfs230* vaccine candidates targeting sexual-stage antigens to prevent human-to-mosquito transmission (NCT02942277). New technologies, such as DNA- and mRNA-based vaccines *(95)*, the ongoing development of adjuvants *(96)*, and delivery platforms such as virus-like particles (VLPs; the delivery platform used for RTS,S/AS01) and vesicle-based technologies are being explored for use in malaria vaccines. WHO has developed guidelines on the quality, safety, and efficacy of the recombinant malaria vaccines targeting pre-erythrocytic and blood stages of *P. falciparum (97)* and a set of preferred product characteristics (PPCs). The PPCs include attributes ranging from safety and efficacy to route of administration, product stability and storage, in order to help support the ongoing development of new malaria vaccines. These PPCs *(98)* are currently being updated to reflect recent advances in malaria vaccine research and development.

National programmes for immunization and malaria

The RTS,S/AS01 malaria vaccine should be provided as part of a comprehensive malaria control strategy. All malaria control interventions provide partial protection and the highest impact is achieved when multiple interventions are used concomitantly. Appropriate mixes of interventions should be identified for different subnational strata. These are defined by national malaria programmes (NMPs) on the basis of the local malaria epidemiology (e.g. transmission intensity, age pattern of severe disease, vector species, insecticide resistance patterns) and contextual factors (e.g. structure and function of the formal health system).

Where applicable, the malaria vaccine should be integrated into relevant immunization guidelines and malaria control strategies, including national strategic plans to define the package of interventions needed to optimize malaria control and elimination in a country. WHO is developing operational guidance on principles for the subnational tailoring of malaria interventions.

Country considerations and planning for malaria vaccine introduction should rely on data-driven decision-making in which NMP and Expanded Programme on Immunization (EPI) staff consider parasite prevalence, disease burden, existing malaria interventions, vaccine delivery, the logistics, strength and support of the immunization programme, and the availability of funding support, among other factors. Decision making on whether to adopt and implement the malaria vaccine should be in close collaboration between the NMP and the EPI and other relevant ministry of health departments. In pilot countries, the NMP actively participated in the vaccine introduction and implementation activities in order to ensure that malaria control perspectives were incorporated and to maximize opportunities for integration. Malaria vaccine technical working groups were established with joint participation from the EPI and NMP to provide technical guidance on decision-making and a forum for alignment. The EPI leads the logistics of vaccine roll-out and delivery to relevant health facilities. The EPI manages the planning and activities required for vaccine introduction and programme implementation, such as vaccine and supplies procurement; advocacy; communications and social mobilization; training and supervision of health personnel; logistics and cold chain for vaccine storage; service delivery; and monitoring and evaluation. Both fixed sites for vaccination at health care facilities and opportunities for mobile vaccination delivery or outreach services should be considered. To increase uptake, periodic mass vaccination campaigns or periodic intensified routine immunization activities can be deployed. Monitoring of coverage levels occurs through routine health facility data; the malaria vaccine can be integrated into the District Health Information Software 2 (DHIS2) platform alongside NMP and EPI indicators.

Please refer to the WHO malaria vaccine position paper for more information on the malaria vaccine *(99)*.

Please refer to WHO Immunization, Vaccines and Biologicals for more resources and published guidance, including the forthcoming "Guide for introducing a malaria vaccine."

Strong recommendation for , High certainty evidence

New

The RTS,S/AS01 malaria vaccine should be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO.

- *The RTS,S/AS01 malaria vaccine should be provided in a four-dose schedule in children from 5 months of age.*
- *Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a five-dose strategy, in areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks.*
- *Countries that choose to introduce the vaccine in a five-dose seasonal strategy are encouraged to document their experiences, including adverse events following immunization.*
- *RTS,S/AS01 malaria vaccine should be provided as part of a comprehensive malaria control strategy.*

Practical Info

Vaccine characteristics, content, dosage, administration and storage

RTS,S/AS01 is a pre-erythrocytic recombinant protein vaccine, based on the RTS,S recombinant antigen. It comprises the hybrid polypeptide RTS, in which regions of the *P. falciparum* circumsporozoite protein known to induce humoral (R region) and cellular (T region) immune responses are covalently bound to the hepatitis B virus surface antigen (S). The vaccine is currently produced as a two-dose RTS,S powder to be reconstituted with a two-dose AS01 adjuvant system suspension. After reconstitution, the total volume is 1ml (two doses of 0.5 ml). No preservative is included in either the RTS,S formulation or the AS01 adjuvant system. The vials should therefore be discarded at the end of the vaccination session, or within six hours after opening, whichever comes first. The reconstituted 0.5ml vaccine should be administered by injection into the deltoid muscle in children aged 5 months or older. The shelf life of the RTS,S/AS01 vaccine is three years. A vaccine vial monitor is on the AS01 vial *(90)*.

Schedule

WHO recommends that the first dose of vaccine be administered from 5 months of age. There should be a minimum interval of four weeks between doses. The vaccine should be administered in a three-dose primary schedule, with a fourth dose provided 12–18 months after the third dose to prolong the duration of protection. However, there can be flexibility in the schedule to optimize delivery, for example, to align the fourth dose with other vaccines given in the second year of life. Children who begin their vaccination series should complete the four-dose schedule *(99)*.

Optional schedule for settings with highly seasonal malaria or perennial malaria with seasonal peaks

Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a five-dose strategy in areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks. This strategy seeks to maximize vaccine impact by ensuring that the period of highest vaccine efficacy (just after vaccination) coincides with the period of highest malaria transmission. The primary series of three doses should be provided at monthly intervals, with additional doses provided annually prior to the peak transmission season. Countries that choose seasonal deployment of the RTS,S/AS01 vaccine are strongly encouraged to document their experiences, including the vaccine's effectiveness, feasibility and occurrence of any adverse events following immunization—as additional input for future updates to the guidance. WHO also encourages international and national funders to support relevant learning opportunities *(99)*.

Co-administration

RTS,S/AS01 given in conjunction with routine childhood vaccines has been evaluated in several trials *(105)(106)*. Non-inferiority criteria were met for all vaccines given with RTS,S/AS01, in comparison with the same vaccines given without RTS,S/AS01. RTS,S/AS01 can be given concomitantly with any of the following monovalent or combination vaccines: diphtheria, tetanus, whole cell pertussis, acellular pertussis, hepatitis B, *Haemophilus influenzae* type b, oral poliovirus, measles, rubella, yellow fever, rotavirus and pneumococcal conjugate vaccines *(90)*. No co-administration studies have been conducted with RTS,S/AS01 and meningococcus A, typhoid conjugate, cholera, Japanese encephalitis, Tick-borne encephalitis, rabies, mumps, influenza or varicella vaccines *(99)*.

Identifying areas for vaccine introduction

Decisions about where to introduce the malaria vaccine should be made in the context of national planning of mixes of malaria interventions and strategies and considering the need for subnational tailoring of packages of interventions. Subnational tailoring considers variations in malaria epidemiology, health system structure and function, and broader contextual considerations.

Current WHO guidance defines moderate or high transmission settings as those with an annual incidence greater than about 250 cases per 1000 population or a prevalence of *P. falciparum* infection in children aged 2—10 years (*Pf*$PR_{2\text{-}10}$) of approximately 10% or more. These are indicative values and should not be used as strict thresholds.

Vaccine safety

The RTS,S/AS01 vaccine is safe and well tolerated. There is a small risk of febrile seizures within seven days (mainly within 2—3 days) of vaccination. As with any vaccine introduction, proper planning and training of staff to conduct appropriate pharmacovigilance should take place beforehand.

The only contraindication to use of RTS,S/AS01 vaccine is severe hypersensitivity to any of the vaccine components*(90)*.

Vaccination of special populations

Malnourished or HIV-positive infants may be vaccinated with the RTS,S/AS01 vaccine using a standard schedule. These children may be at particular risk from malaria infection and the vaccine has been shown to be safe in these groups.

The vaccine should be provided to infants and young children aged 5—17 months of age who relocate to an area of moderate to high transmission, including during emergency situations.

The vaccine has been developed for use in young children living in malaria-endemic settings, and has not undergone full clinical testing in adults, nor is it recommended for adults. The vaccine is not indicated for travellers, who should use chemoprophylaxis and vector control methods to prevent malaria when traveling to endemic settings.

Surveillance

As for all new vaccines, the effectiveness and safety of the RTS,S/AS01 vaccine should be monitored post-introduction. Countries that choose to introduce the vaccine in a five-dose seasonal strategy are encouraged to document their experience, including adverse events following immunization.

Research priorities

The WHO-coordinated Malaria Vaccine Implementation Programme will continue through 2023, with continued monitoring of data on safety, impact, coverage achieved and the added benefit of the fourth dose. In areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks, operational research is needed specifically related to the seasonal delivery of vaccine doses, including annual preseason dosing after a primary series given through the routine health clinics. Further evaluation will be required to determine how best to deliver the combination of SMC and seasonal malaria vaccination in areas. Data should be collected on safety, immunogenicity, and effectiveness of annual doses beyond the fifth dose.

Considerations for immunization and health systems

The additional visits needed for RTS,S/AS01 are opportunities to provide other integrated and preventive health services. Efforts should be made to take advantage of these visits to catch up on missed vaccinations, administer Vitamin A, carry out deworming and other preventive interventions, and remind parents of the importance of continuing to use an ITN every night and seeking prompt diagnosis and treatment for fever.

A framework for allocation of limited supply

Supplies of the RTS,S/AS01 vaccine are expected to be limited in the short to medium term, and demand is expected to be high. WHO is working with partners to develop a framework to guide the allocation of the initial limited doses of malaria vaccine, using a transparent process that incorporates input from key parties, with appropriate representation and consultation. This framework will include dimensions of market dynamics, learning from experience, scientific evidence for high impact, implementation considerations and social values, including fairness and equity.

Evidence To Decision

Benefits and harms

The RTS,S/AS01 vaccine, provided in a four-dose schedule, has been demonstrated in clinical trials and the pilot implementation studies to have meaningful impact, with a substantial reduction in hospitalization for life-threatening severe malaria, which is considered to be a surrogate indicator for the impact on mortality.

- There were significant reductions in clinical malaria (51%); and severe malaria (45%), demonstrated after 12 months' follow-up of the first three doses in the Phase 3 trial *(89)*.
- There were significant reductions in clinical malaria (39%); severe malaria (29%); severe malaria anaemia (61%); malaria-related hospitalization (37%); and the need for blood transfusions (30%), demonstrated over 46 months' follow-up after the first three doses in the Phase 3 trial in children who received a fourth dose 18 months after the third dose *(89)*.
- There were 1774 clinical malaria cases averted per 1000 children vaccinated with four RTS,S/AS01 doses over 46 months' follow-up in the Phase 3 trial *(89)*.
- There were significant reductions in clinical malaria (24%) demonstrated after 7 years' follow-up after vaccination among a subset of children in the Phase 3 trial living in areas of moderate to high transmission; they did not have an excess risk of clinical or severe malaria *(100)*.
- There were significant reductions in hospitalization with severe malaria (29%) and hospitalization with malarial parasitemia or antigenemia (21%), demonstrated among children who were age-eligible for three doses of vaccine

delivered through routine systems by the ministries of health in parts of Ghana, Kenya, and Malawi *(101)*.
- Median estimates ranged from 200 to 700 deaths averted per 100 000 children vaccinated with a 4-dose schedule in areas of moderate to high transmission *(102)*.
- There were substantially greater reductions in uncomplicated malaria (63%), hospital admissions with severe malaria (70%), and death from malaria (73%) among children who received the combination of RTS,S/AS01 seasonal vaccination and SMC when compared to SMC alone. Seasonal vaccination with RTS,S/AS01 before the peak transmission season was non-inferior to SMC in preventing clinical malaria *(91)*.

The RTS,S/AS01 vaccine is safe and well tolerated *(99)*.

- There is a small risk of febrile seizures within seven days (mainly within 2–3 days) of vaccination *(90)*.
- As with any vaccine introduction, proper planning and training of staff to conduct appropriate pharmacovigilance should take place beforehand *(99)*.
- As for all new vaccines, the effectiveness and safety of the RTS,S/AS01 vaccine should be monitored post-introduction *(99)*.

More information can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background paper *(88)* sections 5.3.2 and 6.1 (MVIP safety, methods and results); sections 5.3.3 and 6.2 (MVIP impact, methods and results); sections 7.2 (Phase 3 results); section 8 (Additional data since Phase 3 completion); section 9 (Modelled public health impact and cost-effectiveness estimates).

Further details on “Benefits and harms” are also included in the SAGE/MPAG Evidence-to-Recommendations framework (Annex 9 page 13-16; PDF page 308-311) *(88)*.

Certainty of the Evidence

High

The overall rating of the evidence on RTS,S/AS01 malaria vaccine is considered to be HIGH. The certainty of evidence ranged from very low to high.

Critical outcomes related to effectiveness of RTS,S/AS01 were mostly rated HIGH in the large-scale Phase 3 clinical trial and MODERATE (due to large confidence intervals [CIs]) in the pilot implementation study.

Overall the certainty of evidence for the safety outcomes was rated MODERATE. Three safety signals, thought to be chance findings, were identified in the Phase 3 trial; these rare, unexplained events were graded with LOW and VERY LOW certainty of evidence:

- An excess of meningitis and cerebral malaria (in the context of overall reduction in severe malaria).
- An excess of deaths among girls who had received RTS,S/AS01 (shown in a post hoc analysis compared to boys).

The Malaria Vaccine Pilot Evaluations were designed to answer the outstanding questions related to safety. Evidence on the safety outcomes of meningitis, cerebral malaria, and gender-specific mortality is now graded MODERATE certainty reflecting the wide CIs related to relatively rare events. Multiple WHO advisory committees reviewed the data from the pilot implementation study and concluded that there was no evidence that the Phase 3 safety signals were causally related to RTS,S/AS01. Additionally these safety signals were not seen in the Phase 2 trials *(103)* or subsequent Phase 3 trials *(100)(91)*.

More information can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background paper's *(88)* Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Evidence summary table by the Cochrane Response (Annex 9a page 2-10; PDF page 297-305) and the SAGE/MPAG Evidence-to-Recommendations framework (Annex 9b page 17; PDF page 312).

Preference and values

No substantial variability expected

Malaria remains a primary cause of childhood illness and mortality in much of sub-Saharan Africa.

Preferences and values of the target population have been assessed in several ways:

- Qualitative interviews with caregivers and health providers revealed the perceived value of the vaccine in reducing the severity and frequency of malaria. Positive attitudes and trust among caregivers increased substantially over time, driven mainly by their perception of the vaccine's health benefits in their own children and the broader community.
- Malaria vaccine coverage from cross-sectional household surveys and from routine facility-based administrative data indicated that the vaccine was acceptable to the target population with relatively rapid scale–up for a new vaccine with a unique schedule and dropout between doses comparable to other vaccines (see "Feasibility" section).
- Coverage of other interventions from household survey and routine administrative data in areas where the vaccine has been introduced indicated that the vaccine had no negative effects on the uptake of other childhood vaccinations, on ITN use, or health–seeking behaviour for febrile illness.

Note: Midline surveys and the second round of the qualitative study were conducted between the provision of the third dose and the provision of the fourth dose and thus did not capture data on the uptake/coverage/acceptability of the fourth dose.

More information can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background paper *(88)* sections 5.3.4.2 and 6.3.1 (routine data, methods and results); sections 5.3.4.3 and 6.3.2 (household survey methods and results), and sections 5.3.4.5 and 6.3.4 (qualitative health utilization study methods and results).

Further details on "Values and Preferences" are also included in the SAGE/MPAG Evidence-to-Recommendations framework (Annex 9 page 18 or PDF page 313).

Resources and other considerations

The resources required are likely to be comparable to other new vaccine introductions.

Mathematical models examined the addition of the vaccine to existing malaria control interventions and treatment *(102)*.

- At an assumed vaccine price of US$5 per dose and $PfPR_{2\text{-}10}$ of 10-65%, the models predicted a median ICER compared with no vaccine of $25 (95%CI 16–222) per clinical case averted and $87 (95%CI 48–224) per DALY averted for the four-dose schedule.
- Public health impact and cost-effectiveness tended to be greater at higher levels of transmission.
- Overall, the model estimated that ICERs were only marginally lower for the seasonal vaccination strategies (i.e. more cost-effective) despite the higher number of overall doses delivered.
- Caution is required in the comparison of cost-effectiveness estimates for different interventions evaluated with different methods, outcome measures, time intervals and context (e.g. with different concurrent health interventions and standards of care). Nevertheless, the predictions of RTS,S/AS01 cost per DALY averted are broadly positive and comparable with other new vaccines, based on mathematical models, and other malaria interventions.

Table 1 is based on the evidence reviewed by the RTS,S/AS01 SAGE/MPAG Working Group on the incremental cost estimates of introducing and delivering the RTS,S/AS01 malaria vaccine within routine immunization programmes in subnational areas of the malaria vaccine pilot countries: Ghana, Kenya and Malawi. The line items account for the activities conducted in the first 1–2 years of vaccine implementation (through December 2020).

More information on the evidence can be found in the Full evidence review on the RTS,S/AS01 malaria vaccine background paper *(88)* sections 5.3.4.6 and 6.3.5 (cost of introduction and delivery study methods and results) and section 9 (Modelled public health impact and cost-effectiveness). Further details on "Resource use" and "Cost-effectiveness" are also included in the SAGE/MPAG Evidence-to-recommendations framework (Annex 9 page 19-20; PDF page 314-315).

Table 1: Line items from RTS,S/AS01 cost of delivery and vaccine introduction study

Line item (Resource)	Resource description

Staff	• EPI and NMP, among other ministry of health staff including vaccinators at health facilities • District malaria and health information management coordinators for DHIS2 data analysis
Training	• Training materials development • Readiness assessment for national-level facilitators (orientation) • Training of national-level trainers, regional or sub county-level trainers, health workers (facility-level) • Follow-up training for health workers and supportive supervision • Training of health workers for periodic intensification of routine immunization
Transport	• Distribution of vaccine between cold stores (national to regional to district/ county levels)
Supplies	• RTS,S two-dose vials • 2 mL reconstitution syringes • 0.5 mL auto-destruct injection syringes • Safety boxes (100-syringe capacity) • Printing of training kit books (decks) • Office support supplies
Equipment	• Cold chain equipment (fridges, cold boxes) • Office support supplies like printers, cartridges/ toners, tablets, monitors, projectors, laptops • Vehicles and motorcycles
Monitoring and evaluation	• Development of recording and reporting materials • Printing of monitoring charts, tally books, reporting forms, under-2 registers, defaulter tracing registers, and other tools • Distribution of monitoring tools • Pre-introduction assessments at national, regional, and district/county levels • Post-introduction supportive supervision • Review meetings at health facility level to validate and reconcile EPI data • Supportive supervision by national, regional, and district/county levels • Mapping of unimmunized and under-immunized children
Communication	• Message and information, education, communications material development, validation, pre-testing and translation • Printing of communications materials and field guides • Press release in newspapers, public address system, airing of messages at radio stations, community centres and mobile vans • Spokesperson trainings • Planning meetings • Social mobilization activities including peer education, orientation sessions, social announcements, periodic intensification of routine immunization • Sensitization of district health management teams, community leaders, religious leaders, community health assistants and volunteers, and communities via a house-to-house approach • National and/or regional-level launch events for first vaccination • Stakeholder engagements at national, regional and district/county levels
Governance/programme management	• Meetings for national coordination, subcommittees, technical working groups • Joint meetings between EPI and NMP • Planning and budgeting meetings • Microplanning at district level

Equity

Vaccine uptake was equitable by sex and socioeconomic status.

- Vaccine uptake had no negative effect on the uptake of other childhood vaccinations, ITN use or health-seeking behaviour for febrile illness.
- Introduction of RTS,S/AS01 extended the reach of malaria prevention tools; across the three pilot countries, more than two thirds of the children who reportedly did not sleep under an ITN received at least their first dose of the malaria vaccine.
- Overall, vaccine introduction increased to over 90% the proportion of children in each of the three pilot countries with access to one or more malaria prevention tools (ITN or RTS,S/AS01).

More information on the evidence can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background paper *(88)* section 10 (Equity considerations). Further details on "Equity" are also included in the SAGE/MPAG Evidence-to-Recommendations framework (Annex 9 page 21; PDF page 316).

Acceptability

RTS,S/AS01 malaria vaccine considered acceptable to the following groups:

- **Target population (including eligible children and their caregivers):** This is based on administrative data and household surveys that indicate good uptake and coverage, and modest drop-out rates. Continued increases in uptake suggest that the additional visits needed to receive the vaccine are acceptable to the target populations. Qualitative data indicate high acceptance and desirability of the vaccine.
- **Key stakeholders (including ministries of health and immunization programme managers):** This is based on post-introduction evaluations, the good uptake and coverage of the malaria vaccine, and qualitative study interviews with health providers. Chief concerns from health providers were around the operational challenges faced in introducing and delivering RTS,S/AS01 (i.e. increased workload, training, eligibility).

Household surveys found no impact on the use of ITNs in intervention areas following the introduction of RTS,S/AS01, indicating that both interventions are acceptable and the vaccine has not displaced ITN use. Overall health-seeking behaviour for febrile illness was also similar between the implementing and comparison groups as well as between the baseline and midline surveys.

More information on the evidence can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background paper *(88)* sections 5.3.4.2 and 6.3.1 (routine data, methods and results); sections 5.3.4.3 and 6.3.2 (household survey methods and results), sections 5.3.4.4 and 6.3.3 (post-introduction evaluation methods and results) and sections 5.3.4.5 and 6.3.4 (qualitative health utilization study methods and results). Further details on "Acceptability" are also included in the SAGE/MPAG Evidence-to-Recommendations framework (Annex 9 page 22; PDF page 317).

Feasibility

Vaccine introduction is feasible with good and equitable coverage of RTS,S/AS01 seen through routine immunization systems even in the context of the COVID-19 pandemic.

Administrative data from the start of pilot programme vaccinations in 2019 and April 2021 (24 months in Ghana and Malawi, and 18 months in Kenya) showed that:

- More than 1.7 million RTS,S/AS01 vaccine doses were administered across the three pilot countries and more than 650 000 children received their first dose.
- All three countries reached more than 70% of their target populations with the first RTS,S/AS01 dose and at least 62% with the third RTS,S/AS01 dose *(88)*.

More information on the evidence can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background

paper *(88)* sections 5.3.4.2 and 6.3.1 (routine data, methods and results). Further details on “Feasibility” are also included in the SAGE/MPAG Evidence-to-Recommendations framework (Annex 9 page 23; PDF page 318).

Justification

A Framework for WHO recommendation on RTS,S/AS01 malaria vaccine *(104)*, endorsed by SAGE and MPAG in 2019, provided guidance on how data from the MVIP should inform WHO recommendations, with the aim of ensuring that a recommendation could be made as soon as the risk–benefit of the vaccine was established with the necessary level of confidence, such that the vaccine would not be unnecessarily withheld from countries in need if it was found to be safe and beneficial.

The Framework stated that a WHO recommendation could be made if and when concerns regarding the safety signals were satisfactorily resolved, and evidence on severe malaria or mortality was assessed as consistent with a beneficial impact of the vaccine.

The Framework clarified that a recommendation should not be predicated on attaining high coverage, including high coverage with the fourth vaccine dose, based on: (1) data from the Phase 3 long-term follow up study showing that children living in areas of perennial moderate to high malaria transmission benefit from three or four doses of the vaccine; and (2) experience that it usually takes time for new vaccines to attain high coverage, particularly when administered in the second year of life.

The RTS,S/AS01 vaccine is considered safe and well tolerated. There is a small risk of febrile seizures within seven days (mainly within 2–3 days) of vaccination. As with any vaccine introduction, proper planning and training of staff to conduct appropriate pharmacovigilance should take place beforehand.

RTS,S/AS01 has a demonstrated ability to quickly achieve high coverage and high impact when delivered through routine immunization systems, with a 30% reduction in severe malaria observed after the vaccine was introduced in areas where ITNs are widely used and there is good access to diagnosis and treatment. Modelling shows that the vaccine is cost–effective in areas of moderate to high malaria transmission.

RTS,S/AS01 increases access to malaria prevention with no negative effect on the uptake other childhood vaccinations, ITN use, or health–seeking behaviour for febrile illness.

5. CASE MANAGEMENT

Background
Malaria case management, consisting of early diagnosis and prompt effective treatment, remains a vital component of malaria control and elimination strategies. The WHO Guidelines for the treatment of malaria were first developed in 2006 and have been revised periodically, with the most recent edition published in 2015. WHO guidelines contain recommendations on clinical practice or public health policy intended to guide end-users as to the individual or collective actions that can or should be taken in specific situations to achieve the best possible health outcomes. Such recommendations are also designed to help the user to select and prioritize interventions from a range of potential alternatives. The third edition of the WHO Guidelines for the treatment of malaria consolidated here contains updated recommendations based on new evidence particularly related to dosing in children, and also includes recommendations on the use of drugs to prevent malaria in groups at high risk.

Since publication of the first edition of the *Guidelines for the treatment of malaria* in 2006 and the second edition in 2010, all countries in which *P. falciparum* malaria is endemic have progressively updated their treatment policy from use of monotherapy with drugs such as chloroquine, amodiaquine and sulfadoxine–pyrimethamine (SP) to the currently recommended artemisinin-based combination therapies (ACT). The ACTs are generally highly effective and well tolerated. This has contributed substantially to reductions in global morbidity and mortality from malaria. Unfortunately, resistance to artemisinins has arisen recently in *P. falciparum* in South-East Asia, which threatens these gains.

Core principles
The following core principles were used by the Guidelines Development Group that drew up the Guidelines for the Treatment of Malaria.

1. Early diagnosis and prompt, effective treatment of malaria
Uncomplicated falciparum malaria can progress rapidly to severe forms of the disease, especially in people with no or low immunity, and severe falciparum malaria is almost always fatal without treatment. Therefore, programmes should ensure access to early diagnosis and prompt, effective treatment within 24–48 h of the onset of malaria symptoms.

2. Rational use of antimalarial agents
To reduce the spread of drug resistance, limit unnecessary use of antimalarial drugs and better identify other febrile illnesses in the context of changing malaria epidemiology, antimalarial medicines should be administered only to patients who truly have malaria. Adherence to a full treatment course must be promoted. Universal access to parasitological diagnosis of malaria is now possible with the use of quality-assured rapid diagnostic tests (RDTs), which are also appropriate for use in primary health care and community settings.

3. Combination therapy
Preventing or delaying resistance is essential for the success of both national and global strategies for control and eventual elimination of malaria. To help protect current and future antimalarial medicines, all episodes of malaria should be treated with at least two effective antimalarial medicines with different mechanisms of action (combination therapy).

4. Appropriate weight-based dosing
To prolong their useful therapeutic life and ensure that all patients have an equal chance of being cured, the quality of antimalarial drugs must be ensured, and antimalarial drugs must be given at optimal dosages. Treatment should maximize the likelihood of rapid clinical and parasitological cure and minimize transmission from the treated infection. To achieve this, dosage regimens should be based on the patient's weight and should provide effective concentrations of antimalarial drugs for a sufficient time to eliminate the infection in all target populations.

Please refer to *Malaria case management: operations manual (110)*.

5.1 Diagnosing malaria (2015)

Suspected malaria
The signs and symptoms of malaria are non-specific. Malaria is suspected clinically primarily on the basis of fever or a history of fever. There is no combination of signs or symptoms that reliably distinguishes malaria from other causes of fever; diagnosis based only on clinical features has very low specificity and results in overtreatment. Other possible causes of fever and whether alternative or additional treatment is required must always be carefully considered. The focus of malaria diagnosis should be to identify patients who truly have malaria, to guide rational use of antimalarial medicines.

In malaria-endemic areas, malaria should be suspected in any patient presenting with a history of fever or temperature ≥ 37.5 °C and no other obvious cause. In areas in which malaria transmission is stable (or during the high-transmission period of seasonal malaria), malaria should also be suspected in children with palmar pallor or a haemoglobin concentration of < 8 g/dL. High-transmission settings include many parts of sub-Saharan Africa and some parts of Oceania.

In settings where the incidence of malaria is very low, parasitological diagnosis of all cases of fever may result in considerable expenditure to detect only a few patients with malaria. In these settings, health workers should be trained to identify patients who may have been exposed to malaria (e.g. recent travel to a malaria-endemic area without protective measures) and have fever or a history of fever with no other obvious cause, before they conduct a parasitological test.

In all settings, suspected malaria should be confirmed with a parasitological test. The results of parasitological diagnosis should

be available within a short time (< 2 h) of the patient presenting. In settings where parasitological diagnosis is not possible, a decision to provide antimalarial treatment must be based on the probability that the illness is malaria.

In children < 5 years, the practical algorithms for management of the sick child provided by the WHO–United Nations Children's Fund (UNICEF) strategy for Integrated Management of Childhood Illness *(111)* should be used to ensure full assessment and appropriate case management at first-level health facilities and at the community level.

Parasitological diagnosis

The benefit of parasitological diagnosis relies entirely on an appropriate management response of health care providers. The two methods used routinely for parasitological diagnosis of malaria are light microscopy and immunochromatographic RDTs. The latter detect parasite-specific antigens or enzymes that are either genus or species specific.

Both microscopy and RDTs must be supported by a quality assurance programme. Antimalarial treatment should be limited to cases with positive tests, and patients with negative results should be reassessed for other common causes of fever and treated appropriately.

In nearly all cases of symptomatic malaria, examination of thick and thin blood films by a competent microscopist will reveal malaria parasites. Malaria RDTs should be used if quality-assured malaria microscopy is not readily available. RDTs for detecting PfHRP2 can be useful for patients who have received incomplete antimalarial treatment, in whom blood films can be negative. This is particularly likely if the patient received a recent dose of an artemisinin derivative. If the initial blood film examination is negative in patients with manifestations compatible with severe malaria, a series of blood films should be examined at 6–12 h intervals, or an RDT (preferably one detecting PfHRP2) should be performed. If both the slide examination and the RDT results are negative, malaria is extremely unlikely, and other causes of the illness should be sought and treated.

This document does not include recommendations for use of specific RDTs or for interpreting test results. For guidance, see the WHO manual *Universal access to malaria diagnostic testing (112)*.

Diagnosis of malaria

In patients with suspected severe malaria and in other high-risk groups, such as patients living with HIV/AIDS, absence or delay of parasitological diagnosis should not delay an immediate start of antimalarial treatment.

At present, molecular diagnostic tools based on nucleic-acid amplification techniques (e.g. loop-mediated isothermal amplification or PCR) do not have a role in the clinical management of malaria.

Where *P. vivax* malaria is common and microscopy is not available, it is recommended that a combination RDT be used that allows detection of P. vivax (pLDH antigen from *P. vivax*) or pan-malarial antigens (Pan-pLDH or aldolase).

Light microscopy

Microscopy not only provides a highly sensitive, specific diagnosis of malaria when performed well but also allows quantification of malaria parasites and identification of the infecting species. Light microscopy involves relatively high costs for training and supervision, and the accuracy of diagnosis is strongly dependent on the competence of the microscopist. Microscopy technicians may also contribute to the diagnosis of non-malarial diseases.

Although nucleic acid amplification-based tests are more sensitive, light microscopy is still considered the "field standard" against which the sensitivity and specificity of other methods must be assessed. A skilled microscopist can detect asexual parasites at a density of < 10 per µL of blood, but under typical field conditions, the limit of sensitivity is approximately 100 parasites per µL *(113)*. This limit of detection approximates the lower end of the pyrogenic density range. Thus, microscopy provides good specificity for diagnosing malaria as the cause of a presenting febrile illness. More sensitive methods allow detection of an increasing proportion of cases of incidental parasitaemia in endemic areas, thus reducing the specificity of a positive test. Light microscopy has other important advantages:

- low direct costs, if laboratory infrastructure to maintain the service is available;
- high sensitivity, if the performance of microscopy is high;
- differentiation of Plasmodia species;
- determination of parasite densities – notably identification of hyperparasitaemia;
- detection of gametocytaemia;
- allows monitoring of responses to therapy and
- can be used to diagnose many other conditions.

Good performance of microscopy can be difficult to maintain, because of the requirements for adequate training and supervision of laboratory staff to ensure competence in malaria diagnosis, electricity, good quality slides and stains, provision and maintenance of good microscopes and maintenance of quality assurance *(114)* and control of laboratory services [94][95].

Numerous attempts have been made to improve malaria microscopy, but none has proven to be superior to the classical method of Giemsa staining and oil-immersion microscopy for performance in typical health care settings *(115)*.

Rapid diagnostic tests

Rapid diagnostic tests (RDTs) are immuno-chromatographic tests for detecting parasite-specific antigens in a finger-prick blood sample. Some tests allow detection of only one species (*P. falciparum*); others allow detection of one or more of the other species of human malaria parasites (*P. vivax*, *P. malariae* and *P. ovale*) *(116) (117)(118)*. They are available commercially in various formats, e.g. dipsticks, cassettes and cards. Cassettes and cards are easier to use in difficult conditions outside health

facilities. RDTs are relatively simple to perform and to interpret, and they do not require electricity or special equipment *(119)*.

Since 2012, WHO has recommended that RDTs should be selected in accordance with the following criteria, based on the results of the assessments of the WHO Malaria RDT Product Testing programme *(120)*:

- For detection of *P. falciparum* in all transmission settings, the panel detection score against *P. falciparum* samples should be at least 75% at 200 parasites/µL.
- For detection of *P. vivax* in all transmission settings the panel detection score against *P. vivax* samples should be at least 75% at 200 parasites/µL.
- The false positive rate should be less than 10%.
- The invalid rate should be less than 5%.

Current tests are based on the detection of histidine-rich protein 2 (HRP2), which is specific for *P. falciparum*, pan-specific or species-specific *Plasmodium* lactate dehydrogenase (*p*LDH) or pan-specific aldolase. The different characteristics of these antigens may affect their suitability for use in different situations, and these should be taken into account in programmes for RDT implementation. The tests have many potential advantages, including:

- rapid provision of results and extension of diagnostic services to the lowest-level health facilities and communities;
- fewer requirements for training and skilled personnel (for instance, a general health worker can be trained in 1 day); and
- reinforcement of patient confidence in the diagnosis and in the health service in general.

They also have potential disadvantages, including:

- inability, in the case of *Pf*HRP2-based RDTs, to distinguish new infections from recently and effectively treated infections, due to the persistence of *Pf*HRP2 in the blood for 1–5 weeks after effective treatment;
- the presence in countries in the Amazon region of variable frequencies of HRP2 deletions in *P. falciparum* parasites, making HRP2-based tests not suitable in this region *(121)*;
- poor sensitivity for detecting *P. malariae* and *P. ovale*; and
- the heterogeneous quality of commercially available products and the existence of lot-to-lot variation.

In a systematic review *(122)*, the sensitivity and specificity of RDTs in detecting *P. falciparum* in blood samples from patients in endemic areas attending ambulatory health facilities with symptoms suggestive of malaria were compared with the sensitivity and specificity of microscopy or polymerase chain reaction. The average sensitivity of *Pf*HRP2-detecting RDTs was 95.0% (95% confidence interval [CI], 93.5–96.2%), and the specificity was 95.2% (93.4–99.4%). RDTs for detecting *p*LDH from *P. falciparum* are generally less sensitive and more specific than those for detecting HRP2, with an average sensitivity (95% CI) of 93.2% (88.0–96.2%) and a specificity of 98.5% (96.7–99.4%). Several studies have shown that health workers, volunteers and private sector providers can, with adequate training and supervision, use RDTs correctly and provide accurate malaria diagnoses. The criteria for selecting RDTs or microscopy can be found in the *WHO Recommended selection criteria for the procurement of malaria rapid diagnostic tests (123)*.

Diagnosis with either microscopy or RDTs is expected to reduce overuse of antimalarial medicines by ensuring that treatment is given only to patients with confirmed malaria infection, as opposed to treating all patients with fever *(124)*. Although providers of care may be willing to perform diagnostic tests, they do not, however, always respond appropriately to the results. This is especially true when they are negative. It is therefore important to ensure the accuracy of parasite- based diagnosis and also to demonstrate this to users and to provide them with the resources to manage both positive and negative results adequately *(112)*.

Immunodiagnosis and nucleic acid amplification test methods
Detection of antibodies to parasites, which may be useful for epidemiological studies, is neither sensitive nor specific enough to be of use in the management of patients suspected of having malaria *(125)*.

Techniques to detect parasite nucleic acid, e.g. polymerase chain reaction and loop-mediated isothermal amplification, are highly sensitive and very useful for detecting mixed infections, in particular at low parasite densities that are not detectable by conventional microscopy or with RDTs. They are also useful for studies of drug resistance and other specialized epidemiological investigations *(126)*; however, they are not generally available for large-scale field use in malaria- endemic areas, nor are they appropriate for routine diagnosis in endemic areas where a large proportion of the population may have low-density parasitaemia.

These techniques may be useful for population surveys and focus investigation in malaria elimination programmes.

At present, nucleic acid-based amplification techniques have no role in the clinical management of malaria or in routine surveillance systems *(127)*.

Good practice statement

All cases of suspected malaria should have a parasitological test (microscopy or RDT) to confirm the diagnosis.

Both microscopy and RDTs should be supported by a quality assurance programme.

Justification

Prompt, accurate diagnosis of malaria is part of effective disease management. All patients with suspected malaria should be treated on the basis of a confirmed diagnosis by microscopy examination or RDT testing of a blood sample. Correct diagnosis in malaria-endemic areas is particularly important for the most vulnerable population groups, such as young children and non-immune populations, in whom falciparum malaria can be rapidly fatal. High specificity will reduce unnecessary treatment with antimalarial drugs and improve the diagnosis of other febrile illnesses in all settings.

WHO strongly advocates a policy of "test, treat and track" to improve the quality of care and surveillance.

5.2 Treating uncomplicated malaria

Definition of uncomplicated malaria
A patient who presents with symptoms of malaria and a positive parasitological test (microscopy or RDT) but with no features of severe malaria is defined as having uncomplicated malaria (see section 7.1 for definition of severe malaria).

Therapeutic objectives
The clinical objectives of treating uncomplicated malaria are to cure the infection as rapidly as possible and to prevent progression to severe disease. "Cure" is defined as elimination of all parasites from the body. The public health objectives of treatment are to prevent onward transmission of the infection to others and to prevent the emergence and spread of resistance to antimalarial drugs.

Incorrect approaches to treatment

Use of monotherapy
The continued use of artemisinins or any of the partner medicines alone will compromise the value of ACT by selecting for drug resistance.

As certain patient groups, such as pregnant women, may need specifically tailored combination regimens, single artemisinin derivatives will still be used in selected referral facilities in the public sector, but they should be withdrawn entirely from the private and informal sectors and from peripheral public health care facilities.

Similarly, continued availability of amodiaquine, mefloquine and SP as monotherapies in many countries is expected to shorten their useful therapeutic life as partner drugs of ACT, and they should be withdrawn wherever possible.

Incomplete dosing
In endemic regions, some semi-immune malaria patients are cured by an incomplete course of antimalarial drugs or by a treatment regimen that would be ineffective in patients with no immunity. In the past, this led to different recommendations for patients considered semi-immune and those considered non-immune. As individual immunity can vary considerably, even in areas of moderate-to-high transmission intensity, this practice is no longer recommended. A full treatment course with a highly effective ACT is required whether or not the patient is considered to be semi-immune.

Another potentially dangerous practice is to give only the first dose of a treatment course to patients with suspected but unconfirmed malaria, with the intention of giving the full treatment if the diagnosis is confirmed. This practice is unsafe, could engender resistance, and is not recommended.

Additional considerations for clinical management

Can the patient take oral medication?
Some patients cannot tolerate oral treatment and will require parenteral or rectal administration for 1–2 days, until they can swallow and retain oral medication reliably. Although such patients do not show other signs of severity, they should receive the same initial antimalarial treatments recommended for severe malaria. Initial rectal or parenteral treatment must always be followed by a full 3-day course of ACT.

Use of antipyretics
In young children, high fevers are often associated with vomiting, regurgitation of medication and seizures. They are thus treated with antipyretics and, if necessary, fanning and tepid sponging. Antipyretics should be used if the core temperature is > 38.5 °C. Paracetamol (acetaminophen) at a dose of 15 mg/kg bw every 4 h is widely used; it is safe and well tolerated and can be given orally or as a suppository. Ibuprofen (5 mg/kg bw) has been used successfully as an alternative in the treatment of malaria and other childhood fevers, but, like aspirin and other non-steroidal anti-inflammatory drugs, it is *no longer recommended* because of the risks of gastrointestinal bleeding, renal impairment and Reye's syndrome.

Use of anti-emetics
Vomiting is common in acute malaria and may be severe. Parenteral antimalarial treatment may therefore be required until oral administration is tolerated. Then a full 3-day course of ACT should be given. Anti-emetics are potentially sedative and may have neuropsychiatric adverse effects, which could mask or confound the diagnosis of severe malaria. They should therefore be used with caution.

Management of seizures
Generalized seizures are more common in children with *P. falciparum* malaria than in those with malaria due to other species. This suggests an overlap between the cerebral pathology resulting from falciparum malaria and febrile convulsions. As seizures may be a prodrome of cerebral malaria, patients who have more than two seizures within a 24 h period should be treated as for severe malaria. If the seizures continue,

the airways should be maintained and anticonvulsants given (parenteral or rectal benzodiazepines or intramuscular paraldehyde). When the seizure has stopped, the child should be treated as indicated in section 7.10.5, if his or her core temperature is > 38.5 °C. There is no evidence that prophylactic anticonvulsants are beneficial in otherwise uncomplicated malaria, and they are not recommended.

5.2.1 Artemisinin-based combination therapy

Strong recommendation for , High certainty evidence

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following ACTs:

- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine–pyrimethamine (SP)
- artesunate + pyronaridine (currently unGRADEd, anticipated to be updated in 2022)

Artesunate pyronaridine is included in the WHO list of prequalified medicines for malaria, the Model List of Essential Medicines and the Model List of Medicines for Children. The drug has also received a positive scientific opinion from the European Medicines Agency and undergone a positive review by the WHO Advisory Committee on Safety of Medicinal Products. Countries can consider including this medicine in their national treatment guidelines for the treatment of malaria based on WHO's position on the use of this drug pending the formal recommendation anticipated in 2021. WHO's position was published in the information note The use of artesunate-pyronaridine for the treatment of uncomplicated malaria (122) which clarifies that artesunate pyronaridine can be considered a safe and efficacious ACT for the treatment of uncomplicated malaria in adults and children weighing 5 kg and over in all malaria-endemic areas.

Practical Info

The pipeline for new antimalarial drugs is healthier than ever before, and several new compounds are in various stages of development. Some novel antimalarial agents are already registered in some countries. The decision to recommend antimalarial drugs for general use depends on the strength of the evidence for safety and efficacy and the context of use. In general, when there are no satisfactory alternatives, newly registered drugs may be recommended; however, for global or unrestricted recommendations, considerably more evidence than that submitted for registration is usually required, to provide sufficient confidence for their safety, efficacy and relative merits as compared with currently recommended treatments.

Several new antimalarial drugs or new combinations have been introduced recently. Some are still in the pre-registration phase and are not discussed here. Arterolane + piperaquine, artemisinin + piperaquine base and artemisinin + napththoquine are new ACTs, which are registered and used in some countries. In addition, there are several new generic formulations of existing drugs. None of these yet has a sufficient evidence base for general recommendation (i.e. unrestricted use).

Artesunate + pyronaridine

A systematic review of artesunate + pyronaridine included six trials with a total of 3718 patients. Artesunate + pyronaridine showed good efficacy as compared with artemether + lumefantrine and artesunate + mefloquine in adults and older children with *P. falciparum* malaria, but the current evidence for young children is insufficient to be confident that the drug is as effective as currently recommended options. In addition, regulatory authorities noted slightly higher hepatic transaminase concentrations in artesunate + pyronaridine recipients than in comparison groups and recommended further studies to characterize the risk for hepatotoxicity. Preliminary data from repeat-dosing studies are reassuring.

In 2012, artesunate-pyronaridine was granted a positive scientific opinion under the European Medicines Agency (EMA) Article 58 procedure, but with a restricted label, mainly due to concerns over potential hepatotoxicity of the pyronaridine component, efficacy in children under 5 years of age, and safety, especially with repeat dosing *(126)*. In 2015, an EMA Scientific Advisory Group concluded that cumulative safety data on hepatic events had provided sufficient evidence to alleviate concerns over hepatotoxicity and thus to allow recommendation of the use of artesunate pyronaridine for the treatment and re-treatment of uncomplicated malaria in patients without signs of hepatic injury (including children weighing 5 kg and over).

The EMA therefore modified the product label to remove all

restrictions on repeat dosing, on use only in areas of high antimalarial drug resistance and low malaria transmission, and on requirements to monitor liver function. In addition, it granted a positive scientific opinion for artesunate-pyronaridine granules for the treatment of children with a body weight of 5–20 kg *(125)*. Artesunate-pyronaridine was included in WHO's list of prequalified medicines for malaria in April 2012, based on the EMA's positive scientific opinion of this product in accordance with Article 58. Since labelling provisions are based on EMA conclusions, these provisions were updated as a result of the EMA's 2015 review. Products included in the WHO prequalification list are those that have been assessed through the various mechanisms and found to comply with WHO-recommended regulatory standards and requirements for quality, safety and efficacy.

In June 2017, artesunate-pyronaridine was also added to the WHO Model List of Essential Medicines and Model List of Essential Medicines for Children. Due to the hepatotoxicity concerns identified in 2012, the WHO *Guidelines for the treatment of malaria* (2015) did not recommend the use of artesunate-pyronaridine for general use. A further meeting in December 2017 resulted in the need for GMP to request, in 2018, the support of the WHO Advisory Committee on Safety of Medicinal Products to conduct an independent expert review of all available data and information. Having completed its review, the committee considered that the current safety restrictions on the use of artesunate-pyronaridine (Pyramax®) for the treatment of uncomplicated malaria, as stated in the *Guidelines for the treatment of malaria*, are no longer justified *(126)*. GMP will revise the Guidelines based on new information available in 2021.

Arterolane + piperaquine is a combination of a synthetic ozonide and piperaquine phosphate that is registered in India. There are currently insufficient data to make general recommendations.

Artemisinin + piperaquine base combines two well-established, well-tolerated compounds. It differs from previous treatments in that the piperaquine is in the base form, the artemisinin dose is relatively low, and the current recommendation is for only a 2-day regimen. There are insufficient data from clinical trials for a general recommendation, and there is concern that the artemisinin dose regimen provides insufficient protection against resistance to the piperaquine component.

Artemisinin + naphthoquine is also a combination of two relatively old compounds that is currently being promoted as a single-dose regimen, contrary to WHO advice for 3 days of the artemisinin derivative. There are currently insufficient data from rigorously conducted randomized controlled trials to make general recommendations.

Many ACTs are generics. The bioavailability of generics of currently recommended drugs must be comparable to that of the established, originally registered product, and the satisfactory pharmaceutical quality of the product must be maintained.

Please refer to *Good procurement practices for artemisinin-based antimalaria medicines (127)*.

Evidence To Decision

Benefits and harms

Recommendation: Treat adults and children with uncomplicated *P. falciparum* malaria (including infants, pregnant women in their second and third trimesters and breastfeeding women) with ACT.

Desirable effects

- Studies have consistently demonstrated that the five WHO-recommended ACTs result in < 5% PCR-adjusted treatment failures in settings with no resistance to the partner drug (high- quality evidence).

Undesirable effects

- Increased cost.

Recommendation: Dihydroartemisinin + piperaquine is recommended for general use.

Desirable effects:

- A PCR-adjusted treatment failure rate of < 5% has been seen consistently in trials of dihydroartemisinin + piperaquine (high-quality evidence).
- Dihydroartemisinin + piperaquine has a longer half-life than artemether + lumefantrine, and fewer new infections occur within 9 weeks of treatment with dihydroartemisinin + piperaquine (high-quality evidence).
- Dihydroartemisinin + piperaquine and artesunate + mefloquine have similar half-lives, and a similar frequency of new infections is seen within 9 weeks of treatment (moderate-quality evidence).

Undesirable effects:

- A few more patients receiving dihydroartemisinin + piperaquine than those given artesunate + mefloquine had a prolonged QT interval (low-quality evidence)
- A few more patients receiving dihydroartemisinin + piperaquine than those given artesunate + mefloquine or artemether + lumefantrine had borderline QT prolongation.

Certainty of the Evidence High

For all critical outcomes: High.

Preference and values

Justification

GRADE

In the absence of resistance to the partner drug, the five recommended ACTs have all been shown to achieve a PCR-adjusted treatment failure rate of 5% in many trials in several settings in both adults and children (high-quality evidence) *(123)(124)*.

Other considerations

The guideline development group decided to recommend a menu of approved combinations, from which countries can select first- and second-line treatment.

Remarks

Recommendation: Treat adults and children with uncomplicated *P. falciparum* malaria (including infants, pregnant women in their second and third trimesters and breastfeeding women) with ACT.

The WHO-approved first-line ACT options are: artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, dihydroartemisinin + piperaquine and artesunate + sulfadoxine–pyrimethamine.

These options are recommended for adults and children, including infants, lactating women and pregnant women in their second and third trimester.

In deciding which ACTs to adopt in national treatment policies, national policy- makers should take into account: the pattern of resistance to antimalarial drugs in the country, the relative efficacy and safety of the combinations, their cost, the availability of paediatric formulations and the availability of co-formulated products.

Fixed-dose combinations are preferred to loose tablets or co-blistered products.

The Guideline Development Group decided to recommend a “menu” of approved combinations from which countries can select first- and second- line therapies. Modelling studies suggest that having multiple first-line ACTs available for use may help to prevent or delay the development of resistance.

Recommendation: Dihydroartemisinin + piperaquine is recommended for general use.

A systematic review showed that the dosing regimen of dihydroartemisinin + piperaquine currently recommended by the manufacturers leads to sub-optimal dosing in young children. The group plans to recommend a revised dosing regimen based on models of pharmacokinetics.

Further studies of the risk for QT interval prolongation have been requested by the European Medicines Agency.

ACT is a combination of a rapidly acting artemisinin derivative with a longer-acting (more slowly eliminated) partner drug. The artemisinin component rapidly clears parasites from the blood (reducing parasite numbers by a factor of approximately 10 000 in each 48 h asexual cycle) and is also active against the sexual stages of the gametocytes that mediate onward transmission to mosquitos. The longer- acting partner drug clears the remaining parasites and provides protection against development of resistance to the artemisinin derivative. Partner drugs with longer elimination half-lives also provide a period of post-treatment prophylaxis.

The GDG recommended dihydroartemisinin + piperaquine for use in 2009 but re-evaluated the evidence in 2013 because additional data on its safety had become available. The group noted the small absolute prolongation of the QT interval with dihydroartemisinin + piperaquine but was satisfied that the increase was of comparable magnitude to that observed with chloroquine and was not important clinically *(127)(128)*.

5.2.2 Duration of treatment

A 3-day course of the artemisinin component of ACTs covers two asexual cycles, ensuring that only a small fraction of parasites remain for clearance by the partner drug, thus reducing the potential development of resistance to the partner drug. Shorter courses (1–2 days) are therefore not recommended, as they are less effective, have less effect on gametocytes and provide less protection for the slowly eliminated partner drug.

Treating uncomplicated *P. falciparum* malaria (2015)

Strong recommendation for , High certainty evidence

Duration of ACT treatment: ACT regimens should provide 3 days' treatment with an artemisinin derivative.

Evidence To Decision

Benefits and harms

Desirable effects

- Fewer patients taking ACTs containing 3 days of an artemisinin derivative experience treatment failure within the first 28 days (high-quality evidence).
- Fewer participants taking ACTs containing 3 days of an artemisinin derivative have gametocytaemia at day 7 (high-quality evidence).

Certainty of the Evidence High

For all critical outcomes: High.

Preference and values

Justification

GRADE

In four randomized controlled trials in which the addition of 3 days of artesunate to SP was compared directly with 1 day of artesunate with SP:

- Three days of artesunate reduced the PCR-adjusted treatment failure rate within the first 28 days from that with 1 day of artesunate (RR, 0.45; 95% CI, 0.36–0.55, four trials, 1202 participants, high-quality evidence).
- Three days of artesunate reduced the number of participants who had gametocytaemia at day 7 from that with 1 day of artesunate (RR, 0.74; 95% CI, 0.58–0.93, four trials, 1260 participants, high-quality evidence).

Other considerations

The guideline development group considered that 3 days of artemisinin derivative are necessary to provide sufficient efficacy, promote good adherence and minimize the risk of drug resistance resulting from incomplete treatment.

Remarks

Longer ACT treatment may be required to achieve > 90% cure rate in areas with artemisinin-resistant *P. falciparum*, but there are insufficient trials to make definitive recommendations. A 3-day course of the artemisinin component of ACTs covers two asexual cycles, ensuring that only a small fraction of parasites remain for clearance by the partner drug, thus reducing the potential development of resistance to the partner drug. Shorter courses (1–2 days) are therefore not recommended, as they are less effective, have less effect on gametocytes and provide less protection for the slowly eliminated partner drug.

Rationale for the recommendation:

The Guideline Development Group considers that 3 days of an artemisinin derivative are necessary to provide sufficient efficacy, promote good adherence and minimize the risk for drug resistance due to incomplete treatment.

5.2.3 Dosing of ACTS

ACT regimens must ensure optimal dosing to prolong their useful therapeutic life, i.e. to maximize the likelihood of rapid clinical and parasitological cure, minimize transmission and retard drug resistance.

It is essential to achieve effective antimalarial drug concentrations for a sufficient time (exposure) in all target populations in order to ensure high cure rates. The dosage recommendations below are derived from understanding the relationship between dose and the profiles of exposure to the drug (pharmacokinetics) and the resulting therapeutic efficacy (pharmacodynamics) and safety. Some patient groups, notably younger children, are not dosed optimally with the "dosage regimens recommended by manufacturers, which compromises efficacy and fuels resistance. In these guidelines when there was pharmacological evidence that certain patient groups are not receiving optimal doses, dose regimens were adjusted to ensure similar exposure across all patient groups.

Weight-based dosage recommendations are summarized below. While age-based dosing may be more practical in children, the relation between age and weight differs in different populations. Age-based dosing can therefore result in under- dosing or over-dosing of some patients, unless large, region-specific weight-for-age databases are available to guide dosing in that region.

Factors other than dosage regimen may also affect exposure to a drug and thus treatment efficacy. The drug exposure of an individual patient also depends on factors such as the quality of the drug, the formulation, adherence and, for some drugs, co-administration with fat. Poor adherence is a major cause of treatment failure and drives the emergence and spread of drug resistance. Fixed-dose combinations encourage adherence and are preferred to loose (individual) tablets. Prescribers should take the time necessary to explain to patients why they should complete antimalarial course.

Artemether + lumefantrine
Formulations currently available: Dispersible or standard tablets containing 20 mg artemether and 120 mg lumefantrine, and standard tablets containing 40 mg artemether and 240 mg lumefantrine in a fixed-dose combination formulation. The flavoured dispersible tablet paediatric formulation facilitates use in young children.

Target dose range: A total dose of 5–24 mg/kg bw of artemether and 29–144 mg/ kg bw of lumefantrine

Recommended dosage regimen: Artemether + lumefantrine is given twice a day for 3 days (total, six doses). The first two doses should, ideally, be given 8 h apart.

Body weight (kg)	Dose (mg) of artemether + lumefantrine given twice daily for 3 days
5 to < 15	20 + 120
15 to < 25	40 + 240
25 to < 35	60 + 360
≥ 35	80 + 480

Factors associated with altered drug exposure and treatment response:

- Decreased exposure to lumefantrine has been documented in young children (<3 years) as well as pregnant women, large adults, patients taking mefloquine, rifampicin or efavirenz and in smokers. As these target populations may be at increased risk for treatment failure, their responses to treatment should be monitored more closely and their full adherence ensured.
- Increased exposure to lumefantrine has been observed in patients concomitantly taking lopinavir- lopinavir/ ritonavir-based antiretroviral agents but with no increase in toxicity; therefore, no dosage adjustment is indicated.

Additional comments:

- An advantage of this ACT is that lumefantrine is not available as a monotherapy and has never been used alone for the treatment of malaria.
- Absorption of lumefantrine is enhanced by co-administration with fat. Patients or caregivers should be informed that this ACT should be taken immediately after food or a fat containing drink (e.g. milk), particularly on the second and third days of treatment.

Artesunate + amodiaquine
Formulations currently available: A fixed-dose combination in tablets containing 25 + 67.5 mg, 50 + 135 mg or 100 + 270 mg of artesunate and amodiaquine, respectively

Target dose and range: The target dose (and range) are 4 (2–10) mg/kg bw per day artesunate and 10 (7.5–15) mg/kg bw per day amodiaquine once a day for 3 days. A total therapeutic dose range of 6–30 mg/kg bw per day artesunate and 22.5–45 mg/kg bw per dose amodiaquine is recommended.

Body weight (kg)	Artesunate + amodiaquine dose (mg) given daily for 3 days
4.5 to < 9	25 + 67.5
9 to < 18	50 + 135
18 to < 36	100 + 270
≥ 36	200 + 540

Factors associated with altered drug exposure and treatment

response:

- Treatment failure after amodiaquine monotherapy was more frequent among children who were underweight for their age. Therefore, their response to artesunate + amodiaquine treatment should be closely monitored.
- Artesunate + amodiaquine is associated with severe neutropenia, particularly in patients co-infected with HIV and especially in those on zidovudine and/or cotrimoxazole. Concomitant use of efavirenz increases exposure to amodiaquine and hepatotoxicity. Thus, concomitant use of artesunate + amodiaquine by patients taking zidovudine, efavirenz and cotrimoxazole should be avoided, unless this is the only ACT promptly available.

Additional comments:

- No significant changes in the pharmacokinetics of amodiaquine or its metabolite desethylamodiaquine have been observed during the second and third trimesters of pregnancy; therefore, no dosage adjustments are recommended.
- No effect of age has been observed on the plasma concentrations of amodiaquine and desethylamodiaquine, so no dose adjustment by age is indicated. Few data are available on the pharmacokinetics of amodiaquine in the first year of life.

Artesunate + mefloquine
Formulations currently available: A fixed-dose formulation of paediatric tablets containing 25 mg artesunate and 55 mg mefloquine hydrochloride (equivalent to 50 mg mefloquine base) and adult tablets containing 100 mg artesunate and 220 mg mefloquine hydrochloride (equivalent to 200 mg mefloquine base)

Target dose and range: Target doses (ranges) of 4 (2–10) mg/kg bw per day artesunate and 8.3 (7–11) mg/kg bw per day mefloquine, given once a day for 3 days

Body weight (kg)	Artesunate + mefloquine dose (mg) given daily for 3 days
5 to < 9	25 + 55
9 to < 18	50 + 110
18 to < 30	100 + 220
≥ 30	200 + 440

Additional comments:

- Mefloquine was associated with increased incidences of nausea, vomiting, dizziness, dysphoria and sleep disturbance in clinical trials, but these symptoms are seldom debilitating, and, where this ACT has been used, it has generally been well tolerated. To reduce acute vomiting and optimize absorption, the total mefloquine dose should preferably be split over 3 days, as in current fixed-dose combinations.
- As concomitant use of rifampicin decreases exposure to mefloquine, potentially decreasing its efficacy, patients taking this drug should be followed up carefully to identify treatment failures.

Artesunate + sulfadoxine–pyrimethamine
Formulations: Currently available as blister-packed, scored tablets containing 50 mg artesunate and fixed dose combination tablets comprising 500 mg sulfadoxine + 25 mg pyrimethamine. There is no fixed-dose combination.

Target dose and range: A target dose (range) of 4 (2–10) mg/kg bw per day artesunate given once a day for 3 days and a single administration of at least 25 / 1.25 (25–70 / 1.25–3.5) mg/kg bw sulfadoxine / pyrimethamine given as a single dose on day 1.

Body weight (kg)	Artesunate dose given daily for 3 days (mg)	Sulfadoxine / pyrimethamine dose (mg) given as a single dose on day 1
5 to < 10	25 mg	250 / 12.5
10 to < 25	50 mg	500 / 25
25 to < 50	100 mg	1000 / 50
≥ 50	200 mg	1500 / 75

Factors associated with altered drug exposure and treatment response: The low dose of folic acid (0.4 mg daily) that is required to protect the fetuses of pregnant women from neural tube defects do not reduce the efficacy of SP, whereas higher doses (5 mg daily) do significantly reduce its efficacy and should not be given concomitantly.

Additional comments:

- The disadvantage of this ACT is that it is not available as a fixed-dose combination. This may compromise adherence and increase the risk for distribution of loose artesunate tablets, despite the WHO ban on artesunate monotherapy.
- Resistance is likely to increase with continued widespread use of SP, sulfalene– pyrimethamine and cotrimoxazole (trimethoprim-sulfamethoxazole). Fortunately, molecular markers of resistance to antifols and sulfonamides correlate well with therapeutic responses. These should be monitored in areas in which this drug is used.

Strong recommendation for

Revised dose recommendation for dihydroartemisinin + piperaquine in young children: Children weighing <25kg treated with dihydroartemisinin + piperaquine should receive a minimum of 2.5 mg/kg bw per day of dihydroartemisinin and 20 mg/kg bw per day of piperaquine daily for 3 days.

*unGRADEd recommendation, anticipated to be updated in 2022

Practical Info

Formulations: Currently available as a fixed-dose combination in tablets containing 40 mg dihydroartemisinin and 320 mg piperaquine and paediatric tablets contain 20 mg dihydroartemisinin and 160 mg piperaquine.

Target dose and range: A target dose (range) of 4 (2–10) mg/kg bw per day dihydroartemisinin and 18 (16–27) mg/kg bw per day piperaquine given once a day for 3 days for adults and children weighing ≥ 25 kg. The target doses and ranges for children weighing < 25 kg are 4 (2.5–10) mg/kg bw per day dihydroartemisinin and 24 (20–32) mg/kg bw per day piperaquine once a day for 3 days.

Recommended dosage regimen: The dose regimen currently recommended by the manufacturer provides adequate exposure to piperaquine and excellent cure rates (> 95%), except in children < 5 years, who have a threefold increased risk for treatment failure. Children in this age group have significantly lower plasma piperaquine concentrations than older children and adults given the same mg/kg bw dose. Children weighing < 25 kg should receive at least 2.5 mg/kg bw dihydroartemisinin and 20 mg/kg bw piperaquine to achieve the same exposure as children weighing ≥ 25 kg and adults.

Dihydroartemisinin + piperaquine should be given daily for 3 days.

Body weight (kg)	Dihydroartemisinin + piperaquine dose (mg) given daily for 3 days
5 to < 8	20 + 160
8 to < 11	30 + 240
11 to < 17	40 + 320
17 to < 25	60 + 480
25 to < 36	80 + 640
36 to < 60	120 + 960
60 < 80	160 + 1280
>80	200 + 1600

Factors associated with altered drug exposure and treatment response:

High-fat meals should be avoided, as they significantly accelerate the absorption of piperaquine, thereby increasing the risk for potentially arrhythmogenic delayed ventricular repolarization (prolongation of the corrected electrocardiogram QT interval). Normal meals do not alter the absorption of piperaquine.

As malnourished children are at increased risk for treatment failure, their response to treatment should be monitored closely.

- Dihydroartemisinin exposure is lower in pregnant women.
- Piperaquine is eliminated more rapidly by pregnant women, shortening the post-treatment prophylactic effect of dihydroartemisinin + piperaquine. As this does not affect primary efficacy, no dosage adjustment is recommended for pregnant women.

Additional comments: Piperaquine prolongs the QT interval by approximately the same amount as chloroquine but by less than quinine. It is not necessary to perform an electrocardiogram before prescribing dihydroartemisinin + piperaquine, but this ACT should not be used in patients with congenital QT prolongation or who have a clinical condition or are on medications that prolong the QT interval. There has been no evidence of cardiotoxicity in large randomized trials or in extensive deployment.

Justification

The dosing subgroup reviewed all available dihydroartemisinin-piperaquine pharmacokinetic data (6 published studies and 10 studies from the WWARN database; total 652 patients) *(128)(129)* and then conducted simulations of piperaquine exposures for each weight group. These showed lower exposure in younger children with higher risks of treatment failure. The revised dose regimens are predicted to provide equivalent piperaquine exposures across all age groups.

Other considerations

This dose adjustment is not predicted to result in higher peak piperaquine concentrations than in older children and adults, and as there is no evidence of increased toxicity in young

children, the GRC concluded that the predicted benefits of improved antimalarial exposure are not at the expense of increased risk.

5.2.4 Recurrent falciparum malaria

Recurrence of *P. falciparum* malaria can result from re-infection or recrudescence (treatment failure). Treatment failure may result from drug resistance or inadequate exposure to the drug due to sub-optimal dosing, poor adherence, vomiting, unusual pharmacokinetics in an individual, or substandard medicines. It is important to determine from the patient's history whether he or she vomited the previous treatment or did not complete a full course of treatment.

When possible, treatment failure must be confirmed parasitologically. This may require referring the patient to a facility with microscopy or LDH-based RDTs, as *P. falciparum* histidine-rich protein-2 (*Pf*HRP2)-based tests may remain positive for weeks after the initial infection, even without recrudescence. Referral may be necessary anyway to obtain second-line treatment. In individual patients, it may not be possible to distinguish recrudescence from re-infection, although lack of resolution of fever and parasitaemia or their recurrence within 4 weeks of treatment are considered failures of treatment with currently recommended ACTs. In many cases, treatment failures are missed because patients are not asked whether they received antimalarial treatment within the preceding 1–2 months. Patients who present with malaria should be asked this question routinely.

Failure within 28 days
The recommended second-line treatment is an alternative ACT known to be effective in the region. Adherence to 7-day treatment regimens (with artesunate or quinine both of which should be co-administered with + tetracycline, or doxycycline or clindamycin) is likely to be poor if treatment is not directly observed; these regimens are no longer generally recommended. The distribution and use of oral artesunate monotherapy outside special centres are strongly discouraged, and quinine-containing regimens are not well tolerated.

Failure after 28 days
Recurrence of fever and parasitaemia > 4 weeks after treatment may be due to either recrudescence or a new infection. The distinction can be made only by PCR genotyping of parasites from the initial and the recurrent infections.

As PCR is not routinely used in patient management, all presumed treatment failures after 4 weeks of initial treatment should, from an operational standpoint, be considered new infections and be treated with the first-line ACT. However, reuse of mefloquine within 60 days of first treatment is associated with an increased risk for neuropsychiatric reactions, and an alternative ACT should be used.

5.2.5 Reducing the transmissibility of treated P. falciparum infections in areas of low-intensity transmission

Strong recommendation for , Low certainty evidence

Reducing the transmissibility of treated *P. falciparum* infections: In low-transmission areas, give a single dose of 0.25 mg/kg bw primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. G6PD testing is not required.

Practical Info

In light of concern about the safety of the previously recommended dose of 0.75 mg/kg bw in individuals with G6PD deficiency, a WHO panel reviewed the safety of primaquine as a *P. falciparum* gametocytocide and concluded that a single dose of 0.25 mg/kg bw of primaquine base is unlikely to cause serious toxicity, even in people with G6PD deficiency *(138)*. Thus, where indicated a single dose of 0.25mg/kg bw of primaquine base should be given on the first day of treatment, in addition to an ACT, to all patients with parasitologically confirmed *P. falciparum* malaria except for pregnant women, infants < 6 months of age and women breastfeeding infants < 6 months of age, because there are insufficient data on the safety of its use in these groups.

Dosing table based on the most widely currently available tablet strength (7.5mg base)

Body weight (kg)	Single dose of primaquine (mg base)
10[a] to < 25 3.75	3.75
25 to < 50 7.5	7.5
50 to 100 15	15

[a] Dosing of young children weighing < 10 kg is limited by the tablet sizes currently available.

Please refer to the *Policy brief on single-dose primaquine as a gametocytocide in Plasmodium falciparum malaria (139)*.

Evidence To Decision

Benefits and harms

Desirable effects

- Single doses of primaquine > 0.4 mg/kg bw reduced gametocyte carriage at day 8 by around two thirds (moderate-quality evidence).
- There are too few trials of doses < 0.4 mg/kg bw to quantify the effect on gametocyte carriage (low-quality evidence).
- Analysis of observational data from mosquito feeding studies suggests that 0.25 mg/kg bw may rapidly reduce the infectivity of gametocytes to mosquitoes.

Undesirable effects

- People with severe G6PD deficiency are at risk for haemolysis. At this dose, however, the risk is thought to be small; there are insufficient data to quantify this risk.

Certainty of the Evidence

Low

Overall certainty of evidence for all critical outcomes: low.

Preference and values

Justification

GRADE

In an analysis of observational studies of single-dose primaquine, data from mosquito feeding studies on 180 people suggest that adding 0.25 mg/kg primaquine to treatment with an ACT can rapidly reduce the infectivity of gametocytes to mosquitoes.

In a systematic review of eight randomized controlled trials of the efficacy of adding single-dose primaquine to ACTs for reducing the transmission of malaria, in comparison with ACTs alone *(136)*:

- single doses of > 0.4 mg/kg bw primaquine reduced gametocyte carriage at day 8 by about two thirds (RR, 0.34; 95% CI, 0.19–0.59, two trials, 269 participants, *high-certainty evidence*); and
- single doses of primaquine > 0.6 mg/kg bw reduced gametocyte carriage at day 8 by about two thirds (RR, 0.29; 95% CI, 0.22–0.37, seven trials, 1380 participants, *high-certainty evidence*).

There have been no randomized controlled trials of the effects on the incidence of malaria or on transmission to mosquitos.

Other considerations

The guideline development group considered that the evidence of a dose– response relation from observational studies of mosquito feeding was sufficient to conclude the primaquine dose of 0.25mg/kg bw significantly reduced *P. falciparum* transmissibility.

The population benefits of reducing malaria transmission with gametocytocidal drugs such as primaquine require that a very high proportion of treated patients receive these medicines and that there is no large transmission reservoir of asymptomatic parasite carriers. This strategy is therefore likely to be effective only in areas of low-intensity malaria transmission, as a component of elimination programmes.

Remarks

This recommendation excludes high-transmission settings, as symptomatic patients make up only a small proportion of the total population carrying gametocytes within a community, and primaquine is unlikely to affect transmission.

A major concern of national policy-makers in using primaquine has been the small risk for haemolytic toxicity in G6PD-deficient people, especially where G6PD testing is not available.

Life-threatening haemolysis is considered unlikely with the 0.25mg/kg bw dose and without G6PD testing *(137)*.

Rationale for the recommendation: The Guideline Development Group considered the evidence on

dose–response relations in the observational mosquito-feeding studies of reduced transmissibility with the dose of 0.25 mg/kg bw and the judgement of the WHO Evidence Review Group (November 2012). Their view was that the potential public health benefits of single low-dose (0.25 mg/kg bw) primaquine in addition to an ACT for falciparum malaria, without G6PD testing, outweigh the potential risk for adverse effects.

5.3 Treating special risk groups

Several important patient sub-populations, including young children, pregnant women and patients taking potent enzyme inducers (e.g. rifampicin, efavirenz), have altered pharmacokinetics, resulting in sub-optimal exposure to antimalarial drugs. This increases the rate of treatment failure with current dosage regimens. The rates of treatment failure are substantially higher in hyperparasitaemic patients and patients in areas with artemisinin-resistant falciparum malaria, and these groups require greater exposure to antimalarial drugs (longer duration of therapeutic concentrations) than is achieved with current ACT dosage recommendations. It is often uncertain how best to achieve this. Options include increasing individual doses, changing the frequency or duration of dosing, or adding an additional antimalarial drug. Increasing individual doses may not, however, achieve the desired exposure (e.g., lumefantrine absorption becomes saturated), or the dose may be toxic due to transiently high plasma concentrations (piperaquine, mefloquine, amodiaquine, pyronaridine). An additional advantage of lengthening the duration of treatment (by giving a 5-day regimen) is that it provides additional exposure of the asexual cycle to the artemisinin component as well as augmenting exposure to the partner drug. The acceptability, tolerability, safety and effectiveness of augmented ACT regimens in these special circumstances should be evaluated urgently.

Large and obese adults

Large adults are at risk for under-dosing when they are dosed by age or in standard pre-packaged adult weight-based treatments. In principle, dosing of large adults should be based on achieving the target mg/kg bw dose for each antimalarial regimen. The practical consequence is that two packs of an antimalarial drug might have to be opened to ensure adequate treatment. For obese patients, less drug is often distributed to fat than to other tissues; therefore, they should be dosed on the basis of an estimate of lean body weight, ideal body weight. Patients who are heavy but not obese require the same mg/kg bw doses as lighter patients.

In the past, maximum doses have been recommended, but there is no evidence or justification for this practice. As the evidence for an association between dose, pharmacokinetics and treatment outcome in overweight or large adults is limited, and alternative dosing options have not been assessed in treatment trials, it is recommended that this gap in knowledge be assessed urgently. In the absence of data, treatment providers should attempt to follow up the treatment outcomes of large adults whenever possible.

5.3.1 Pregnant and lactating women

Malaria in pregnancy is associated with low-birth-weight infants, increased anaemia and, in low-transmission areas, increased risks for severe malaria, pregnancy loss and death. In high-transmission settings, despite the adverse effects on fetal growth, malaria is usually asymptomatic in pregnancy or is associated with only mild, non-specific symptoms. There is insufficient information on the safety, efficacy and pharmacokinetics of most antimalarial agents in pregnancy, particularly during the first trimester.

First trimester of pregnancy

See Justification under recommendation.

Second and third trimesters

Experience with artemisinin derivatives in the second and third trimesters (over 4000 documented pregnancies) is increasingly reassuring: no adverse effects on the mother or fetus have been reported. The current assessment of risk–benefit suggests that ACTs should be used to treat uncomplicated falciparum malaria in the second and third trimesters of pregnancy. The current standard six-dose artemether + lumefantrine regimen for the treatment of uncomplicated falciparum malaria has been evaluated in > 1000 women in the second and third trimesters in controlled trials and has been found to be well tolerated and safe. In a low-transmission setting on the Myanmar–Thailand border, however, the efficacy of the standard six-dose artemether + lumefantrine regimen was inferior to 7 days of artesunate monotherapy. The lower efficacy may have been due to lower drug concentrations in pregnancy, as was also recently observed in a high-transmission area in Uganda and the United Republic of Tanzania. Although many women in the second and third trimesters of pregnancy in Africa have been exposed to artemether + lumefantrine, further studies are under way to evaluate its efficacy, pharmacokinetics and safety in pregnant women. Similarly, many pregnant women in Africa have been treated with amodiaquine alone or combined with SP or artesunate; however, amodiaquine use for the treatment of malaria in pregnancy has been formally documented in only > 1300 pregnancies. Use of amodiaquine in women in Ghana in the second and third trimesters of pregnancy was associated with frequent minor side- effects but not with liver toxicity, bone marrow depression or adverse neonatal outcomes.

Dihydroartemisinin + piperaquine was used successfully in the

second and third trimesters of pregnancy in > 2000 women on the Myanmar–Thailand border for rescue therapy and in Indonesia for first-line treatment. SP, although considered safe, is not appropriate for use as an artesunate partner drug in many areas because of resistance to SP. If artesunate + SP is used for treatment, co-administration of daily high doses (5 mg) of folate supplementation should be avoided, as this compromises the efficacy of SP. A lower dose of folate (0.4–0.5 mg bw/day) or a treatment other than artesunate + SP should be used.

Mefloquine is considered safe for the treatment of malaria during the second and third trimesters; however, it should be given only in combination with an artemisinin derivative.

Quinine is associated with an increased risk for hypoglycaemia in late pregnancy, and it should be used (with clindamycin) only if effective alternatives are not available.

Primaquine and tetracyclines should not be used in pregnancy.

Dosing in pregnancy

Data on the pharmacokinetics of antimalarial agents used during pregnancy are limited. Those available indicate that pharmacokinetic properties are often altered during pregnancy but that the alterations are insufficient to warrant dose modifications at this time. With quinine, no significant differences in exposure have been seen during pregnancy. Studies of the pharmacokinetics of SP used in IPTp in many sites show significantly decreased exposure to sulfadoxine, but the findings on exposure to pyrimethamine are inconsistent. Therefore, no dose modification is warranted at this time.

Studies are available of the pharmacokinetics of artemether + lumefantrine, artesunate + mefloquine and dihydroartemisinin + piperaquine. Most data exist for artemether + lumefantrine; these suggest decreased overall exposure during the second and third trimesters. Simulations suggest that a standard six-dose regimen of lumefantrine given over 5 days, rather than 3 days, improves exposure, but the data are insufficient to recommend this alternative regimen at present. Limited data on pregnant women treated with dihydroartemesinin + piperaquine suggest lower dihydroartemisinin exposure and no overall difference in total piperaquine exposure, but a shortened piperaquine elimination half-life was noted. The data on artesunate + mefloquine are insufficient to recommend an adjustment of dosage. No data are available on the pharmacokinetics of artesunate + amodiaquine in pregnant women with falciparum malaria, although drug exposure was similar in pregnant and non-pregnant women with vivax malaria.

Lactating women

The amounts of antimalarial drugs that enter breast milk and are consumed by breastfeeding infants are relatively small. Tetracycline is contraindicated in breastfeeding mothers because of its potential effect on infants' bones and teeth. Pending further information on excretion in breast milk, primaquine should not be used for nursing women, unless the breastfed infant has been checked for G6PD deficiency.

Strong recommendation for

Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.

*unGRADEd recommendation, anticipated to be updated in 2022

Practical Info

Because organogenesis occurs mainly in the first trimester, this is the time of greatest concern for potential teratogenicity, although development of the nervous system continues throughout pregnancy. The antimalarial medicines considered safe in the first trimester of pregnancy are quinine, chloroquine, clindamycin and proguanil.

The safest treatment regimen for pregnant women in the first trimester with uncomplicated falciparum malaria is therefore quinine + clindamycin (10mg/kg bw twice a day) for 7 days (or quinine monotherapy if clindamycin is not available). An ACT or oral artesunate + clindamycin is an alternative if quinine + clindamycin is not available or fails.

In reality, women often do not declare their pregnancy in the first trimester or may not yet be aware that they are pregnant. Therefore, all women of childbearing age should be asked about the possibility that they are pregnant before they are given antimalarial agents; this is standard practice for administering any medicine to potentially pregnant women. Nevertheless, women in early pregnancy will often be exposed inadvertently to the available first-line treatment, mostly ACT. Published prospective data on 700 women exposed in the first trimester of pregnancy indicate no adverse effects of artemisinins (or the partner drugs) on pregnancy or on the health of fetuses or neonates. The available data are sufficient to exclude a ≥ 4.2-fold increase in risk of any major defect detectable at birth (background prevalence assumed to be 0.9%), if half the exposures occur during the embryo-sensitive period (4–9 weeks post-conception). These data provide assurance in counselling women exposed to an antimalarial drug early in the first trimester and indicate that there is no need for them to have their pregnancy interrupted because of this exposure.

Dosing in pregnancy
Data on the pharmacokinetics of antimalarial agents used during pregnancy are limited. Those available indicate that pharmacokinetic properties are often altered during pregnancy but that the alterations are insufficient to warrant dose modifications at this time. With quinine, no significant differences in exposure have been seen during pregnancy. Studies of the pharmacokinetics of SP used in IPTp in many sites show significantly decreased exposure to sulfadoxine, but the findings on exposure to pyrimethamine are inconsistent. Therefore, no dose modification is warranted at this time.

Studies are available of the pharmacokinetics of artemether + lumefantrine, artesunate + mefloquine and dihydroartemisinin + piperaquine. Most data exist for artemether + lumefantrine; these suggest decreased overall exposure during the second and third trimesters. Simulations suggest that a standard six-dose regimen of lumefantrine given over 5 days, rather than 3 days, improves exposure, but the data are insufficient to recommend this alternative regimen at present. Limited data on pregnant women treated with dihydroartemesinin + piperaquine suggest lower dihydroartemisinin exposure and no overall difference in total piperaquine exposure, but a shortened piperaquine elimination half-life was noted. The data on artesunate + mefloquine are insufficient to recommend an adjustment of dosage. No data are available on the pharmacokinetics of artesunate + amodiaquine in pregnant women with falciparum malaria, although drug exposure was similar in pregnant and non-pregnant women with vivax malaria.

Evidence To Decision

Benefits and harms

Undesirable effects:

- Published prospective data on 700 women exposed in the first trimester of pregnancy have not indicated any adverse effects of artemisinin-derivatives on pregnancy or on the health of the fetus or neonate.
- The currently available data are only sufficient to exclude a ≥ 4.2-fold increase in risk of any major defect detectable at birth (background prevalence assumed to be 0.9%), if half the exposures occur during the embryo-sensitive period (4–9 weeks post-conception).

Preference and values

Justification

Evidence supporting the recommendation
Data available were not suitable for evaluation using the GRADE methodology, as there is no /almost no evidence for alternative treatment using ACT.

Safety assessment from published prospective data on 700 women exposed in the first trimester of pregnancy has not indicated any adverse effects of artemisinin-derivatives on pregnancy or on the health of the fetus or neonate.

The currently available data are only sufficient to exclude a ≥ 4.2-fold increase in risk of any major defect detectable at birth (background prevalence assumed to be 0.9%), if half the exposures occur during the embryo-sensitive period (4–9 weeks post-conception).

Other considerations
The limited data available on the safety of artemisinin-derivatives in early pregnancy allow for some reassurance in counselling women accidentally exposed to an artemisinin-derivative early in the first trimester. There is no need for them to have their pregnancy interrupted because of this exposure.

In the absence of adequate safety data on the artemisinin-derivatives in the first trimester of pregnancy the Guideline Development Group was unable to make recommendations beyond reiterating the status quo.

Remarks
Previous data indicated that the antimalarial medicines considered safe in the first trimester of pregnancy are quinine, chloroquine, clindamycin and proguanil. This evidence was not revisited during this guideline process.

The limited data available on the safety of artemisinin-derivatives in early pregnancy allow for some reassurance in counselling women accidentally exposed to an artemisinin-derivative early in the first trimester, and there is no need for them to have their pregnancy interrupted because of this exposure *(134)(135)*.

Rationale for the recommendation
In the absence of adequate safety data on the artemisinin-derivatives in the first trimester of pregnancy the Guideline Development Group was unable to make recommendations beyond reiterating the status quo.

5.3.2 Young children and infants

Artemisinin derivatives are safe and well tolerated by young children; therefore, the choice of ACT is determined largely by the safety and tolerability of the partner drug.

SP (with artesunate) should be avoided in the first weeks of life because it displaces bilirubin competitively and could thus aggravate neonatal hyperbilibinaemia. Primaquine should be avoided in the first 6 months of life (although there are no data on its toxicity in infants), and tetracyclines should be avoided throughout infancy. With these exceptions, none of the other currently recommended antimalarial treatments has shown serious toxicity in infancy.

Delay in treating *P. falciparum* malaria in infants and young children can have fatal consequences, particularly for more severe infections. The uncertainties noted above should not delay treatment with the most effective drugs available. In treating young children, it is important to ensure accurate dosing and retention of the administered dose, as infants are more likely to vomit or regurgitate antimalarial treatment than older children or adults. Taste, volume, consistency and gastrointestinal tolerability are important determinants of whether the child retains the treatment. Mothers often need advice on techniques of drug administration and the importance of administering the drug again if it is regurgitated within 1 h of administration. Because deterioration in infants can be rapid, the threshold for use of parenteral treatment should be much lower.

Optimal antimalarial dosing in young children
Although dosing on the basis of body area is recommended for many drugs in young children, for the sake of simplicity, antimalarial drugs have been administered as a standard dose per kg bw for all patients, including young children and infants. This approach does not take into account changes in drug disposition that occur with development. The currently recommended doses of lumefantrine, piperaquine, SP, artesunate and chloroquine result in lower drug concentrations in young children and infants than in older patients. Adjustments to previous dosing regimens for dihydroartemisinin + piperaquine in uncomplicated malaria and for artesunate in severe malaria are now recommended to improve the drug exposure in this vulnerable population. The available evidence for artemether + lumefantrine, SP and chloroquine does not indicate dose modification at this time, but young children should be closely monitored, as reduced drug exposure may increase the risk for treatment failure. Limited studies of amodiaquine and mefloquine showed no significant effect of age on plasma concentration profiles.

In community situations where parenteral treatment is needed but cannot be given, such as for infants and young children who vomit antimalarial drugs repeatedly or are too weak to swallow or are very ill, give rectal artesunate and transfer the patient to a facility in which parenteral treatment is possible. Rectal administration of a single dose of artesunate as pre-referral treatment reduces the risks for death and neurological disability, as long as this initial treatment is followed by appropriate parenteral antimalarial treatment in hospital. Further evidence on pre-referral rectal administration of artesunate and other antimalarial drugs is given in section 5.5.3 Treating severe malaria - pre-referral treatment options.

Optimal antimalarial dosing in infants
See recommendation for Infants less than 5 kg body weight below.

Optimal antimalarial dosing in malnourished young children
Malaria and malnutrition frequently coexist. Malnutrition may result in inaccurate dosing when doses are based on age (a dose may be too high for an infant with a low weight for age) or on weight (a dose may be too low for an infant with a low weight for age). Although many studies of the efficacy of antimalarial drugs have been conducted in populations and settings where malnutrition was prevalent, there are few studies of the disposition of the drugs specifically in malnourished individuals, and these seldom distinguished between acute and chronic malnutrition. Oral absorption of drugs may be reduced if there is diarrhoea or vomiting, or rapid gut transit or atrophy of the small bowel mucosa. Absorption of intramuscular and possibly intrarectal drugs may be slower, and diminished muscle mass may make it difficult to administer repeated intramuscular injections to malnourished patients. The volume of distribution of some drugs may be larger and the plasma concentrations lower. Hypoalbuminaemia may reduce protein binding and increase metabolic clearance, but concomitant hepatic dysfunction may reduce the metabolism of some drugs; the net result is uncertain.

Small studies of the pharmacokinetics of quinine and chloroquine showed alterations in people with different degrees of malnutrition. Studies of SP in IPTp and of amodiaquine monotherapy and dihydroartemisinin + piperaquine for treatment suggest reduced efficacy in malnourished children. A pooled analysis of data for individual patients showed that the concentrations of lumefantrine on day 7 were lower in children < 3 years who were underweight for age than in adequately nourished children and adults. Although these findings are concerning, they are insufficient to warrant dose modifications (in mg/kg bw) of any antimalarial drug in patients with malnutrition.

Infants less than 5kg body weight (2015)

Strong recommendation for

Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with ACT at the same mg/kg bw target dose as for children weighing 5 kg.

*unGRADEd recommendation, anticipated to be updated in 2022

Practical Info

The pharmacokinetics properties of many medicines in infants differ markedly from those in adults because of the physiological changes that occur in the first year of life. Accurate dosing is particularly important for infants. The only antimalarial agent that is currently contraindicated for infants (< 6 months) is primaquine.

ACT is recommended and should be given according to body weight at the same mg/kg bw dose for all infants, including those weighing < 5 kg, with close monitoring of treatment response. The lack of infant formulations of most antimalarial drugs often necessitates division of adult tablets, which can lead to inaccurate dosing. When available, paediatric formulations and strengths are preferred, as they improve the effectiveness and accuracy of ACT dosing.

Evidence To Decision

Benefits and harms

Undesirable effects:

- There is some evidence that artemether + lumefantrine and dihydroartemisinin + piperaquine may achieve lower plasma concentrations in infants than in older children and adults.

Preference and values

Justification

Evidence supporting the recommendation

Data available were not suitable for evaluation using the GRADE methodology.

In most clinical studies, subgroups of infants and older children were not distinguished, and the evidence for young infants (< 5 kg) is insufficient for confidence in current treatment recommendations. Nevertheless, despite these uncertainties, infants need prompt, effective treatment of malaria. There is limited evidence that artemether + lumefantrine and dihydroartemisinin + piperaquine achieve lower plasma concentrations in infants than in older children and adults.

Other considerations

The Guideline Development Group considered the currently available evidence too limited to warrant formal evidence review at this stage, and was unable to recommend any changes beyond the status quo. Further research is warranted.

Rationale for the recommendation

Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with an ACT. The weight-adjusted dose should achieve the same mg/kg bw target dose as for children weighing 5 kg.

5.3.3 Patients co-infected with HIV

There is considerable geographical overlap between malaria and HIV infection, and many people are co-infected. Worsening HIV-related immunosuppression may lead to more severe manifestations of malaria. In HIV-infected pregnant women, the adverse effects of placental malaria on birth weight are increased. In areas of stable endemic malaria, HIV-infected patients who are partially immune to malaria may have more frequent, higher-density infections, while in areas of unstable transmission, HIV infection is associated with increased risks for severe malaria and malaria-related deaths. Limited information is available on how HIV infection modifies therapeutic responses to ACTs. Early studies suggested that increasing HIV-related immunosuppression was associated with decreased treatment response to antimalarial drugs.

There is presently insufficient information to modify the general malaria treatment recommendations for patients with HIV/AIDS.

Patients co-infected with tuberculosis
Rifamycins, in particular rifampicin, are potent CYP3A4 inducers with weak antimalarial activity. Concomitant administration of rifampicin during quinine treatment of adults with malaria was associated with a significant decrease in exposure to quinine and a five-fold higher recrudescence rate. Similarly, concomitant rifampicin with mefloquine in healthy adults was associated with a three-fold decrease in exposure to mefloquine. In adults co-infected with HIV and tuberculosis who were being treated with rifampicin, administration of artemether + lumefantrine resulted in significantly lower exposure to artemether, dihydroartemisinin and lumefantrine (nine-, six- and three-fold decreases, respectively).There is insufficient evidence at this time to change the current mg/kg bw dosing recommendations; however, as these patients are at higher risk of recrudescent infections they should be monitored closely.

Patients co-infected with HIV (2015)

Good practice statement

Patients co-infected with HIV: In people who have HIV/AIDS and uncomplicated *P. falciparum* malaria, avoid artesunate + SP if they are being treated with co-trimoxazole, and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.

Justification

More data are available on use of artemether + lumefantrine with antiretroviral treatment. A study in children with uncomplicated malaria in a high-transmission area of Africa showed a decreased risk for recurrent malaria after treatment with artemether + lumefantrine in children receiving lopinavir–ritonavir-based antiretroviral treatment as compared with non-nucleoside reverse transcriptase inhibitor-based antiretroviral treatment. Evaluation of pharmacokinetics in these children and in healthy volunteers showed significantly higher exposure to lumefantrine and lower exposure to dihydroartemisinin with lopinavir–ritonavir-based antiretroviral treatment, but no adverse consequences. Conversely, efavirenz-based antiretroviral treatment was associated with a two- to fourfold decrease in exposure to lumefantrine in healthy volunteers and malaria-infected adults and children, with increased rates of recurrent malaria after treatment. Close monitoring is required. Increasing artemether + lumefantrine dosing with efavirenz-based antiretroviral treatment has not yet been studied. Exposure to lumefantrine and other non-nucleoside reverse transcriptase inhibitor-based antiretroviral treatment, namely nevirapine and etravirine, did not show consistent changes that would require dose adjustment.

Studies of administration of quinine with lopinavir–ritonavir or ritonavir alone in healthy volunteers gave conflicting results. The combined data are insufficient to justify dose adjustment. Single-dose atovaquone–proguanil with efavirenz, lopinavir–ritonavir or atazanavir–ritonavir were all associated with a significantly decreased area under the concentration–time curve for atovaquone (two- to fourfold) and proguanil (twofold), which could well compromise treatment or prophylactic efficacy. There is insufficient evidence to change the current mg/kg bw dosing recommendations; however, these patients should also be monitored closely.

5.3.4 Non-immune travellers

Travellers who acquire malaria are often non-immune people living in cities in endemic countries with little or no transmission or are visitors from non-endemic countries travelling to areas with malaria transmission. Both are at higher risk for severe malaria. In a malaria-endemic country, they should be treated according to national policy, provided the treatment recommended has a recent proven cure rate > 90%. Travellers who return to a non-endemic country and then develop malaria present a particular problem, and the case fatality rate is often high; doctors in non-malarious areas may be unfamiliar with malaria and the diagnosis is commonly delayed, and effective antimalarial drugs may not be registered or may be unavailable. However, prevention of transmission or the emergence of resistance are not relevant outside malaria-endemic areas. If the patient has taken chemoprophylaxis, the same medicine should not be used for treatment. Treatment of *P. vivax*, *P. ovale* and *P. malariae* malaria in travellers should be the same as for patients in endemic areas (see section 5.4).

There may be delays in obtaining artesunate, artemether or quinine for the management of severe malaria outside endemic areas. If only parenteral quinidine is available, it should be given, with careful clinical and electrocardiographic monitoring (see section 5.5 Treating severe malaria).

Non-immune travellers (2015)

Strong recommendation for , High certainty evidence

Treat travellers with uncomplicated *P. falciparum* malaria returning to non-endemic settings with ACT.

Evidence To Decision

Certainty of the Evidence High

Preference and values

Justification

GRADE
Studies have consistently demonstrated that the five WHO recommended ACTs have less than 5% PCR-adjusted treatment failure rates in settings without resistance to the partner drug (high quality evidence).

Other considerations
The Guideline Development Group considered the evidence of superiority of ACTs over non-ACTs from endemic settings to be equally applicable to those travelling from non-endemic settings.

5.3.5 Uncomplicated hyperparasitaemia

Uncomplicated hyperparasitaemia is present in patients who have ≥ 4% parasitaemia but no signs of severity. They are at increased risk for severe malaria and for treatment failure and are considered an important source of antimalarial drug resistance.

Hyperparasitaemia (2015)

Good practice statement

People with *P. falciparum* hyperparasitaemia are at increased risk for treatment failure, severe malaria and death and should be closely monitored, in addition to receiving ACT.

Justification

In falciparum malaria, the risk for progression to severe malaria with vital organ dysfunction increases at higher parasite densities. In low-transmission settings, mortality begins to increase when the parasite density exceeds 100 000/µL (~2% parasitaemia). On the north-west border of Thailand, before the general introduction of ACT, parasitaemia > 4% without signs of severity was associated with a 3% mortality rate (about 30-times higher than from uncomplicated falciparum malaria with lower densities) and a six-times higher risk of treatment failure. The relationship between parasitaemia and risks depends on the epidemiological context: in higher-transmission settings, the risk of developing severe malaria in patients with high parasitaemia is lower, but “uncomplicated hyperparasitaemia” is still associated with a significantly higher rate of treatment failure.

Patients with a parasitaemia of 4–10% and no signs of severity also require close monitoring, and, if feasible, admission to hospital. They have high rates of treatment failure. Non-immune people such as travellers and individuals in low-transmission settings with a parasitaemia > 2% are at increased risk and also require close attention. Parasitaemia > 10% is considered to indicate severe malaria in all settings.

It is difficult to make a general recommendation about treatment of uncomplicated hyperparasitaemia, for several reasons: recognizing these patients requires an accurate, quantitative parasite count (they will not be identified from semi-quantitative thick film counts or RDTs), the risks for severe malaria vary considerably, and the risks for treatment failure also vary. Furthermore, little information is available on therapeutic responses in uncomplicated

hyperparasitaemia. As the artemisinin component of an ACT is essential in preventing progression to severe malaria, absorption of the first dose must be ensured (atovaquone – proguanil alone should not be used for travellers presenting with uncomplicated hyperparasitaemia). Longer courses of treatment are more effective; both giving longer courses of ACT and preceding the standard 3-day ACT regimen with parenteral or oral artesunate have been used.

5.4 Treating uncomplicated malaria caused by P. vivax, P. ovale, P. malariae or P. knowlesi

Plasmodium vivax accounts for approximately half of all malaria cases outside Africa *(3)(142)(143)*. It is prevalent in the Middle East, Asia, the Western Pacific and Central and South America. With the exception of the Horn, it is rarer in Africa, where there is a high prevalence of the Duffy-negative phenotype, particularly in West Africa, although cases are reported in both Mauritania and Mali *(143)*. In most areas where *P. vivax* is prevalent, the malaria transmission rates are low (except on the island of New Guinea). Affected populations achieve only partial immunity to this parasite, and so people of all ages are at risk for *P. vivax* malaria *(143)*. Where both *P. falciparum* and *P. vivax* are prevalent, the incidence rates of *P. vivax* tend to peak at a younger age than for *P. falciparum*. This is because each *P. vivax* inoculation may be followed by several relapses. The other human malaria parasite species, *P. malariae* and *P. ovale* (which is in fact two sympatric species), are less common. *P. knowlesi*, a simian parasite, causes occasional cases of malaria in or near forested areas of South-East Asia and the Indian subcontinent *(144)*. In parts of the island of Borneo, *P. knowlesi* is the predominant cause of human malaria and an important cause of severe malaria

Of the six species of *Plasmodium* that affect humans, only *P. vivax* and the two species of *P. ovale (145)* form hypnozoites, which are dormant parasite stages in the liver that cause relapse weeks to years after the primary infection. *P. vivax* preferentially invades reticulocytes, and repeated illness causes chronic anaemia, which can be debilitating and sometimes life-threatening, particularly in young children *(146)*. Recurrent vivax malaria is an important impediment to human and economic development in affected populations. In areas where *P. falciparum* and *P. vivax* co-exist, intensive malaria control often has a greater effect on *P. falciparum*, as *P. vivax*, is more resilient to interventions.

Although *P. vivax* has been considered to be a benign form of malaria, it may sometimes cause severe disease *(147)*. The major complication is anaemia in young children. In Papua province, Indonesia *(147)*, and in Papua New Guinea *(148)*, where malaria transmission is intense, *P. vivax* is an important cause of malaria morbidity and mortality, particularly in young infants and children. Occasionally, older patients develop vital organ involvement similar to that in severe and complicated *P. falciparum* malaria *(149)(150)*. During pregnancy, infection with *P. vivax*, as with *P. falciparum*, increases the risk for abortion and reduces birth weight *(151)(140)*. In primigravidae, the reduction in birth weight is approximately two thirds that associated with *P. falciparum*. In one large series, this effect increased with successive pregnancies *(151)*.

P. knowlesi is a zoonosis that normally affects long- and pig-tailed macaque monkeys. It has a daily asexual cycle, resulting in a rapid replication rate and high parasitaemia. *P. knowlesi* may cause a fulminant disease similar to severe falciparum malaria (with the exception of coma, which does not occur) *(152)(153)*. Co-infection with other species is common.

Diagnosis

Diagnosis of *P. vivax*, *P. ovale*, and *P. malariae* malaria is based on microscopy. *P. knowlesi* is frequently misdiagnosed under the microscope, as the young ring forms are similar to those of *P. falciparum*, the late trophozoites are similar to those of *P. malariae*, and parasite development is asynchronous. Rapid diagnostic tests based on immunochromatographic methods are available for the detection of *P. vivax* malaria; however, they are relatively insensitive for detecting *P. malariae* and *P. ovale* parasitaemia. Rapid diagnostic antigen tests for human *Plasmodium* species show poor sensitivity for *P. knowlesi* infections in humans with low parasitaemia *(154)*.

Treatment

The objectives of treatment of vivax malaria are twofold: to cure the acute blood stage infection and to clear hypnozoites from the liver to prevent future relapses. This is known as “radical cure”.

In areas with chloroquine-sensitive *P. vivax*

For chloroquine-sensitive vivax malaria, oral chloroquine at a total dose of 25 mg base/kg bw is effective and well tolerated. Lower total doses are not recommended, as these encourage the emergence of resistance. Chloroquine is given at an initial dose of 10 mg base/kg bw, followed by 10 mg/kg bw on the second day and 5 mg/kg bw on the third day. In the past, the initial 10 mg/kg bw dose was followed by 5 mg/kg bw at 6 h, 24 h and 48 h. As residual chloroquine suppresses the first relapse of tropical *P. vivax* (which emerges about 3 weeks after onset of the primary illness), relapses begin to occur 5–7 weeks after treatment if radical curative treatment with primaquine is not given.

ACTs are highly effective in the treatment of vivax malaria, allowing simplification (unification) of malaria treatment; i.e. all malaria infections can be treated with an ACT. The exception is artesunate + SP, where resistance significantly compromises its efficacy. Although good efficacy of artesunate + SP was reported in one study in Afghanistan, in several other areas (such as South-East Asia) *P. vivax* has become resistant to SP more rapidly than *P. falciparum*. The initial response to all ACTs is rapid in vivax malaria, reflecting the high sensitivity to artemisinin derivatives, but, unless primaquine is given, relapses commonly follow. The subsequent recurrence patterns differ, reflecting the elimination kinetics of the partner drugs. Thus, recurrences, presumed to be relapses, occur earlier after artemether + lumefantrine than after dihydroartemisinin + piperaquine or artesunate + mefloquine because lumefantrine is eliminated

more rapidly than either mefloquine or piperaquine. A similar temporal pattern of recurrence with each of the drugs is seen in the *P. vivax* infections that follow up to one third of acute falciparum malaria infections in South-East Asia.

In areas with chloroquine-resistant *P. vivax*
ACTs containing piperaquine, mefloquine or lumefantrine are the recommended treatment, although artesunate + amodiaquine may also be effective in some areas.

In the systematic review of ACTs for treating *P. vivax* malaria, dihydroartemisinin + piperaquine provided a longer prophylactic effect than ACTs with shorter half-lives (artemether + lumefantrine, artesunate + amodiaquine), with significantly fewer recurrent parasitaemias during 9 weeks of follow-up (RR, 0.57; 95% CI, 0.40–0.82, three trials, 1066 participants). The half-life of mefloquine is similar to that of piperaquine, but use of dihydroartemisinin + piperaquine in *P. vivax* mono-infections has not been compared directly in trials with use of artesunate + mefloquine.

Uncomplicated *P. ovale*, *P. malariae* or *P. knowlesi* malaria
Resistance of *P. ovale*, *P. malariae* and *P. knowlesi* to antimalarial drugs is not well characterized, and infections caused by these three species are generally considered to be sensitive to chloroquine. In only one study, conducted in Indonesia, was resistance to chloroquine reported in *P. malariae*.

The blood stages of *P. ovale*, *P. malariae* and *P. knowlesi* should therefore be treated with the standard regimen of ACT or chloroquine, as for vivax malaria.

Mixed malaria infections
Mixed malaria infections are common in endemic areas. For example, in Thailand, despite low levels of malaria transmission, 8% of patients with acute vivax malaria also have *P. falciparum* infections, and one third of acute *P. falciparum* infections are followed by a presumed relapse of vivax malaria (making vivax malaria the most common complication of falciparum malaria).

Mixed infections are best detected by nucleic acid-based amplification techniques, such as PCR; they may be underestimated with routine microscopy. Cryptic *P. falciparum* infections in vivax malaria can be revealed in approximately 75% of cases by RDTs based on the *Pf*HRP2 antigen, but several RDTs cannot detect mixed infection or have low sensitivity for detecting cryptic vivax malaria. ACTs are effective against all malaria species and so are the treatment of choice for mixed infections.

[3][119][120][120][120][121][122][123][124][124][125][126][127][128]

Blood stage infection (2015)

Good practice statement

If the malaria species is not known with certainty, treat as for uncomplicated.

Strong recommendation for , High certainty evidence

In areas with chloroquine-susceptible infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria with either ACT (except pregnant women in their first trimester) or chloroquine.

In areas with chloroquine-resistant infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria (except pregnant women in their first trimester) with ACT.

Practical Info

In areas with chloroquine-sensitive *P. vivax*
For chloroquine-sensitive vivax malaria, oral chloroquine at a total dose of 25 mg base/kg bw is effective and well tolerated. Lower total doses are not recommended, as these encourage the emergence of resistance. Chloroquine is given at an initial dose of 10 mg base/kg bw, followed by 10 mg/kg bw on the second day and 5 mg/kg bw on the third day. In the past, the initial 10-mg/kg bw dose was followed by 5 mg/kg bw at 6 h, 24 h and 48 h. As residual chloroquine suppresses the first relapse of tropical *P. vivax* (which emerges about 3 weeks after onset of the primary illness), relapses begin to occur 5–7 weeks after treatment if radical curative treatment with primaquine is not given.

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occur earlier after artemether + lumefantrine than after dihydroartemisinin + piperaquine or artesunate + mefloquine because lumefantrine is eliminated more rapidly than either mefloquine or piperaquine. A similar temporal pattern of recurrence with each of the drugs is seen in the *P. vivax* infections that follow up to one third of acute falciparum malaria infections in South-East Asia.

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Uncomplicated *P. ovale*, *P. malariae* or *P. knowlesi malaria*
Resistance of *P. ovale*, *P. malariae* and *P. knowlesi* to antimalarial drugs is not well characterized, and infections caused by these three species are generally considered to be sensitive to chloroquine. In only one study, conducted in Indonesia, was resistance to chloroquine reported in *P. malariae*.

The blood stages of *P. ovale*, *P. malariae* and *P. knowlesi* should therefore be treated with the standard regimen of ACT or chloroquine, as for vivax malaria.

Mixed Malaria Infections
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Mixed infections are best detected by nucleic acid-based amplification techniques, such as PCR; they may be underestimated with routine microscopy. Cryptic *P. falciparum* infections in vivax malaria can be revealed in approximately 75% of cases by RDTs based on the *Pf*HRP2 antigen, but several RDTs cannot detect mixed infection or have low sensitivity for detecting cryptic vivax malaria. ACTs are effective against all malaria species and so are the treatment of choice for mixed infections.

Evidence To Decision

Benefits and harms

Desirable effects:

- ACTs clear parasites more quickly than chloroquine (high-quality evidence).
- ACTs with long half-lives provide a longer period of suppressive post-treatment prophylaxis against relapses and new infections (high-quality evidence).
- Simplified national protocols for all forms of uncomplicated malaria.
- Adequate treatment of undiagnosed *P. falciparum* in mixed infections.

Certainty of the Evidence

High

Overall certainty of evidence for all critical outcomes: high.

Preference and values

Justification

GRADE
In a systematic review of ACTs for the treatment of *P. vivax* malaria *(149)*, five trials were conducted in Afghanistan, Cambodia, India, Indonesia and Thailand between 2002 and 2011 with a total of 1622 participants which compared ACTs directly with chloroquine. In comparison with chloroquine:

ACTs cleared parasites from the peripheral blood more quickly (parasitaemia after 24 h of treatment: RR, 0.42; 95% CI, 0.36–0.50, four trials, 1652 participants, high-quality evidence); and

ACTs were at least as effective in preventing recurrent parasitaemia before day 28 (RR, 0.58; 95% CI, 0.18–1.90, five trials, 1622 participants, high-quality evidence).

In four of these trials, few cases of recurrent parasitaemia were seen before day 28 with both chloroquine and ACTs. In the fifth trial, in Thailand in 2011, increased recurrent parasitaemia was seen after treatment with chloroquine (9%), but was

infrequent after ACT (2%) (RR, 0.25; 95% CI, 0.09–0.66, one trial, 437 participants).

ACT combinations with long half-lives provided a longer prophylactic effect after treatment, with significantly fewer cases of recurrent parasitaemia between day 28 and day 42 or day 63 (RR, 0.57; 95% CI, 0.40–0.82, three trials, 1066 participants, moderate-quality evidence).

Other considerations
The guideline development group recognized that, in the few settings in which *P. vivax* is the only endemic species and where chloroquine resistance remains low, the increased cost of ACT may not be worth the small additional benefits. Countries where chloroquine is used for treatment of vivax malaria should monitor for chloroquine resistance and change to ACT when the treatment failure rate is > 10% at day 28.

Remarks
Current methods cannot distinguish recrudescence from relapse or relapse from newly acquired infections, but the aim of treatment is to ensure that the rates of recurrent parasitaemia of any origin are < 10%.

Primaquine has significant asexual stage activity against vivax malaria and augments the therapeutic response to chloroquine. When primaquine is given routinely for 14 days, it may mask low-level chloroquine resistance and prevent vivax recurrence within 28 days.

Rationale for the recommendation
The Guideline Development Group recognized that, in the few settings in which *P. vivax* is the only endemic species and where chloroquine resistance remains low, the increased cost of ACT may not be worth the small additional benefits. In these settings, chloroquine may still be considered, but countries should monitor chloroquine resistance and change to ACT when the treatment failure rate is > 10% on day 28.

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Remarks
Current methods do not distinguish recrudescence from relapse or relapse from newly acquired infection, but the aim of treatment is to ensure that the rates of recurrent parasitaemia of any origin is < 10% within 28 days.

When primaquine is not given for radical cure, slowly eliminated ACT that prevents recurrent parasitaemia before day 28 should be used (dihydroartemisinin + piperaquine or artesunate + mefloquine).

Primaquine has significant asexual stage activity against vivax malaria and augments the therapeutic response to chloroquine. When primaquine is given routinely for 14 days, it may mask low-level chloroquine resistance and prevent vivax recurrence within 28 days.

When primaquine is given routinely for 14 days, ACTs with shorter half-lives (artemether + lumefantrine, or artesunate + amodiaquine) may be sufficient to keep the rate of recurrent parasitaemia before day 28 below 10%.

Rationale for the recommendation
The Guideline Development Group recognized that, in the few settings in which *P. vivax* is the only endemic species and where chloroquine resistance remains low, the increased cost of ACT may not be worth the small additional benefits. In these settings, chloroquine may still be considered, but countries should monitor chloroquine resistance and change to ACT when the treatment failure rate is > 10% on day 28.

Blood stage infection (2015)

Strong recommendation for , Very low certainty evidence

Treat pregnant women in their first trimester who have chloroquine-resistant *P. vivax* malaria with quinine.

Evidence To Decision

Certainty of the Evidence — Very low

Preference and values

Justification

In areas with chloroquine-resistant *P. vivax*
In the first-trimester of pregnancy, quinine should be used in place of ACTs (section 5.3.1).

Good practice statement

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.

Practical Info

Please refer to *Testing for G6PD deficiency for safe use of primaquine in radical cure of P. vivax and P. ovale (Policy brief)* *(150)* and *Guide to G6PD deficiency rapid diagnostic testing to support P. vivax radical cure* *(151)*.

Strong recommendation for , High certainty evidence

To prevent relapse, treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) with a 14-day course of primaquine in all transmission settings.

Practical Info

Primaquine for preventing relapse

To achieve radical cure (cure and prevention of relapse), relapses originating from liver hypnozoites must be prevented by giving primaquine. The frequency and pattern of relapses varies geographically, with relapse rates generally ranging from 8% to 80%. Temperate long-latency *P. vivax* strains are still prevalent in many areas. Recent evidence suggests that, in endemic areas where people are inoculated frequently with *P. vivax*, a significant proportion of the population harbours dormant but “activatable” hypnozoites. The exact mechanism of activation of dormant hypnozoites is unclear. There is evidence that systemic parasitic and bacterial infections, but not viral infections, can activate *P. vivax* hypnozoites, which explains why *P. vivax* commonly follows *P. falciparum* infections in endemic areas where both parasites are prevalent. Thus, the radical curative efficacy of primaquine must be set against the prevalent relapse frequency and the likely burden of “activatable” hypnozoites. Experimental studies on vivax malaria and the relapsing simian malaria *P. cynomolgi* suggest that the total dose of 8-aminoquinoline given is the main determinant of radical curative efficacy. In most therapeutic assessments, primaquine has been given for 14 days. Total doses of 3.5 mg base/kg bw (0.25 mg/kg bw per day) are required for temperate strains and 7 mg base/kg bw (0.5 mg/kg bw per day) is needed for the tropical, frequent-relapsing *P. vivax* prevalent in East Asia and Oceania. Primaquine causes dose-limiting abdominal discomfort when taken on an empty stomach; it should always be taken with food.

Use of primaquine to prevent relapse in high-transmission settings was not recommended previously, as the risk for new infections was considered to outweigh any benefits of preventing relapse. This may have been based on underestimates of the morbidity and mortality associated with multiple relapses, particularly in young children. Given the benefits of preventing relapse and in the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, the group now recommends that primaquine be used in all settings.

Primaquine formulation: If available, administer scored tablets containing 7.5 or 15 mg of primaquine. Smaller-dose tablets containing 2.5 and 5 mg base are available in some areas and facilitate accurate dosing in children. When scored tablets are not available, 5 mg tablets can be used.

Therapeutic dose: 0.25–0.5 mg/kg bw per day primaquine once a day for 14 days.

Use of primaquine to prevent relapse in high-transmission settings was not recommended previously, as the risk for new infections was considered to outweigh any benefits of preventing relapse. This may have been based on underestimates of the morbidity and mortality associated with multiple relapses, particularly in young children. Given the benefits of preventing relapse and in the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, the group now recommends that primaquine be used in all settings.

Evidence To Decision

Benefits and harms

Desirable effects:

- 14-day courses of primaquine added to chloroquine reduce relapse rates to a greater extent than chloroquine alone (high-quality evidence).
- 14-day courses of primaquine added to chloroquine may result in fewer relapses than 7-day courses (low-quality

evidence).

Undesirable effects:
- Primaquine is known to cause haemolysis in people with G6PD deficiency.
- Of the 15 trials included in the Cochrane review, 12 explicitly excluded people with G6PD deficiency; in three trials, it was unclear whether participants were tested for G6PD deficiency or excluded. None of the trials reported serious or treatment-limiting adverse events.

Certainty of the Evidence

High

Overall certainty of evidence for all critical outcomes: high.

Preference and values

Justification

GRADE

In a systematic review of primaquine for radical cure of *P. vivax* malaria *(152)*, 14 days of primaquine was compared with placebo or no treatment in 10 trials, and 14 days was compared with 7 days in one trial. The trials were conducted in Colombia, Ethiopia, India, Pakistan and Thailand between 1992 and 2006.

In comparison with placebo or no primaquine:

- 14 days of primaquine (0.25 mg/kg bw per day) reduced relapses during 15 months of follow-up by about 40% (RR, 0.60; 95% CI, 0.48–0.75, 10 trials, 1740 participants, high-quality evidence).

In comparison with 7 days of primaquine:

- 14 days of primaquine (0.25 mg/kg bw per day) reduced relapses during 6 months of follow-up by over 50% (RR, 0.45; 95% CI, 0.25–0.81, one trial, 126 participants, low-quality evidence).

No direct comparison has been made of higher doses (0.5 mg/kg bw for 14 days) with the standard regimen (0.25 mg/kg bw for 14 days).

Twelve of the 15 trials included in the review explicitly excluded people with G6PD deficiency; the remaining three did not report on this aspect. No serious adverse events were reported.

Other considerations

In the absence of evidence to recommend alternatives, the guideline development group considers 0.75 mg/kg bw primaquine given once weekly for 8 weeks to be the safest regimen for people with mild-to-moderate G6PD deficiency.

Remarks

The widely used primaquine regimen of 0.25 mg base/kg bw per day for 14 days is based on studies of long-latency Korean *P. vivax*.

In South-East Asia and Oceania, *P. vivax* relapses at 3-week intervals and is more resistant to primaquine. Consequently, higher doses of primaquine have been used (0.375–0.5 mg base/kg bw per day), but there are few data from comparative trials.

Primaquine is contraindicated in pregnancy and lactation < 6 months post-partum, unless the infant has been tested for G6PD deficiency. It could be given to women who have delivered and ceased breastfeeding.

Rationale for the recommendation:

Primaquine has not previously been recommended in high-transmission settings, where the risk of new infections was considered to outweigh any benefits of reduced spontaneous relapses.

In the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, the group now recommends primaquine for radical cure of *P. vivax* in all settings.

Conditional recommendation , Very low certainty evidence

In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced haemolysis.

Practical Info

- In patients known to be G6PD deficient, primaquine may be considered at a dose of 0.75 mg base/kg bw once a week for 8 weeks. The decision to give or withhold primaquine should depend on the possibility of giving the treatment under close medical supervision, with ready access to health facilities with blood transfusion services.
- Some heterozygote females who test as normal or not deficient in qualitative G6PD screening tests have intermediate G6PD activity and can still haemolyse substantially. Intermediate deficiency (30–80% of normal) and normal enzyme activity (> 80% of normal) can be differentiated only with a quantitative test. In the absence of quantitative testing, all females should be considered as potentially having intermediate G6PD activity and given the 14-day regimen of primaquine, with counselling on how to recognize symptoms and signs of haemolytic anaemia. They should be advised to stop primaquine and be told where to seek care should these signs develop.
- If G6PD testing is not available, a decision to prescribe or withhold primaquine should be based on the balance of the probability and benefits of preventing relapse against the risks of primaquine-induced haemolytic anaemia. This depends on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes and on the capacity of health services to identify and manage primaquine-induced haemolytic reactions.

Evidence To Decision

Benefits and harms

Desirable effects:

- There are no comparative trials of the efficacy or safety of primaquine in people with G6PD deficiency.

Undesirable effects:

- Primaquine is known to cause haemolysis in people with G6PD deficiency.
- Of the 15 trials included in the systematic review, 12 explicitly excluded people with G6PD deficiency; in three trials, it was unclear whether participants were tested for G6PD deficiency or excluded. None of the trials reported serious or treatment-limiting adverse events.

Certainty of the Evidence

Very low

Overall certainty of evidence for all critical outcomes: very low.

Preference and values

Justification

GRADE

In a systematic review of primaquine for radical cure of *P. vivax* malaria *(152)*, 14 days of primaquine was compared with placebo or no treatment in 10 trials, and 14 days was compared with 7 days in one trial. The trials were conducted in Colombia, Ethiopia, India, Pakistan and Thailand between 1992 and 2006.

In comparison with placebo or no primaquine:

14 days of primaquine (0.25 mg/kg bw per day) reduced relapses during 15 months of follow-up by about 40% (RR, 0.60; 95% CI, 0.48–0.75, 10 trials, 1740 participants, high-quality evidence).

In comparison with 7 days of primaquine:

14 days of primaquine (0.25 mg/kg bw per day) reduced relapses during 6 months of follow-up by over 50% (RR, 0.45; 95% CI, 0.25–0.81, one trial, 126 participants, low-quality evidence).

No direct comparison has been made of higher doses (0.5 mg/

kg bw for 14 days) with the standard regimen (0.25 mg/kg bw for 14 days).

Twelve of the 15 trials included in the review explicitly excluded people with G6PD deficiency; the remaining three did not report on this aspect. No serious adverse events were reported.

Other considerations
In the absence of evidence to recommend alternatives, the guideline development group considers 0.75 mg/kg bw primaquine given once weekly for 8 weeks to be the safest regimen for people with mild-to-moderate G6PD deficiency.

Primaquine and glucose-6-phosphate dehydrogenase deficiency
Any person (male or female) with red cell G6PD activity < 30% of the normal mean has G6PD deficiency and will experience haemolysis after primaquine. Heterozygote females with higher mean red cell activities may still show substantial haemolysis. G6PD deficiency is an inherited sex-linked genetic disorder, which is associated with some protection against *P. falciparum* and *P. vivax* malaria but increased susceptibility to oxidant haemolysis. The prevalence of G6PD deficiency varies, but in tropical areas it is typically 3–35%; high frequencies are found only in areas where malaria is or has been endemic. There are many (> 180) different G6PD deficiency genetic variants; nearly all of which make the red cells susceptible to oxidant haemolysis, but the severity of haemolysis may vary. Primaquine generates reactive intermediate metabolites that are oxidant and cause variable haemolysis in G6PD-deficient individuals. It also causes methemoglobinaemia. The severity of haemolytic anaemia depends on the dose of primaquine and on the variant of the G6PD enzyme. Fortunately, primaquine is eliminated rapidly so haemolysis is self-limiting once the drug is stopped. In the absence of exposure to primaquine or another oxidant agent, G6PD deficiency rarely causes clinical manifestations so, many patients are unaware of their G6PD status. Screening for G6PD deficiency is not widely available outside hospitals, but rapid screening tests that can be used at points of care have recently become commercially available.

Remarks
Primaquine is contraindicated in pregnancy and lactation, unless the infant has been tested for G6PD deficiency. It could be given to women once they have delivered and ceased breastfeeding.

Rationale for the recommendation:
In the absence of evidence to recommend alternatives, the Guideline Development Group considers a regimen of 0.75 mg/kg bw primaquine given once weekly for 8 weeks to be the safest for people with G6PD deficiency.

[139]

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

Good practice statement

When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.

Justification

If G6PD testing is not available, a decision to prescribe or withhold primaquine should be based on the balance of the probability and benefits of preventing relapse against the risks of primaquine-induced haemolytic anaemia. This depends on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes and on the capacity of health services to identify and manage primaquine-induced haemolytic reactions.

Conditional recommendation , Moderate certainty evidence

Pregnant and breastfeeding women: In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.

Practical Info

Primaquine is contraindicated in pregnant women and in lactating women (unless the infant is known not to be G6PD deficient).

As an alternative, chloroquine prophylaxis could be given to suppress relapses after acute vivax malaria during pregnancy.

Once the infant has been delivered and the mother has completed breastfeeding, primaquine could then be given to achieve radical cure.

Few data are available on the safety of primaquine in infancy, and in the past primaquine was not recommended for infants.

There is, however, no specific reason why primaquine should not be given to children aged 6 months to 1 year (provided they do not have G6PD deficiency), as this age group may suffer multiple relapses from vivax malaria. The guideline development group therefore recommended lowering the age restriction to 6 months.

Evidence To Decision

Benefits and harms

Desirable effects:

- Chloroquine prophylaxis reduced recurrent *P. vivax* malaria in pregnant women (moderate-quality evidence).

Certainty of the Evidence

Moderate

Overall certainty of evidence for all critical outcomes: moderate.

Preference and values

Justification

GRADE

In a systematic review of malaria chemoprophylaxis in pregnant women *(153)*, chloroquine prophylaxis against *P. vivax* during pregnancy was directly evaluated in one trial conducted in Thailand in 2001. In comparison with no chemoprophylaxis:

- Chloroquine prophylaxis substantially reduced recurrent *P. vivax* malaria (RR, 0.02; 95% CI, 0.00–0.26, one trial, 951 participants, moderate- quality evidence).

Recommendation

Primaquine is contraindicated in pregnant or breastfeeding women with *P. vivax* malaria. Therefore, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then treat with 14 days of primaquine to prevent future relapse.

5.5 Treating severe malaria

Mortality from untreated severe malaria (particularly cerebral malaria) approaches 100%. With prompt, effective antimalarial treatment and supportive care, the rate falls to 10–20% overall. Within the broad definition of severe malaria some syndromes are associated with lower mortality rates (e.g. severe anaemia) and others with higher mortality rates (e.g. acidosis). The risk for death increases in the presence of multiple complications.

Any patient with malaria who is unable to take oral medications reliably, shows any evidence of vital organ dysfunction or has a high parasite count is at increased risk for dying. The exact risk depends on the species of infecting malaria parasite, the number of systems affected, the degree of vital organ dysfunction, age, background immunity, pre-morbid, and concomitant diseases, and access to appropriate treatment. Tests such as a parasite count, haematocrit and blood glucose may all be performed immediately at the point of care, but the results of other laboratory measures, if any, may be available only after hours or days. As severe malaria is potentially fatal, any patient considered to be at increased risk should be given the benefit of the highest level of care available. The attending clinician should not worry unduly about definitions: the severely ill patient requires immediate supportive care, and, if severe malaria is a possibility, parenteral antimalarial drug treatment should be started without delay.

Definitions

Severe falciparum malaria: For epidemiological purposes, severe falciparum malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia.

- Impaired consciousness: A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children
- Prostration: Generalized weakness so that the person is unable to sit, stand or walk without assistance
- Multiple convulsions: More than two episodes within 24 h
- Acidosis: A base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing).
- Hypoglycaemia: Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)
- Severe malarial anaemia: Haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤ 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) with a parasite count > 10 000/µL
- Renal impairment: Plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L
- Jaundice: Plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100 000/ µL

- Pulmonary oedema: Radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation
- Significant bleeding: Including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena
- Shock: Compensated shock is defined as capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
- Hyperparasitaemia: *P. falciparum* parasitaemia > 10%

Severe vivax and knowlesi malaria: defined as for falciparum malaria but with no parasite density thresholds.

Severe knowlesi malaria is defined as for falciparum malaria but with two differences:

- *P. knowlesi* hyperparasitaemia: parasite density > 100 000/μL
- Jaundice and parasite density > 20 000/μL.

Therapeutic objectives
The main objective of the treatment of severe malaria is to prevent the patient from dying. Secondary objectives are prevention of disabilities and prevention of recrudescent infection.

Death from severe malaria often occurs within hours of admission to a hospital or clinic, so it is essential that therapeutic concentrations of a highly effective antimalarial drug be achieved as soon as possible. Management of severe malaria comprises mainly clinical assessment of the patient, specific antimalarial treatment, additional treatment and supportive care.

Clinical assessment
Severe malaria is a medical emergency. An open airway should be secured in unconscious patients and breathing and circulation assessed. The patient should be weighed or body weight estimated, so that medicines, including antimalarial drugs and fluids, can be given appropriately. An intravenous cannula should be inserted, and blood glucose (rapid test), haematocrit or haemoglobin, parasitaemia and, in adults, renal function should be measured immediately. A detailed clinical examination should be conducted, including a record of the coma score. Several coma scores have been advocated: the Glasgow coma scale is suitable for adults, and the simple Blantyre modification is easily performed in children. Unconscious patients should undergo a lumbar puncture for cerebrospinal fluid analysis to exclude bacterial meningitis.

The degree of acidosis is an important determinant of outcome; the plasma bicarbonate or venous lactate concentration should be measured, if possible. If facilities are available, arterial or capillary blood pH and gases should be measured in patients who are unconscious, hyperventilating or in shock. Blood should be taken for cross-matching, a full blood count, a platelet count, clotting studies, blood culture and full biochemistry (if possible). Careful attention should be paid to the patient's fluid balance in severe malaria in order to avoid over- or under-hydration. Individual requirements vary widely and depend on fluid losses before admission.

The differential diagnosis of fever in a severely ill patient is broad. Coma and fever may be due to meningoencephalitis or malaria. Cerebral malaria is not associated with signs of meningeal irritation (neck stiffness, photophobia or Kernig's sign), but the patient may be opisthotonic. As untreated bacterial meningitis is almost invariably fatal, a diagnostic lumbar puncture should be performed to exclude this condition. There is also considerable clinical overlap between septicaemia, pneumonia and severe malaria, and these conditions may coexist. When possible, blood should always be taken on admission for bacterial culture. In malaria-endemic areas, particularly where parasitaemia is common in young age groups, it is difficult to rule out septicaemia immediately in a shocked or severely ill obtunded child. In all such cases, empirical parenteral broad-spectrum antibiotics should be started immediately, together with antimalarial treatment.

Treatment of severe malaria
It is essential that full doses of effective parenteral (or rectal) antimalarial treatment be given promptly in the initial treatment of severe malaria. This should be followed by a full dose of effective ACT orally. Two classes of medicine are available for parenteral treatment of severe malaria: artemisinin derivatives (artesunate or artemether) and the cinchona alkaloids (quinine and quinidine). Parenteral artesunate is the treatment of choice for all severe malaria. The largest randomized clinical trials ever conducted on severe falciparum malaria showed a substantial reduction in mortality with intravenous or intramuscular artesunate as compared with parenteral quinine. The reduction in mortality was not associated with an increase in neurological sequelae in artesunate-treated survivors. Furthermore, artesunate is simpler and safer to use.

Pre-referral treatment options
See recommendation.

Adjustment of parenteral dosing in renal failure or hepatic dysfunction
The dosage of artemisinin derivatives does not have to be adjusted for patients with vital organ dysfunction. However quinine accumulates in severe vital organ dysfunction. If a patient with severe malaria has persisting acute kidney injury or there is no clinical improvement by 48 h, the dose of quinine should be reduced by one third, to 10 mg salt/kg bw every 12 h. Dosage adjustments are not necessary if patients are receiving either haemodialysis or haemofiltration.

Follow-on treatment
The current recommendation of experts is to give parenteral antimalarial drugs for the treatment of severe malaria for a minimum of 24 h once started (irrespective of the patient's ability to tolerate oral medication earlier) or until the patient can tolerate oral medication, before giving the oral follow-up treatment.

After initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial drug by giving a full course of effective ACT (artesunate + amodiaquine, artemether + lumefantrine or dihydroartemisinin + piperaquine). If the patient presented initially with impaired consciousness, ACTs containing mefloquine should be avoided because of an increased incidence of neuropsychiatric complications. When an ACT is not available, artesunate + clindamycin, artesunate + doxycycline, quinine + clindamycin or quinine + doxycycline can be used for follow-on treatment. Doxycycline is preferred to other tetracyclines because it can be given once daily and does not accumulate in cases of renal failure, but it should not be given to children < 8 years or pregnant women. As treatment with doxycycline is begun only when the patient has recovered sufficiently, the 7-day doxycycline course finishes after the artesunate, artemether or quinine course. When available, clindamycin may be substituted in children and pregnant women.

Continuing supportive care

Patients with severe malaria require intensive nursing care, preferably in an intensive care unit where possible. Clinical observations should be made as frequently as possible and should include monitoring of vital signs, coma score and urine output. Blood glucose should be monitored every 4 h, if possible, particularly in unconscious patients.

Management of complications

Severe malaria is associated with a variety of manifestations and complications, which must be recognized promptly and treated as shown below.

Immediate clinical management of severe manifestations and complications of *P. falciparum* malaria

Manifestation or complication	Immediate management[a]
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatments, intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, a cooling blanket and paracetamol.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam, lorazepam, midazolam or intramuscular paraldehyde. Check blood glucose.
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion. Although hypoglycaemia is defined as glucose < 2.2 mmol/L, the threshold for intervention is < 3 mmol/L for children < 5 years and <2.2 mmol/L for older children and adults.
Severe anaemia	Transfuse with screened fresh whole blood.
Acute pulmonary oedemab	Prop patient up at an angle of 45o, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure or continuous positive airway pressure in life-threatening hypoxaemia.
Acute kidney injury	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure, add haemofiltration or haemodialysis, or, if not available, peritoneal dialysis.
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection.
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add haemofiltration or haemodialysis.
Shock	Suspect septicaemia, take blood for cultures; give parenteral broad- spectrum antimicrobials, correct haemodynamic disturbances.

[a] It is assumed that appropriate antimalarial treatment will have been started in all cases.

[b] Prevent by avoiding excess hydration

Additional aspects of management

Fluid therapy

Fluid requirements should be assessed individually. Adults with severe malaria are very vulnerable to fluid overload, while children are more likely to be dehydrated. The fluid regimen must also be adapted to the infusion of antimalarial drugs. Rapid bolus infusion of colloid or crystalloids is contraindicated. If available, haemofiltration should be started early for acute kidney injury or severe metabolic acidosis, which do not respond to rehydration. As the degree of fluid depletion varies considerably in patients with severe malaria, it is not possible to give general recommendations on fluid replacement; each patient must be assessed individually and fluid resuscitation based on the estimated deficit. In high-transmission settings, children commonly present with severe anaemia and hyperventilation (sometimes termed “respiratory distress”) resulting from severe metabolic acidosis and anaemia; they should be treated by blood transfusion. In adults, there is a very thin dividing line between over-hydration, which may produce pulmonary oedema, and under-hydration, which contributes to shock, worsening acidosis and renal impairment. Careful, frequent evaluation of jugular venous pressure, peripheral perfusion, venous filling, skin turgor and urine output should be made.

Blood transfusion

Severe malaria is associated with rapid development of anaemia,

as infected, once infected and uninfected erythrocytes are haemolysed and/or removed from the circulation by the spleen. Ideally, fresh, cross-matched blood should be transfused; however, in most settings, cross-matched virus-free blood is in short supply. As for fluid resuscitation, there are not enough studies to make strong evidence-based recommendations on the indications for transfusion; the recommendations given here are based on expert opinion. In high-transmission settings, blood transfusion is generally recommended for children with a haemoglobin level of < 5 g/100 mL (haematocrit < 15%). In low-transmission settings, a threshold of 20% (haemoglobin, 7 g/100 mL) is recommended. These general recommendations must, however, be adapted to the individual, as the pathological consequences of rapid development of anaemia are worse than those of chronic or acute anaemia when there has been adaptation and a compensatory right shift in the oxygen dissociation curve.

Exchange blood transfusion
Many anecdotal reports and several series have claimed the benefit of exchange blood transfusion in severe malaria, but there have been no comparative trials, and there is no consensus on whether it reduces mortality or how it might work. Various rationales have been proposed:

- removing infected red blood cells from the circulation and therefore lowering the parasite burden (although only the circulating, relatively non-pathogenic stages are removed, and this is also achieved rapidly with artemisinin derivatives);
- rapidly reducing both the antigen load and the burden of parasite-derived toxins, metabolites and toxic mediators produced by the host; and
- replacing the rigid unparasitized red cells by more easily deformable cells, therefore alleviating microcirculatory obstruction.

Exchange blood transfusion requires intensive nursing care and a relatively large volume of blood, and it carries significant risks. There is no consensus on the indications, benefits and dangers involved or on practical details such as the volume of blood that should be exchanged. It is, therefore, not possible to make any recommendation regarding the use of exchange blood transfusion.

Concomitant use of antibiotics
The threshold for administering antibiotic treatment should be low in severe malaria. Septicaemia and severe malaria are associated, and there is substantial diagnostic overlap,particularly in children in areas of moderate and high transmission.Thus broad- spectrum antibiotic treatment *should be given* with antimalarial drugs to all children with suspected severe malaria in areas of moderate and high transmission until a bacterial infection is excluded. After the start of antimalarial treatment, unexplained deterioration may result from a supervening bacterial infection.Enteric bacteria (notably *Salmonella*) predominated in many trial series in Africa, but a variety of bacteria have been cultured from the blood of patients with a diagnosis of severe malaria.

Patients with secondary pneumonia or with clear evidence of aspiration should be given empirical treatment with an appropriate broad-spectrum antibiotic. In children with persistent fever despite parasite clearance, other possible causes of fever should be excluded, such as systemic *Salmonella* infections and urinary tract infections, especially in catheterized patients. In the majority of cases of persistent fever, however, no other pathogen is identified after parasite clearance. Antibiotic treatment should be based on culture and sensitivity results or,if not available, local antibiotic sensitivity patterns.

Use of anticonvulsants
The treatment of convulsions in cerebral malaria with intravenous (or, if this is not possible, rectal) benzodiazepines or intramuscular paraldehyde is similar to that for repeated seizures from any cause. In a large, double-blind, placebo-controlled evaluation of a single prophylactic intramuscular injection of 20 mg/kg bw of phenobarbital to children with cerebral malaria, the frequency of seizures was reduced but the mortality rate was increased significantly. This resulted from respiratory arrest and was associated with additional use of benzodiazepine.

A 20 mg/kg bw dose of phenobarbital should not be given without respiratory support. It is not known whether a lower dose would be effective and safer or whether mortality would not increase if ventilation were given. In the absence of further information, prophylactic anticonvulsants are not recommended.

Treatments that are not recommended
In an attempt to reduce the high mortality from severe malaria, various adjunctive treatments have been evaluated, but none has proved effective and many have been shown to be harmful. Heparin, prostacyclin, desferroxamine, pentoxifylline, low-molecular-mass dextran, urea, high-dose corticosteroids, aspirin anti-TNF antibody, cyclosporine A,dichloroacetate, adrenaline, hyperimmune serum,*N*-acetylcysteine and bolus administration of albumin are not recommended.In addition,use of corticosteroids increases the risk for gastrointestinal bleeding and seizures and has been associated with prolonged coma resolution times when compared with placebo.

Treatment of severe malaria during pregnancy
Women in the second and third trimesters of pregnancy are more likely to have severe malaria than other adults, and, in low-transmission settings, this is often complicated by pulmonary oedema and hypoglycaemia. Maternal mortality is approximately 50%, which is higher than in non-pregnant adults. Fetal death and premature labour are common.
Parenteral antimalarial drugs should be given to pregnant women with severe malaria in full doses without delay. Parenteral artesunate is the treatment of choice in all trimesters. Treatment must not be delayed. If artesunate is unavailable, intramuscular artemether should be given, and if this is unavailable then parenteral quinine should be started immediately until artesunate is obtained.

Obstetric advice should be sought at an early stage, a paediatrician alerted and blood glucose checked frequently. Hypoglycaemia should be expected, and it is often recurrent if

the patient is receiving quinine. Severe malaria may also present immediately after delivery. Postpartum bacterial infection is a common complication and should be managed appropriately.

Treatment of severe *P. vivax* malaria

Although *P. vivax* malaria is considered to be benign, with a low case-fatality rate, it may cause a debilitating febrile illness with progressive anaemia and can also occasionally cause severe disease, as in *P. falciparum* malaria. Reported manifestations of severe *P. vivax* malaria include severe anaemia, thrombocytopenia, acute pulmonary oedema and, less commonly, cerebral malaria, pancytopenia, jaundice, splenic rupture, haemoglobinuria, acute renal failure and shock.

Prompt effective treatment and case management should be the same as for severe *P. falciparum* malaria (see section 5.5.1). Following parenteral artesunate, treatment can be completed with a full treatment course of oral ACT or chloroquine (in countries where chloroquine is the treatment of choice). A full course of radical treatment with primaquine should be given after recovery.

Please refer to *Management of severe malaria - A practical handbook, 3rd edition (160)*.

5.5.1 Artesunate

Strong recommendation for , High certainty evidence

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT.

Practical Info

Artesunate is dispensed as a powder of artesunic acid, which is dissolved in sodium bicarbonate (5%) to form sodium artesunate. The solution is then diluted in approximately 5 mL of 5% dextrose and given by intravenous injection or by intramuscular injection into the anterior thigh.

The solution should be prepared freshly for each administration and should not be stored. Artesunate is rapidly hydrolysed in-vivo to dihydroartemisinin, which provides the main antimalarial effect. Studies of the pharmacokinetics of parenteral artesunate in children with severe malaria suggest that they have less exposure than older children and adults to both artesunate and the biologically active metabolite dihydroartemisinin. Body weight has been identified as a significant covariate in studies of the pharmacokinetics of orally and rectally administered artesunate, which suggests that young children have a larger apparent volume of distribution for both compounds and should therefore receive a slightly higher dose of parenteral artesunate to achieve exposure comparable to that of older children and adults.

Artesunate and post-treatment haemolysis

Delayed haemolysis starting >1 week after artesunate treatment of severe malaria has been reported in hyperparasitaemic non-immune travellers. Between 2010 and 2012, there were six reports involving a total of 19 European travellers with severe malaria who were treated with artesunate injection and developed delayed haemolysis. All except one were adults (median age, 50 years; range, 5–71 years). In a prospective study involving African children, the same phenomenon was reported in 5 (7%) of the 72 hyperparasitaemic children studied. Artesunate rapidly kills ring-stage parasites, which are then taken out of the red cells by the spleen; these infected erythrocytes are then returned to the circulation but with a shortened life span, resulting in the observed haemolysis. Thus, post-treatment haemolysis is a predictable event related to the life-saving effect of artesunate. Hyperparasitaemic patients must be followed up carefully to identify late-onset anaemia.

Please refer to the *Information note on delayed haemolytic anaemia following treatment with artesunate (156)*.

Evidence To Decision

Benefits and harms

Desirable effects:

- In both adults and children, parenteral artesunate prevented more deaths than parenteral quinine (high-quality evidence).
- For intravenous administration, artesunate is given as a bolus, whereas quinine requires slow infusion.
- For intramuscular administration, artesunate is given in a smaller volume than quinine.

Undesirable effects:

- Artesunate is associated with a small increase in neurological sequelae at the time of hospital discharge (moderate-quality evidence). The difference is no longer evident on day 28 after discharge (moderate-quality evidence).

Certainty of the Evidence

High

Overall certainty of evidence for all critical outcomes: high.

Preference and values

Justification

GRADE

In a systematic review of artesunate for severe malaria *(155)*, eight randomized controlled trials with a total of 1664 adults and 5765 children, directly compared parenteral artesunate with parenteral quinine. The trials were conducted in various African and Asian countries between 1989 and 2010.

In comparison with quinine, parenteral artesunate:

- reduced mortality from severe malaria by about 40% in adults (RR, 0.61; 95% CI, 0.50–0.75, five trials, 1664 participants, high-quality evidence);
- reduced mortality from severe malaria by about 25% in children (RR, 0.76; 95% CI, 0.65–0.90, four trials, 5765 participants, high-quality evidence); and
- was associated with a small increase in neurological sequelae in children at the time of hospital discharge (RR, 1.36; 95% CI, 1.01–1.83, three trials, 5163 participants, moderate-quality evidence), most of which, however, slowly resolved, with little or no difference between artesunate and quinine 28 days later (moderate-quality evidence).

Other considerations

The guideline development group considered that the small increase in neurological sequelae at discharge after treatment with artesunate was due to the delayed recovery of the severely ill patients, who would have died had they received quinine. This should not be interpreted as a sign of neurotoxicity. Although the safety of artesunate given in the first trimester of pregnancy has not been firmly established, the guideline development group considered that the proven benefits to the mother outweigh any potential harm to the developing fetus.

Remarks

Parenteral artesunate is recommended as first-line treatment for adults, children, infants and pregnant women in all trimesters of pregnancy.

Rationale for the recommendation

The Guideline Development Group considered the small increase in neurological sequelae at discharge associated with artesunate to be due to prolonged recovery of severely ill patients who would have died if they had received quinine. This should not be interpreted as a sign of neurotoxicity.

Although the safety of artesunate in the first trimester of pregnancy has not been firmly established, the group considered that the proven benefits to the mother outweigh the potential harms to the developing fetus.

Strong recommendation for

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.

*unGRADEd recommendation based on pharmacokinetic modelling, anticipated to be updated in 2022

Practical Info

Artesunate is dispensed as a powder of artesunic acid, which is dissolved in sodium bicarbonate (5%) to form sodium artesunate. The solution is then diluted in approximately 5 mL of 5% dextrose and given by intravenous injection or by intramuscular injection into the anterior thigh.

The solution should be prepared freshly for each administration and should not be stored. Artesunate is rapidly hydrolysed in-vivo to dihydroartemisinin, which provides the main antimalarial effect. Studies of the

pharmacokinetics of parenteral artesunate in children with severe malaria suggest that they have less exposure than older children and adults to both artesunate and the biologically active metabolite dihydroartemisinin. Body weight has been identified as a significant covariate in studies of the pharmacokinetics of orally and rectally administered artesunate, which suggests that young children have a larger apparent volume of distribution for both compounds and should therefore receive a slightly higher dose of parenteral artesunate to achieve exposure comparable to that of older children and adults.

Artesunate and post-treatment haemolysis
Delayed haemolysis starting >1 week after artesunate treatment of severe malaria has been reported in hyperparasitaemic non-immune travellers. Between 2010 and 2012, there were six reports involving a total of 19 European travellers with severe malaria who were treated with artesunate injection and developed delayed haemolysis. All except one were adults (median age, 50 years; range, 5–71 years). In a prospective study involving African children, the same phenomenon was reported in 5 (7%) of the 72 hyperparasitaemic children studied. Artesunate rapidly kills ring-stage parasites, which are then taken out of the red cells by the spleen; these infected erythrocytes are then returned to the circulation but with a shortened life span, resulting in the observed haemolysis. Thus, post-treatment haemolysis is a predictable event related to the life-saving effect of artesunate. Hyperparasitaemic patients must be followed up carefully to identify late-onset anaemia.

Justification

The dosing subgroup reviewed all available pharmacokinetic data on artesunate and the main biologically active metabolite dihydroartemisinin following administration of artesunate in severe malaria (published pharmacokinetic studies from 71 adults and 265 children) *(157)(158)*. Simulations of artesunate and dihydroartemisinin exposures were conducted for each age group. These showed underexposure in younger children. The revised parenteral dose regimens are predicted to provide equivalent artesunate and dihydroartemisinin exposures across all age groups.

Other considerations
Individual parenteral artesunate doses between 1.75 and 4 mg/kg have been studied and no toxicity has been observed. The GRC concluded that the predicted benefits of improved antimalarial exposure in children are not at the expense of increased risk.

5.5.2 Parenteral alternatives when artesunate is not available

Conditional recommendation , Low certainty evidence

If artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.

Practical Info

Artemether
Artemether is two to three times less active than its main metabolite dihydroartemisinin. Artemether can be given as an oil-based intramuscular injection or orally. In severe falciparum malaria, the concentration of the parent compound predominates after intramuscular injection, whereas parenteral artesunate is hydrolysed rapidly and almost completely to dihydroartemisinin. Given intramuscularly, artemether may be absorbed more slowly and more erratically than water-soluble artesunate, which is absorbed rapidly and reliably after intramuscular injection. These pharmacological advantages may explain the clinical superiority of parenteral artesunate over artemether in severe malaria.

Artemether is dispensed dissolved in oil (groundnut, sesame seed) and given by intramuscular injection into the anterior thigh.

Therapeutic dose: The initial dose of artemether is 3.2 mg/kg bw intramuscularly (to the anterior thigh). The maintenance dose is 1.6 mg/kg bw intramuscularly daily.

Quinine
Quinine treatment for severe malaria was established before the methods for modern clinical trials were developed. Several salts of quinine have been formulated for parenteral use, but the dihydrochloride is the most widely used. The peak concentrations after intramuscular quinine in severe malaria are similar to those after intravenous infusion. Studies of pharmacokinetics show that a loading dose of quinine (20 mg salt/kg bw, twice the maintenance dose) provides therapeutic plasma concentrations within 4 h. The maintenance dose of quinine (10 mg salt/ kg bw) is administered at 8-h intervals, starting 8 h after the first dose. If there is no improvement in the patient's condition within 48 h, the dose should be reduced by one third, i.e. to 10 mg salt/kg bw every 12 h.

Rapid intravenous administration of quinine is dangerous. Each dose of parenteral quinine must be administered as a slow, rate-controlled infusion (usually diluted in 5% dextrose

and infused over 4 h). The infusion rate should not exceed 5 mg salt/kg bw per h.

Whereas many antimalarial drugs are prescribed in terms of base, for historical reasons quinine doses are usually recommended in terms of salt (usually sulphate for oral use and dihydrochloride for parenteral use). Recommendations for the doses of this and other antimalarial agents should state clearly whether the salt or the base is being referred to; doses with different salts must have the same base equivalents. Quinine must never be given by intravenous bolus injection, as lethal hypotension may result.

Quinine dihydrochloride should be given by rate-controlled infusion in saline or dextrose solution. If this is not possible, it should be given by intramuscular injection to the anterior thigh; quinine should not be injected into the buttock in order to avoid sciatic nerve injury. The first dose should be split, with 10 mg/kg bw into each thigh. Undiluted quinine dihydrochloride at a concentration of 300 mg/ mL is acidic (pH 2) and painful when given by intramuscular injection, so it is best to administer it either in a buffered formulation or diluted to a concentration of 60–100 mg/mL for intramuscular injection. Gluconate salts are less acidic and better tolerated than the dihydrochloride salt when given by the intramuscular and rectal routes.

As the first (loading) dose is the most important in the treatment of severe malaria, it should be reduced only if there is clear evidence of adequate pre-treatment before presentation. Although quinine can cause hypotension if administered rapidly, and overdose is associated with blindness and deafness, these adverse effects are rare in the treatment of severe malaria. The dangers of insufficient treatment (i.e. death from malaria) exceed those of excessive initial treatment.

Evidence To Decision

Benefits and harms

Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?

Desirable effects:

- In children > 12 years and adults, parenteral artesunate probably prevents more deaths than intramuscular artemether (moderate-quality evidence).
- No randomized controlled trials have been conducted in children aged ≤ 12 years.

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Is intramuscular artemether superior to parenteral quinine in preventing death from severe malaria?

Desirable effects:

- In children, artemether is probably equivalent to quinine in preventing death (moderate-quality evidence).
- In children > 5 years and adults, artemether may be superior to quinine (moderate-quality evidence).
- Artemether is easier to administer, requiring a smaller fluid volume for intramuscular injection.

Certainty of the Evidence

Low

Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?

Overall certainty of evidence for all critical outcomes: moderate.

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Is intramuscular artemether superior to parenteral quinine in preventing death from severe malaria?

Overall certainty of evidence for all critical outcomes: moderate.

Preference and values

Justification

GRADE

A systematic review of intramuscular artemether for severe malaria comprised two randomized controlled trials in Viet Nam in which artemether was compared with artesunate in 494 adults, and 16 trials in Africa and Asia in which artemether was compared with quinine in 716 adults and

1447 children *(159)*. The trials were conducted between 1991 and 2009.

In comparison with artesunate, intramuscular artemether was not as effective at preventing deaths in adults in Asia (RR, 1.80; 95% CI, 1.09–2.97; two trials, 494 participants, moderate-quality evidence).

Artemether and artesunate have not been directly compared in randomized trials in African children.

In comparison with quinine:

- Intramuscular artemether prevented a similar number of deaths in children in Africa (RR, 0.96; 95% CI, 0.76–1.20; 12 trials, 1447 participants, moderate-quality evidence).
- Intramuscular artemether prevented more deaths in adults in Asia (RR, 0.59; 95% CI, 0.42–0.83; four trials, 716 participants, moderate-quality evidence).

Other considerations
Indirect comparisons of parenteral artesunate and quinine and of artemether and quinine were considered by the guideline development group with what is known about the pharmacokinetics of the two drugs. They judged the accumulated indirect evidence to be sufficient to recommend parenteral artesunate rather than intramuscular artemether for use in all age groups.
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Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?

Remarks
Intramuscular artemether should be considered only when parenteral artesunate is not available.

Recommendation
Treat children and adults with severe malaria with parenteral artesunate for at least 24 h.

Strength of recommendation: Strong for.

Rationale for the recommendation
Indirect comparisons of artesunate and quinine and of artemether and quinine were considered by the Guideline Development Group, with what is known about the pharmacokinetics of the two drugs. The group considered that the accumulated indirect evidence is sufficient to recommend artesunate over artemether for all age groups.
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Is intramuscular artemether superior to parenteral quinine in preventing death from severe malaria?

Remarks
Quinine is retained as an option for treating severe malaria when artesunate or artemether is not available or is contraindicated.

Recommendation
If parenteral artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.

Strength of recommendation: conditional for.

Rationale for the recommendation
The Guideline Development Group considered the possible superiority, the ease of administration and the better adverse-event profile of artemether as sufficient to recommend artemether over quinine as a second-line treatment option for severe malaria.

5.5.3 Pre-referral treatment options

The risk for death from severe malaria is greatest in the first 24 h, yet, in most malaria-endemic countries, the transit time between referral and arrival at a health facility where intravenous treatment can be administered is usually long, thus delaying the start of appropriate antimalarial treatment. During this time, the patient may deteriorate or die. It is therefore recommended that patients, particularly young children, be treated with a first dose of one of the recommended treatments before referral (unless the referral time is <6 h).

The recommended pre-referral treatment options for children <6 years, in descending order of preference, are intramuscular artesunate; rectal artesunate; intramuscular artemether; and intramuscular quinine. For older children and adults, the recommended pre-referral treatment options, in descending order of preference, are intramuscular injections of artesunate; artemether; and quinine.

Administration of an artemisinin derivative by the rectal route as pre-referral treatment is feasible and acceptable even at community level. The only trial of rectal artesunate as pre-referral treatment showed the expected reduction in mortality of young children but unexpectedly found increased mortality in older children and adults. As a consequence, rectal artesunate is recommended for use only in children aged <6 years and only when intramuscular artesunate is not available.

When rectal artesunate is used, patients should be transported immediately to a higher-level facility where intramuscular or intravenous treatment is available. If referral is impossible, rectal treatment could be continued until the patient can tolerate oral medication. At this point, a full course of the recommended ACT for uncomplicated malaria should be administered.

The single dose of 10 mg/kg bw of artesunate when given as a suppository should be administered rectally as soon as a presumptive diagnosis of severe malaria is made. If the suppository is expelled from the rectum within 30 min of insertion, a second suppository should be inserted and the

buttocks held together for 10 min to ensure retention of the dose.

Strong recommendation for , Moderate certainty evidence

Where complete treatment of severe malaria is not possible, but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care. Where intramuscular artesunate is not available use intramuscular artemether or, if that is not available, use intramuscular quinine.

Where intramuscular injection of artesunate is not available, treat children < 6 years with a single rectal dose (10mg/kg bw) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults.

Practical Info

Adjustment of parenteral dosing in renal failure of hepatic dysfunction

The dosage of artemisinin derivatives does not have to be adjusted for patients with vital organ dysfunction. However, quinine accumulates in severe vital organ dysfunction. If a patient with severe malaria has persisting acute kidney injury or there is no clinical improvement by 48 h, the dose of quinine should be reduced by one third, to 10 mg salt/kg bw every 12 h. Dosage adjustments are not necessary if patients are receiving either haemodialysis or haemofiltration.

Follow-on treatment

The current recommendation of experts is to give parenteral antimalarial drugs for the treatment of severe malaria for a minimum of 24 h ounce started (irrespective of the patient's ability to tolerate oral medication earlier) or until the patient can tolerate oral medication, before giving the oral follow-up treatment.

After initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial drug by giving a full course of effective ACT (artesunate + amodiaquine, artemether + lumefantrine or dihydroartemisinin + piperaquine). If the patient presented initially with impaired consciousness, ACTs containing mefloquine should be avoided because of an increased incidence of neuropsychiatric complications. When an ACT is not available, artesunate + clindamycin, artesunate + doxycycline, quinine + clindamycin or quinine + doxycycline can be used for follow-on treatment. Doxycycline is preferred to other tetracyclines because it can be given once daily and does not accumulate in cases of renal failure, but it should not be given to children < 8 years or pregnant women. As treatment with doxycycline is begun only when the patient has recovered sufficiently, the 7-day doxycycline course finishes after the artesunate, artemether or quinine course. When available, clindamycin may be substituted in children and pregnant women.

Continuing supportive care

Patients with severe malaria require intensive nursing care, preferably in an intensive care unit where possible. Clinical observations should be made as frequently as possible and should include monitoring of vital signs, coma score and urine output. Blood glucose should be monitored every 4 h, if possible, particularly in unconscious patients.

Please refer to *Rectal artesunate for pre-referral treatment of severe malaria (161)*.

Evidence To Decision

Benefits and harms

Desirable effects:

- No studies of direct comparison of rectal artesunate with parenteral antimalarial drugs for pre-referral treatment.
- In hospital care, parenteral artesunate reduces the number of deaths to a greater extent than parenteral quinine (high-quality evidence) and probably reduces the number of deaths from that with intramuscular artemether (moderate-quality evidence).

Certainty of the Evidence

Moderate

Overall certainty of evidence for all critical outcomes: moderate.

Preference and values

Justification

GRADE

In a systematic review of pre-referral treatment for suspected severe malaria, in a single large randomized controlled trial of 17 826 children and adults in Bangladesh, Ghana and the United Republic of Tanzania, pre-referral rectal artesunate was compared with placebo *(160)*.

In comparison with placebo:

- Rectal artesunate reduced mortality by about 25% in children < 6 years (RR, 0.74; 95% CI, 0.59–0.93; one trial, 8050 participants, moderate- quality evidence).
- Rectal artesunate was associated with more deaths in older children and adults (RR, 2.21; 95% CI, 1.18–4.15; one trial 4018 participants, low- quality evidence).

Other considerations

The guideline development group could find no plausible explanation for the finding of increased mortality among older children and adults in Asia who received rectal artesunate, which may be due to chance. Further trials would provide clarification but are unlikely to be done. The group was therefore unable to recommend its use in older children and adults.

In the absence of direct evaluations of parenteral antimalarial drugs for pre- referral treatment, the guideline development group considered the known benefits of artesunate in hospitalized patients and downgraded the quality of evidence for pre-referral situations. When intramuscular injections can be given, the group recommends intramuscular artesunate in preference to rectal artesunate.

Remarks

This recommendation applies to all people with suspected severe malaria, including infants, lactating women and pregnant women in all trimesters.

Where intramuscular artesunate is not available, use rectal artesunate (in children < 6 years), intramuscular artemether or intramuscular quinine.

Rationale for the recommendation

In the absence of direct comparative evaluations of parenteral antimalarial drugs for pre-referral treatment, the Guideline Development Group considered the known benefits of artesunate in hospitalized patients and downgraded the quality of evidence for use in pre-referral situations. When intramuscular injections can be given, the panel recommends intramuscular artesunate in preference to rectal artesunate.

5.6 Other considerations in treating malaria

5.6.1 Management of malaria cases in special situations

Epidemics and humanitarian emergencies

Environmental, political and economic changes, population movement and war can all contribute to the emergence or re-emergence of malaria in areas where it was previously eliminated or well controlled. The displacement of large numbers of people with little or no immunity within malaria-endemic areas increases the risk for malaria epidemics among the displaced population, while displacement of people from an endemic area to an area where malaria has been eliminated can result in re-introduction of transmission and a risk for epidemics in the resident population.

Climate change may also alter transmission patterns and the malaria burden globally by producing conditions that favour vector breeding and thereby increasing the risks for malaria transmission and epidemics.

Parasitological diagnosis during epidemics

In the acute phase of epidemics and complex emergency situations, facilities for laboratory diagnosis with good-quality equipment and reagents and skilled technicians are often not available or are overwhelmed. Attempts should be made to improve diagnostic capacity rapidly, including provision of RDTs. If diagnostic testing is not feasible, the most practical approach is to treat all febrile patients as suspected malaria cases, with the inevitable consequences of over-treatment of malaria and potentially poor management of other febrile conditions. If this approach is used, it is imperative to monitor intermittently the prevalence of malaria as a true cause of fever and revise the policy appropriately. This approach has sometimes been termed “mass fever treatment”. This is not the same as and should not be confused with “mass drug administration”, which is administration of a complete treatment course of antimalarial medicines to every individual in a geographically defined area without testing for infection and regardless of the presence of symptoms.

Management of uncomplicated falciparum malaria during epidemics

The principles of treatment of uncomplicated malaria are the same as those outlined in section 5.2. Active case detection should be undertaken to ensure that as many patients as possible receive adequate treatment, rather than relying on

patients to come to a clinic.

Epidemics of mixed falciparum and vivax or vivax malaria

ACTs (except artesunate + SP) should be used to treat uncomplicated malaria in mixed-infection epidemics, as they are highly effective against all malaria species. In areas with pure *P. vivax* epidemics, ACTs or chloroquine (if prevalent strains are sensitive) should be used.

Anti-relapse therapy for *P. vivax* malaria

Administration of 14-day primaquine anti-relapse therapy for vivax malaria may be impractical in epidemic situations because of the duration of treatment and the difficulty of ensuring adherence. If adequate records are kept, therapy can be given in the post-epidemic period to patients who have been treated with blood schizontocides.

Malaria elimination settings

Use of gametocytocidal drugs to reduce transmission
ACT reduces *P. falciparum* gametocyte carriage and transmission markedly, but this effect is incomplete, and patients presenting with gametocytaemia may be infectious for days or occasionally weeks, despite ACT. The strategy of using a single dose of primaquine to reduce infectivity and thus *P. falciparum* transmission has been widely used in low transmission settings.
Use of primaquine as a *P. falciparum* gametocytocide has a particular role in programmes to eliminate *P. falciparum* malaria. The population benefits of reducing malaria transmission by gametocytocidal drugs require that a high proportion of patients receive these medicines. WHO recommends the addition of a single dose of primaquine (0.25 mg base/kg bw) to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine, particularly as a component of elimination programmes. A recent review of the evidence on the safety and effectiveness of primaquine as a gametocytocide of *P. falciparum* indicates that a single dose of 0.25 mg base/kg bw is effective in blocking infectivity to mosquitos and is unlikely to cause serious toxicity in people with any of the G6PD variants. Thus, the G6PD status of the patient does not have to be known before primaquine is used for this indication.

Artemisinin-resistant falciparum malaria
Artemisinin resistance in *P. falciparum* is now prevalent in parts of Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. There is currently no evidence for artemisinin resistance outside these areas. The particular advantage of artemisinins over other antimalarial drugs is that they kill circulating ring-stage parasites and thus accelerate therapeutic responses. This is lost in resistance to artemisinin. As a consequence, parasite clearance is slowed, and ACT failure rates and gametocytaemia both increase. The reduced efficacy of artemisinin places greater selective pressure on the partner drugs, to which resistance is also increasing. This situation poses a grave threat. In the past chloroquine resistant parasites emerged near the Cambodia–Thailand border and then spread throughout Asia and Africa at a cost of millions of lives. In Cambodia, where artemisinin resistance is worst, none of the currently recommended treatment regimens provides acceptable cure rates (> 90%), and continued use of ineffective drug regimens fuels the spread of resistance. In Cambodia use of atovaquone–proguanil instead of ACT resulted in very rapid emergence of resistance to atovaquone.

In this dangerous, rapidly changing situation, local treatment guidelines cannot be based on a solid evidence base; however, the risks associated with continued use of ineffective regimens are likely to exceed the risks of new, untried regimens with generally safe antimalarial drugs. At the current levels of resistance, the artemisinin derivatives still provide significant antimalarial activity; therefore, longer courses of treatment with existing or new augmented combinations or treatment with new partner medicines (e.g. artesunate + pyronaridine) may be effective. Studies to determine the best treatments for artemisinin-resistant malaria are needed urgently.

It is strongly recommended that single-dose primaquine (as a gametocytocide) be added to all falciparum malaria treatment regimens as described in section 5.2.5. For the treatment of severe malaria in areas with established artemisinin resistance, it is recommended that parenteral artesunate and parenteral quinine be given together in full doses, as described in section 5.5.

5.6.2 Quality of antimalarial drugs

The two general classes of poor-quality medicines are those that are *falsified* (counterfeit), in which there is criminal intent to deceive and the drug contains little or no active ingredient (and often other potentially harmful substances), and those that are *substandard*, in which a legitimate producer has included incorrect amounts of active drug and/or excipients in the medicine, or the medicine has been stored incorrectly or for too long and has degraded. Falsified antimalarial tablets and ampoules containing little or no active pharmaceutical ingredients are a major problem in some areas. They may be impossible to distinguish at points of care from the genuine product and may lead to under-dosage and high levels of treatment failure, giving a mistaken impression of resistance, or encourage the development of resistance by providing sub-therapeutic blood levels. They may also contain toxic ingredients.

Substandard drugs result from poor-quality manufacture and formulation, chemical instability or improper or prolonged storage. Artemisinin and its derivatives in particular have built-in chemical instability, which is necessary for their biological action but which causes pharmaceutical problems both in their manufacture and in their co-formulation with other compounds. The problems of instability are accelerated under tropical conditions. The requirement for stringent quality

standards is particularly important for this class of compounds. Many antimalarial drugs are stored in conditions of high heat and humidity and sold beyond their expiry dates.

In many malaria-endemic areas, a large proportion of the antimalarial drugs used are generic products purchased in the private sector. They may contain the correct amounts of antimalarial drug, but, because of their formulation, are inadequately absorbed. Antimalarial medicines must be manufactured according to good manufacturing practice, have the correct drug and excipient contents, be proved to have bioavailability that is similar to that of the reference product, have been stored under appropriate conditions and be dispensed before their expiry date.

Tools to assess drug quality at points of sale are being developed, but the capacity of medicines regulatory agencies in most countries to monitor drug quality is still limited. Legal and regulatory frameworks must be strengthened, and there should be greater collaboration between law enforcement agencies, customs and excise authorities and medicines regulatory agencies to deal more effectively with falsified medicines. Private sector drug distribution outlets should have more information and active engagement with regulatory agencies. WHO, in collaboration with other United Nations agencies, has established an international mechanism to prequalify manufacturers of ACTs on the basis of their compliance with internationally recommended standards of manufacture and quality. Manufacturers of antimalarial medicines with prequalified status are listed on the prequalification web site *(168)*.

Antimalarial drug quality (2015)

Good practice statement

National drug and regulatory authorities should ensure that the antimalarial medicines provided in both the public and the private sectors are of acceptable quality, through regulation, inspection and law enforcement.

5.6.3 Monitoring efficacy and safety of antimalarial drugs and resistance

When adapting and implementing these guidelines, countries should also strengthen their systems for monitoring and evaluating their national programmes. The systems should allow countries to track the implementation and impact of new recommendations, better target their programmes to the areas and populations at greatest need and detect decreasing antimalarial efficacy and drug resistance as early as possible.

Routine surveillance
WHO promotes universal coverage with diagnostic testing and antimalarial treatment and strengthened malaria surveillance systems. In the “test, track, treat” initiative, it is recommended that every *suspected* malaria case is tested, that every *confirmed* case is treated with a quality-assured antimalarial medicine and that the disease is tracked by timely, accurate surveillance systems. Surveillance and treatment based on confirmed malaria cases will lead to better understanding of the disease burden and enable national malaria control programmes to direct better their resources to where they are most needed.

Therapeutic efficacy
Monitoring of therapeutic efficacy in falciparum malaria involves assessing clinical and parasitological outcomes of treatment for at least 28 days after the start of adequate treatment and monitoring for the reappearance of parasites in blood. The exact duration of post-treatment follow-up is based on the elimination half- life of the partner drug in the ACT being evaluated. Tools for monitoring antimalaria drug efficacy can be found on the WHO website *(169)*.

PCR genotyping should be used in therapeutic monitoring of antimalarial drug efficacy against *P. falciparum* to distinguish between recrudescence (true treatment failure) and new infections.

An antimalarial medicine that is recommended in the national malaria treatment policy should be changed if the total treatment failure proportion is ≥ 10%, as assessed in vivo by monitoring therapeutic efficacy. A significantly declining trend in treatment efficacy over time, even if failure rates have not yet fallen to the ≥ 10% cut-off, should alert programmes to undertake more frequent monitoring and to prepare for a potential policy change.

Resistance
Antimalarial drug resistance is the ability of a parasite strain to survive and/or multiply despite administration and absorption of an antimalarial drug given in doses equal to or higher than those usually recommended, provided that drug exposure is adequate. Resistance to antimalarial drugs arises because of selection of parasites with genetic changes (mutations or gene amplifications) that confer reduced susceptibility. Resistance has been documented to all classes of antimalarial medicines, including the artemisinin derivatives, and it is a major threat to malaria control.

Widespread inappropriate use of antimalarial drugs exerts a strong selective pressure on malaria parasites to develop high levels of resistance. Resistance can be prevented, or its onset slowed considerably by combining antimalarial drugs with different mechanisms of action and ensuring high cure rates

through full adherence to correct dose regimens. If different drugs with different mechanisms of resistance are used together, the emergence and spread of resistance should be slowed.

Clinical and parasitological assessment of therapeutic efficacy should include:

- confirmation of the quality of the antimalarial medicines tested;
- molecular genotyping to distinguish between re-infections and recrudescence and to identify genetic markers of drug resistance;
- studies of parasite susceptibility to antimalarial drugs in culture; and
- measurement of antimalarial drug levels to assess exposure in cases of slow therapeutic response or treatment failure

Pharmacovigilance
Governments should have effective pharmacovigilance systems (such as the WHO pregnancy registry) to monitor the safety of all drugs, including antimalarial medicines. The safety profiles of the currently recommended antimalarial drugs are reasonably well described and supported by an evidence base of several thousand participants (mainly from clinical trials); however, rare but serious adverse drug reactions will not be detected in clinical trials of this size, particularly if they occur primarily in young children, pregnant women or people with concurrent illness, who are usually under-represented in clinical trials. Rare but serious adverse drug reactions are therefore detected only in prospective phase IV post-marketing studies or population-based pharmacovigilance systems. In particular, more data are urgently needed on the safety of ACTs during the first trimester of pregnancy and on potential interactions between antimalarial and other commonly used medicines.

Good practice statement

All malaria programmes should regularly monitor the therapeutic efficacy of antimalarial drugs using the standard WHO protocols.

Practical Info

Routine monitoring of antimalarial drug efficacy is necessary to ensure effective case management and for early detection of resistance. WHO recommends that the efficacy of first- and second-line antimalarial treatments be tested at least once every 24 months at all sentinel sites. Data collected from studies conducted according to the standard protocol inform national treatment policies.

Please refer to the tools for monitoring antimalarial drug efficacy *(163)* and Methods for surveillance of antimalarial drug efficacy *(164)* which includes tools and materials to conduct routine therapeutic efficacy studies (TES). It is a reference for national programmes and investigators conducting routine surveillance studies to assess the efficacy of medicines that have already been registered.

Additional references include:

- Methods and techniques for clinical trials on antimalarial drug efficacy: Genotyping to identify parasite populations *(165)*
- Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010-2019) *(166)*

5.7 National adaptation and implementation

These guidelines provide a generic framework for malaria diagnosis and treatment policies worldwide; however, national policy-makers will be required to adapt these recommendations on the basis of local priorities, malaria epidemiology, parasite resistance and national resources.

National decision-making
National decision-makers are encouraged to adopt inclusive, transparent, rigorous approaches. Broad, inclusive stakeholder engagement in the design and implementation of national malaria control programmes will help to ensure they are feasible, appropriate, equitable and acceptable. Transparency and freedom from financial conflicts of interest will reduce mistrust and conflict, while rigorous evidence-based processes will ensure that the best possible decisions are made for the population.

Information required for national decision-making
Selection of first- and second-line antimalarial medicines will require reliable national data on their efficacy and parasite resistance, which in turn require that appropriate surveillance and monitoring systems are in place (see Monitoring efficacy and safety of antimalaria drugs). In some countries, the group adapting the guidelines for national use might have to re-evaluate the global evidence base with respect to their own context. The GRADE tables may serve as a starting-point for this assessment. Decisions about coverage, feasibility, acceptability and cost may require input from various health professionals, community representatives, health economists, academics and health system managers.

Opportunities and risks

The recommendations made in these guidelines provide an opportunity to improve malaria case management further, to reduce unnecessary morbidity and mortality and to contribute to continued efforts towards elimination. Failure to implement the basic principles of combination therapy and rational use of antimalarial medicines will risk promoting the emergence and spread of drug resistance, which could undo all the recent gains in malaria control and elimination.

General guiding principles for choosing a case management strategy and tools

Choosing a diagnostic strategy

The two methods currently considered suitable for routine patient management are light microscopy and RDTs. Different strategies may be adopted in different health care settings. The choice between RDTs and microscopy depends on local circumstances, including the skills available, the patient case-load, the epidemiology of malaria and use of microscopy for the diagnosis of other diseases. When the case-load of patients with fever is high, the cost of each microscopy test is likely to be less than that of an RDT; however, high-throughput, high-quality microscopy may be less operationally feasible. Although several RDTs allow diagnosis of both *P. falciparum* and *P. vivax* infections, microscopy has further advantages, including accurate parasite counting (and thus identification of high parasite density), prognostication in severe malaria, speciation of other malaria parasites and sequential assessment of the response to antimalarial treatment. Microscopy may help to identify other causes of fever. High-quality light microscopy requires well-trained, skilled staff, good staining reagents, clean slides and, often, electricity to power the microscope. It requires a quality assurance system, which is often not well implemented in malaria-endemic countries.

In many areas, malaria patients are treated outside the formal health services, e.g. in the community, at home or by private providers. Microscopy is generally not feasible in the community, but RDTs might be available, allowing access to confirmatory diagnosis of malaria and the correct management of febrile illnesses. The average sensitivity of HRP2-detecting RDTs is generally greater than that of RDTs for detecting *p*LDH of *P. falciparum*, but the latter are slightly more specific because the HRP2 antigen may persist in blood for days or weeks after effective treatment. HRP2-detecting RDTs are not suitable for detecting treatment failure. RDTs are slightly less sensitive for detecting *P. malariae* and *P. ovale*. The WHO Malaria RDT Product Testing programme provides comparative data on the performance of RDT products to guide procurement. Since 2008, 210 products have been evaluated in five rounds of product testing *(120)(123)*.

For the diagnosis of severe malaria, microscopy is preferred, as it provides a diagnosis of malaria and assessment of other important parameters of prognostic relevance in severely ill patients (such as parasite count and stage of parasite development and intra-leukocyte pigment). In severe malaria, an RDT can be used to confirm malaria rapidly so that parenteral antimalarial treatment can be started immediately. Where possible, however, blood smears should be examined by microscopy, with frequent monitoring of parasitaemia (e.g. every 12 h) during the first 2–3 days of treatment in order to monitor the response.

Choosing ACT

In the absence of resistance, all the recommended ACTs have been shown to result in parasitological cure rates of > 95%. Although there are minor differences in the oral absorption, bioavailability and tolerability of the different artemisinin derivatives, there is no evidence that these differences are clinically significant in currently available formulations. It is the properties of the partner medicine and the level of resistance to it that determine the efficacy of a formulation.

Policy-makers should also consider:

- local data on the therapeutic efficacy of the ACT,
- local data on drug resistance,
- the adverse effect profiles of ACT partner drugs,
- the availability of appropriate formulations to ensure adherence,
- cost.

In parts of South-East Asia, artemisinin resistance is compromising the efficacy of ACTs and placing greater selection pressure on resistance to the partner medicines. Elsewhere, there is no convincing evidence for reduced susceptibility to the artemisinins; therefore, the performance of the partner drugs is the determining factor in the choice of ACT, and the following principles apply:

- Resistance to mefloquine has been found in parts of mainland South-East Asia where this drug has been used intensively. Nevertheless, the combination with artesunate is very effective, unless there is also resistance to artemisinin. Resistance to both components has compromised the efficacy of artesunate + mefloquine in western Cambodia, eastern Myanmar and eastern Thailand.
- Lumefantrine shares some cross-resistance with mefloquine, but this has not compromised its efficacy in any of the areas in which artemether + lumefantrine has been used outside South-East Asia.
- Until recently, there was no evidence of resistance to piperaquine anywhere, but there is now reduced susceptibility in western Cambodia. Elsewhere, the dihydroartemisinin + piperaquine combination is highly effective.
- Resistance to SP limits its use in combination with artesunate to the few areas in which susceptibility is retained.
- Amodiaquine remains effective in combination with artesunate in parts of Africa and the Americas, although elsewhere resistance to this drug was prevalent before its introduction in an ACT.

Considerations in use of artemisinin-based combination therapy

Oral artemisinin and its derivatives (e.g. artesunate, artemether, dihydroartemisinin) should not be used alone. In order to simplify use, improve adherence and minimize the availability of oral

artemisinin monotherapy, fixed-dose combination ACTs are strongly preferred to co-blistered or co-dispensed loose tablets and should be used when they are readily available. Fixed-dose combinations of all recommended ACT are now available, except artesunate + SP. Fixed-dose artesunate + amodiaquine performs better than loose tablets, presumably by ensuring adequate dosing. Unfortunately, paediatric formulations are not yet available for all ACTs.

The choice of ACT in a country or region should be based on optimal efficacy and adherence, which can be achieved by:

- minimizing the number of formulations available for each recommended treatment regimen
- using, where available, solid formulations instead of liquid formulations, even for young patients.

Although there are some minor differences in the oral absorption and bioavailability of different artemisinin derivatives, there is no evidence that such differences in currently available formulations are clinically significant. It is the pharmacokinetic properties of the partner medicine and the level of resistance to it that largely determine the efficacy and choice of combinations. Outside South-East Asia, there is no convincing evidence yet for reduced susceptibility to the artemisinins; therefore, the performance of the partner drug is the main determinant in the choice of ACT, according to the following principles:

- Drugs used in IPTp, SMC or chemoprophylaxis should not be used as first-line treatment in the same country or region.
- Resistance to SP limits use of artesunate + SP to areas in which susceptibility is retained.Thus, in the majority of malaria-endemic countries, first-line ACTs remain highly effective, although resistance patterns change over time and should be closely monitored.

Choosing among formulations

Use of fixed-dose combination formulations will ensure strict adherence to the central principle of combination therapy. Monotherapies should not be used, except as parenteral therapy for severe malaria or SP chemoprevention, and steps should be taken to reduce and remove their market availability. Fixed-dose combination formulations are now available for all recommended ACTs except artesunate + SP.

Paediatric formulations should allow accurate dosing without having to break tablets and should promote adherence by their acceptability to children. Paediatric formulations are currently available for artemether + lumefantrine, dihydroartemisinin + piperaquine and artesunate + mefloquine.

Other operational issues in managing effective treatment

Individual patients derive the maximum benefit from an ACT if they can access it within 24–48 h of the onset of malaria symptoms. The impact in reducing transmission at a population level depends on high coverage rates and the transmission intensity. Thus, to optimize the benefits of deploying ACTs, they should be available in the public health delivery system, the private sector and the community, with no financial or physical barrier to access. A strategy for ensuring full access (including community management of malaria in the context of integrated case management) must be based on analyses of national and local health systems and may require legislative changes and regulatory approval, with additional local adjustment as indicated by programme monitoring and operational research. To optimize the benefits of effective treatment, wide dissemination of national treatment guidelines, clear recommendations, appropriate information, education and communication materials, monitoring of the deployment process, access and coverage, and provision of adequately packaged antimalarial drugs are needed.

Community case management of malaria

Community case management is recommended by WHO to improve access to prompt, effective treatment of malaria episodes by trained community members living as close as possible to the patients. Use of ACTs in this context is feasible, acceptable and effective *(173)*. Pre-referral treatment for severe malaria with rectal artesunate and use of RDTs are also recommended in this context. Community case management should be integrated into community management of childhood illnesses, which ensures coverage of priority childhood illnesses outside of health facilities.

Health education From the hospital to the community, education is vital to optimizing antimalarial treatment. Clear guidelines in the language understood by local users, posters, wall charts, educational videos and other teaching materials, public awareness campaigns, education and provision of information materials to shopkeepers and other dispensers can improve the understanding of malaria. They will increase the likelihood of better prescribing and adherence, appropriate referral and reduce unnecessary use of antimalarial medicines.

Adherence to treatment

Patient adherence is a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision. Studies on adherence suggest that 3-day regimens of medicines such as ACTs are completed reasonably well, provided that patients or caregivers are given an adequate explanation at the time of prescribing or dispensing. Prescribers, shopkeepers and vendors should therefore give clear, comprehensible explanations of how to use the medicines. Co-formulation probably contributes importantly to adherence. User- friendly packaging (e.g. blister packs) also encourages completion of a treatment course and correct dosing.

Good practice statement

The choice of ACTs in a country or region should be based on optimal efficacy, safety and adherence.

Practical Info

Pharmacovigilance is the practice of monitoring the effects of medical drugs after they have been licensed for use, especially to identify and evaluate previously unreported adverse reactions. *A practical handbook on the pharmacovigilance of antimalarial medicines (168)* provides a step-by-step approach for antimalarial pharmacovigilance. Designed for health officials, planners, and other health workers, it focuses on active and passive pharmacovigilance, reporting, event monitoring and other key factors.

National adaptation and implementation (2015)

Good practice statement

Drugs used in IPTp, SMC and IPTi should not be used as a component of first- line treatments in the same country or region.

National adaptation and implementation (2015)

Good practice statement

When possible, use:

- fixed-dose combinations rather than co-blistered or loose, single-agent formulations; and
- for young children and infants, paediatric formulations, with a preference for solid formulations (e.g. dispersible tablets) rather than liquid formulations.

6. ELIMINATION

Recommendations for Elimination are currently in development and are anticipated to be published in 2021.

In 2017, WHO published A framework for malaria elimination *(7)* to provide guidance on the tools, activities, and dynamic strategies required to achieve interruption of transmission and to prevent re-establishment of malaria. It also describes the process for obtaining WHO certification of malaria elimination. The framework is meant to serve as a basis for national malaria elimination strategic plans and should be adapted to local contexts.

The document emphasizes that all countries should work towards the goal of malaria elimination, regardless of the intensity of transmission. Countries should establish tools and systems that will allow them to reduce the disease burden (when and where transmission is high) and progress to elimination of malaria as soon as possible. While malaria elimination should be the ultimate goal for all malaria-endemic countries, the guidance given here is intended mostly for areas of low transmission that are progressing to zero.

Mass drug administration for elimination

In an analysis of 38 mass drug administration projects carried out since 1932 *(175)*, only one was reported to have succeeded in interrupting malaria transmission permanently. In this study, chloroquine, SP and primaquine were provided weekly to the small population of Aneityum Island in Vanuatu for 9 weeks before the rainy season, in combination with distribution of insecticide-treated nets *(176)*.

There is considerable divergence of opinion about the benefits and risks of mass antimalarial drug administration. As a consequence, it has been little used in recent years; however, renewed interest in malaria elimination and the emerging threat of artemisinin resistance has been accompanied by reconsideration of mass drug administration as a means for rapidly eliminating malaria in a specific region or area.

In the past, vivax elimination programmes were based on pre-seasonal mass radical treatment with primaquine (0.25 mg/kg/for 14 days) without testing for G6PD deficiency or monitoring primaquine-induced haemolysis, although in some cases interrupted regimens were used: 4 days' treatment, 3 days of no treatment, then continuation to complete the course (usually 11 days) if the drug was well tolerated *(177)*.

Once mass drug administration is terminated, if malaria transmission is not interrupted or importation of malaria is not prevented, then malaria endemicity in the area will eventually return to its original levels (unless the vectorial capacity is reduced in parallel and maintained at a very low level). The time it takes to return to the original levels of transmission will depend on the prevailing vectorial capacity. If malaria is not eliminated from the target population, then mass drug administration may provide a significant selective pressure for the emergence of resistance. The rebound in malaria may be associated temporarily with higher morbidity and mortality if drug administration was maintained long enough for people to lose herd immunity against malaria.

For this reason, mass drug administration should not be started unless there is a good chance that focal elimination will be achieved. In some circumstances (e.g. containment of artemisinin-resistant *P. falciparum*), elimination of only one species may be the objective.

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" *(178)*.

Pillar 3 of the *Global technical strategy for malaria 2016–2030* *(4)* is transformation of 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 does not go through the GRADE process, it is the basis of operational activities in settings of any level of transmission and is included in these Guidelines as reference. The objective of surveillance is to support reduction of the burden of malaria, eliminate the disease and prevent its re-establishment. In settings in which transmission remains relatively high and the aim of national programmes is to reduce the burdens 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 in which 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, its role 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* *(29)*.

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)*) *(179)*. 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 the case management is delivered will vary according to factors such as health-seeking behavior, the accessibility and functioning of the public health infrastructure, availability of the private retail sector and the potential of 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 the strategic goals. As countries will rarely have all the resources they need to fully implement the ideal plan, a careful resource prioritization process is then required to maximise 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 GMP across the topics covered in this guideline *(180)(181)(182)* and a description of the joint process (with the 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 Group and an external Guidelines Development Group (GDGs); formulating key recommendation questions using the PICO (Population, Intervention, Comparison, Outcome) format; commissioning evidence reviews; applying GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to assess the certainty of evidence; and using an evidence-to-decision (EtD) framework to take the GRADE results and contextual factors into account in developing recommendations. This methodology ensured that the link between the evidence base and the recommendations was transparent. The Guidelines have been consolidated and will be continuously updated as new evidence becomes available in the online MAGICapp publication platform (www.magicapp.org) 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 the drafting of the scope of the Guidelines and preparing the planning proposal, including formulating key questions, as well as suggesting potential members for the Guidelines Development Group (GDG). 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.

Guidelines Development Groups (GDGs), external bodies of experts and stakeholders, were responsible for the development of the evidence-based recommendations contained in the Guidelines, the specific tasks of the GDG included:

- providing inputs on the scope of the Guidelines;
- building on the work of the Guidelines Steering Group 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 measure of outcomes of interest to be included in evidence reviews;
- validating the list of included and excluded studies;
- reviewing the meta-analysis GRADE evidence profiles or other assessments of the certainty of evidence used to inform the recommendations;
- interpreting the evidence, considering the different factors included in the EtD, particularly the overall balance of benefits and harms;
- formulating recommendations, taking into account benefits, harms, values and preferences, feasibility, equity, acceptability, resource requirements 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 are identified and managed appropriately within the GMP (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 the 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 in ensure that equity, human rights, gender and social determinants were taken into consideration in efforts to improve public health outcomes.

External Review Groups (ExRGs) (see Section 10: Contributors and interests) for each technical area for malaria were identified by the respective Steering Group. Each external review group was composed of people interested in the subject of the Guidelines and included members of the MPAG and individuals affected by or interested in the recommendations, such as technical experts, end-users, programme managers, advocacy groups and funders. The ExRG reviewed the draft guideline prior to its submission to the GRC for approval. The role of the group was to identify any errors or missing evidence and to provide comment on clarity, context-specific issues, and implications for implementation. The group was not expected to change the recommendations formulated by the GDG. For those cases where major concerns related to the recommendations were raised by the external reviewers, 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 GDG.

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, the translation of evidence into recommendations and guideline development processes. The methodologists supported the planning, scoping and the development of key questions and assisted the GDG to formulate evidence-informed recommendations in a transparent and explicit manner. The methodologist 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.

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); density of immature vector stages; 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 had 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 may be 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 GDG 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 evidence-to-decision (EtD) framework considered several criteria to arrive at a recommendation for or against an intervention; these were *(181)*:

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 1-4 relate to the health effects of recommendations, criteria 5-9 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. 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.

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 referred 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.

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.

Certainty of evidence	Interpretation
Low	The Group has low confidence in the estimate of effect and considers the 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 were taken into account through discussions on the relative value beneficiaries place on the outcomes of the intervention. Given that 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 singularly or in combination, is 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 some cases, anonymous voting was used for judging the different criteria and developing the final recommendation 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 were presented in the Guidelines.

- GRADEd recommendations: These recommendations were formulated by a GDG using the GRADE approach, supported by systematic reviews of the evidence, with formal assessment of the certainty of evidence.
- Good practice statements: These statements reflect a consensus among a 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 usually not 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 Technical Expert Group on Malaria Vector Control (VCTEG) or Malaria Policy Advisory Group (MPAG) – previously the Malaria Policy Advisory Committee (MPAC). 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, according to the GRADE system *(182)*. A strong recommendation is one for which the GDG was confident that the desirable effects of adhering to the recommendation outweigh 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. The reasons that favoured making a conditional recommendation included lower certainty evidence; variability or uncertainty in the values and preferences of individuals regarding the outcomes of interventions; a tight balance between benefits and harms; high costs; equity related concerns, feasibility issues, and acceptability issues. The implications of strong and conditional recommendations for various groups are given in Table 2.

Table 2: Interpretations of recommendations

Strength of recommendation	Interpretation		
	For policy-makers	For programme managers/ technicians	For end-users
Strong	This recommendation can be adopted as policy in most situations.	Most individuals should receive the recommended intervention.	Most people in your situation would want the recommended intervention, and only a small proportion would not.
Conditional	Substantial debate as to whether to adopt the recommendation is required at the policy making level, with the involvement of various stakeholders.	Some individuals should receive the recommended intervention, but this depends on a number of contextual factors, such as feasibility.	The majority of people in your situation would want the recommended intervention, but many would not.

Presentation of evidence and recommendations

For clarity, the recommendations are presented in individual boxes on the MAGICapp platform, with colour-coded strength of recommendations and labelled by strength based on the evidence

reviewed. More information is available by expanding the tabs directly below the recommendation, the research evidence; the EtD framework; the justification including remarks from 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 sources for the estimates of effect).

Management of conflicts of interest

All members of the GDGs were requested to make declarations of interests, which were managed in accordance with WHO procedures and summarized at the beginning of each meeting to all participants. Where necessary, GDG members may have been excluded from the discussion and/or decision-making for 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, which includes dossier review, consistency testing or performance evaluation, and site visits to manufacturers. This information, in conjunction with other procurement criteria, is used by the UN 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 *(104)*, 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 *(183)(184)(185)*.

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

Please also refer to the *WHO malaria terminology (186)* for additional information and notes on the glossary contained here. Definitions not yet captured in the *WHO malaria terminology* document are indicated with an asterisk.

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

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
biological insecticide*	Pesticides made from natural materials that are meant to kill or control insects. These natural source materials may include animals, plants, bacteria or minerals
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, gametocidal	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	Each complete round of ovarian development in the female mosquito, usually after ingestion of a blood meal, to yield a batch of eggs. Gonotrophic harmony is achieved when every blood meal results in one batch of eggs from the gonotrophic cycle.
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 a given *Plasmodium* strain to establish infection in susceptible humans and develop in competent *Anopheles* mosquitoes *[and undergo development until the mosquito has sporozoites in its salivary glands]
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 in infants (IPTi)	A full therapeutic course of sulfadoxine-pyrimethamine delivered to infants in co-administration with DTP2/Penta2, DTP3/Penta3 and measles immunization, regardless of whether the infant is infected with malaria
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 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 antimalarial treatment to all age groups of a defined population or every person living 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	Testing an entire population and treating individuals with a positive test result
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.
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. The three categories of insecticide-treated net are: • conventionally treated net: a mosquito net that has been treated by dipping it into a WHO-recommended insecticide. To ensure its continued insecticidal effect, the net should be re-treated periodically. • long-lasting insecticidal net: a factory-treated mosquito net made of netting material with insecticide incorporated within 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. • pyrethroid-PBO net: a mosquito net that includes both a pyrethroid insecticide and the synergist piperonyl butoxide. To date, pyrethroid-PBO nets have not met required thresholds to qualify as long-lasting insecticidal nets.
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
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)
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
public health value*	A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans, at the individual level, community level or both
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 focal screening, testing, treating or drug administration	Screening, testing, treating or administering drugs to a subset of a population in a given area in response to the detection of an infected person
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
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

synergist*	A substance that does not itself have insecticidal properties, but that, when mixed and applied with insecticides of a particular class, considerably enhances their potency by inhibiting an enzyme that normally acts to detoxify the insecticide in the insect system
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 many contributors to the development of the recommendations are acknowledged in the subsections 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, the RTS,S/AS01 SAGE/MPAG Working Group, and the generation of additional evidence on the first malaria vaccine relied on 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 its support in the consolidation of the Guidelines on the MAGICapp platform.

10.1 Guidelines for malaria vector control

The following outlines the constitution of the Guidelines Development Group, Guidelines Steering Group, and External Review Group for recommendations drafted in 2019 and in 2021. Also indicated are members of the systematic review production and management team and Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis subgroup, 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 Guidelines Development Group (2019)

The WHO Technical Expert Group on Malaria Vector Control (VCTEG) served as the Guidelines Development Group 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, People's Republic of 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
- 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 (2019)
The WHO Malaria Policy Advisory Committee (MPAC) served as the External Review Group 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
- Professor Brian Greenwood, Manson Professor of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine, United Kingdom
- 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, People's Republic of 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
- Mr Joe Pryce, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Ms Marty Richardson, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Dr Vittoria Lutje, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Dr Deirdre Walshe, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Prof Paul Garner, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

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 secondment in 2017 to develop a vector control strategy on mosquitoproof 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 (2021)

- Dr Dorothy Achu, Programme manager, National Malaria Control Programme, Yaoundé, Cameroon, AFRO (Female – Expertise: end-user perspective, service-user, Case management & chemoprevention)
- Prof Basil Brooke, Associate professor, University Witwatersrand/National Institute for Communicable Disease, Johannesburg, South Africa, AFRO (Male – Expertise: entomology, programmatic vector control, policy)
- Prof Ahmadali Enayati, Head, Medical Entomology Department, School of Public Health, Mazandaran University of Medical Sciences, Sari, Islamic Republic of Iran, EMRO (Male – Expertise: service-user, entomology)
- Dr Seth Irish, Research entomologist, Centers for Disease Control and Prevention, Atlanta, United States of America, AMRO (Male – Expertise: entomology, vector control, programme implementing partner)
- Prof Fang Jing, Director, Institute for Health Sciences, Kunming Medical University, Yunnan Province, People's Republic of China, WPRO (Female – Expertise: maternal and child health, gender, equity, ecohealth)
- Dr Keziah Malm, Programme manager, National Malaria Control Programme, Accra, Ghana, AFRO (Female – Expertise: end-user perspective, service-user, public health, field epidemiology)
- Dr Kui Muraya, Social scientist, KEMRI-Wellcome Trust, Nairobi, Kenya, AFRO (Female – Expertise: child health, gender and social determinants of health)
- Prof Martha Quiñones, Professor, Universidad Nacional de Colombia, Bogotá, Colombia, AMOR (Female – Expertise: service-user, entomology, insecticide resistance)
- Dr Christina Rundi, Health director, Sabah Health Department, Ministry of Health, Sabah, Malaysia, WPRO (Female – Expertise: end-user perspective, health programme delivery)
- Dr Tanya Russell, Research fellow, James Cook University, Cairns, Australia, WPRO (Female – Expertise: Entomology, vector control)
- Dr Lucy Tusting, Assistant professor, Faculty of Infectious Tropical Disease, LSHTM, London, United Kingdom, EURO (Female – Expertise: housing interventions for malaria control & larval source management)
- Dr Josh Yukich, Associate professor, Department of Tropical Medicine Tulane University School of Public Health and Tropical Medicine, New Orleans, United States of America, PAHO (Male – Expertise: epidemiology, mathematical modelling, economics, vector control)

Members of the Guidelines Steering Group (2021)

- 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 (2021)

- Dr Jenifer Armistead, Malaria Division, United States Agency for International Development (USAID), Unites States of America
- Prof Maureen Coetzee, University of the Witwatersrand, South 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)

- Prof Paul Garner, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Dr Jo Leonardi-Bee, University of Nottingham, United Kingdom
- Prof Jo Lines, London School of Hygiene and Tropical Medicine, London, United Kingdom
- Dr Elisa Martello, University of Nottingham, United Kingdom
- Dr Lucy Paintain, London School of Hygiene and Tropical Medicine, London, United Kingdom
- Dr Rebecca Thomas, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Dr Gowsika Yogeswaran, University of Nottingham, United Kingdom

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

Declaration of interests (2021)
Members of the GDG and ExRG 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:

Lucy Tusting: 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.

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

Umberto d'Allessandro: the declared interests regarding the remuneration for acting on the advisory board, travel and the value of the donated drugs were considered financially significant, however the subjects of these interests were not related to the topics of the review. The projects associated with housing modifications or improvements (2 to 4) were related to the subject of discussion. However, as the remit of the ExRG 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 his contributions would be valuable given his vast field experience.

Jennifer Armistead: The declared interests were considered financially significant. Projects 1 and 2 were not related to the subject of the review. The fourth project was evaluating larviciding, which, although part of larval source management, was not an intervention for which revisions were being made in the vector control guidelines. The project associated with housing modifications (3) was related to the subject of discussion. However, as reviewers were not being asked to change the meaning of the recommendations themselves, it was concluded that her contributions would be valuable particularly in commenting on uptake of the recommendations given her vast field implementation experience.

Maureen Coetzee: The declared interests regarding the funding provided were considered financially significant. Project 3 investigated housing characteristics that were associated with the risk of mosquito biting but did not evaluate the impact of housing modifications on malaria. Given her vast field experience, it was concluded that her review of the vector control guidelines would be valuable especially in commenting on implications for implementation.

Caroline Jones: Endectocides and vaccines were not topics of discussion for this review and so these projects were not considered a potential conflict of interest. The second project above 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 ExRG, it did not seek to systematically evaluate a particular tool. The third project was linked to one of the subjects being discussed as part of the review. As with Prof D'Alessandro and Prof Coetzee, because the review was limited to identifying factual errors and commenting on clarity and implementation of the recommendations, it was felt that Dr Jones could provide useful insight on factors to be considered associated with gender and social determinants, equity, and human rights.

Neil Lobo: The declared interests regarding the funding provided and provision of research materials were considered financially significant. None of the projects where companies had provided support were deemed to be related to the subject of the review. Only the topic of research project 7, 'Screening mosquito entry points into houses with novel long lasting insecticidal netting to reduce indoor vector densities and mitigate pyrethroid resistance' was considered to be related to the subject of the review. As the ExRG was not being asked to comment on the

recommendations themselves, but rather to ensure the wording was clear, accurate and supporting uptake by end-users, it was felt that Prof Lobo could provide a useful review given his vast experience working with national programmes.

Melanie Renshaw: While the amount received was deemed significant, the nature of her work did not address the specific topics under review and so did not represent a conflict of interest.

10.2 Malaria vaccine recommendation

The following outlines the constitution of MPAG, SAGE, the RTS,S/AS01 MPAG/SAGE Working Group, and the External Review Group for the recommendations drafted in 2021. 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 MPAG:

- Dr 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 Tom Burkot, Professor and Tropical Leader, Australian Institute for Topical Health and Medicine, James Cook University, Cairns, Australia
- Dr Gabriel Carrasquilla, Director of ASIESALUD for consultancy and research in epidemiology and public health
- Professor Maureen Coetzee, Professor and Director, Wits Research Institute for Malaria, University of the Witwatersrand, Johannesburg, South Africa
- Professor Umberto d'Alessandro, Director, Medical Research Council Unit, Gambia
- Professor Abdoulaye Djimde, Head, Molecular Epidemiology and Drug Resistance Unit, Faculty of Medicine, University of Mali, Mali
- 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
- Dr Caroline Jones, Senior Social Scientist, KEMRI-Wellcome Trust Research Programme, Kenya
- Dr S. Patrick Kachur, Columbia University Irving Medical Center, 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 at Ifakara Health Institute, United Republic of Tanzania
- Dr Arantxa Roca Feltrer, Head of Surveillance, Monitoring and Evaluation, Malaria Consortium, Madagascar
- Professor Dyann Wirth, Director, Harvard Life Sciences, Harvard T.H. Chan School of Public Health, United States of America (MPAG Chair)

Members of SAGE:

- Professor Rakesh Aggarwal, Director, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India
- Professor Alejandro Cravioto, Professor Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico (SAGE Chair)
- Dr Ilesh Jani, Director General, National Institute of Health, Ministry of Health, Mozambique
- Dr Jaleela Jawad, Head of the Immunization Group, Public Health Directorate, Ministry of Health, Bahrain
- Dr Sonali Kochhar, Clinical Associate Professor, Department of Global Health, University of Washington, United States of America
- Professor Noni MacDonald, Professor of Paediatrics, Division of Paediatric Infectious Diseases, Dalhousie University, Canada
- Professor Shabir Madhi, Professor of Vaccinology, University of the Witwatersrand, South Africa
- 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 (GHD), The Eastern Mediterranean Public Health Network (EMPHNET), 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
- Dr Folake Olayinka, USAID Immunization Team Lead, United States of America
- Professor Punnee Pitisuttithum, Head, Department of Clinical Tropical Medicine, Mahidol University, Thailand
- Professor Andrew J. Pollard, Professor, Department of Paediatrics, University of Oxford, United Kingdom of Great Britain and Northern Ireland

Members of the RTS,S/AS01 MPAG/SAGE Working Group

- Professor Ifedayo Adetifa, KEMRI-Wellcome Trust Research Programme, Kenya
- Professor Nick Andrews, Public Health England, United

Kingdom of Great Britain and Northern Ireland
- 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 (CVD), University of Maryland School of Medicine, United States of America
- The late Ms Adelaide Shearley, John Snow Inc., Zimbabwe
- Professor Peter Smith, London School of Hygiene & 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 RTS,S/AS01 MPAG/SAGE Working Group Secretariat

- Dr Pedro Alonso, Global Malaria Programme
- Dr Tracey Goodman, Expanded Programme on Immunization
- Mr John Grove, Quality Assurance / Norms & Standards
- Dr Joachim Hombach, Agenda, Policy & Strategy
- Dr Melanie Marti, Agenda, Policy & Strategy
- Dr Kate O'Brien, Immunization, Vaccines and Biologicals
- Dr Vaseeharan Sathiyamoorthy, Research for Health
- Rapporteur: Ms Cynthia Bergstrom, Consultant for WHO

Members of the WHO Editorial Board

- Dr Madhava Ram Balakrishnan
- Dr Shalini Desai, Expanded Programme on Immunization
- Ms Eliane Furrer, 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 Dianliang Lei, Norms, Standards and Biologicals
- Dr Melanie Marti, Immunization, Vaccines and Biologicals
- Dr Marie-Perre Preziosi, Immunization, Vaccines and Biologicals
- Dr David Schellenberg, Global Malaria Programme
- Ms Erin Shutes, Global Malaria Programme

Members of the Peer review group (External review group)

Members of the Peer review group include SAGE, MPAG, WHO Regional Offices, external subject matter experts, selected national immunization and malaria programme managers, other interested parties (who have 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 Association and the Developing Country Vaccine Manufacturer Network. The list of external reviewers is available upon request from the SAGE secretariat.

Guidelines methodologist and systematic review team

Two methodologists from the Cochrane Response – Gemma Villanueva 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).

Declaration of interests

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 zero SAGE 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 17 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 five MPAG members reported relevant interests. Three members (Evelyn Ansah, Abdoulaye Djimde and Azra Ghani) recused themselves from the discussion and decision-making during the malaria vaccine session. It was assessed that the remaining members could fully participate in all sessions. The full summary of interests for MPAG members is available on the meeting website.

- Professor Evelyn Ansah, University of Health & Allied Sciences, Ghana: declared research support and her role as the Ghana Co-Investigator on funding from PATH for the Health Utilization Study on a qualitative assessment of the pilot implementation of RTS,S. This interest was assessed as non-personal, specific and financially significant.
- Professor Abdoulaye Djimde, Head, Molecular Epidemiology Drug Resistance Unit, University of Mali, Mali: declared his role as a sub-investigator on the RTS,S – SMC

trial which contributed minimal salary support through the London School of Tropical Medicine & Hygiene. Professor Djimde was a co-author on: Chandramohan D, Zongo I, Sagara I, Cairns M, Yerbanga RS, Diarra M, Nikièma F, Tapily A, Sompougdou F, Issiaka D, Zoungrana C, Sanogo K, Haro A, Kaya M, Sienou AA, Traore S, Mahamar A, Thera I, Diarra K, Dolo A, Kuepfer I, Snell P, Milligan P, Ockenhouse C, Ofori-Anyinam O, Tinto H, Djimde A, Ouédraogo JB, Dicko A, Greenwood B. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. N Engl J Med. 2021 Sep 9;385(11):1005-1017. doi: 10.1056/NEJMoa2026330. Epub 2021 Aug 25. PMID: 34432975. This interest is assessed as non-personal, specific and financially significant.

- Professor Azra Ghani, Infectious Diseases Epidemiology, Imperial College, UK: declared research support to Imperial College from the Global Fund on different projects related to modelling impact estimates for malaria including global scenarios that incorporate RTS,s from 2016 to 2019 and in 2021. This interest is assessed as non-personal, specific and financially significant; and research support funding from multiple organizations for work on malaria and COVID-19 research including Bill & Melinda Gates Foundation (BMGF), MVI, MMV, IVCC, MRC, Wellcome Trust, NIH over three years (current). Included data analysis and modelling of public health impact of routine implementation and assessment of seasonal implementation related to RTS,s. This interest is assessed as non-personal, specific and financially significant.
- Professor Caroline Jones, Senior Social Scientist, KEMRI-Wellcome Trust Research, Kenya: declared her role as a mentor for a post-doctorate student on the study conducted in collaboration with PATH entitled “Dynamics of health care utilization strategies in the context of RTS,S/AS01 vaccine introduction: a qualitative longitudinal study in Kenya” (2018- 2020). The institution received support for the post-doc who has now left the institution. This interest is assessed as non-personal, specific and non-financially significant.* Although specific to the malaria vaccine, the interest was assessed as that of the post-doc, not Professor Jones as the mentor.
- Professor Dyann Wirth, Richard Pearson Strong Professor and Chair, Harvard T.H. Chan School of Public Health, USA: declared a research grant to Harvard University received from PATH and her role as the Principal Investigator for Mal095 using RTS,S to look at the issue of allele specific immunity. This interest is assessed as non-personal, specific and financially significant.* Although related to the malaria vaccine, this work is to understand gaps in immunity provided by RTS,S and will inform the development of future malaria vaccines. This research is not being considered as evidence for the decision on the malaria vaccine and the work will continue regardless of the outcome.

10.3 Guidelines for the treatment of malaria

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.

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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.

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Annex: All evidence profiles, sorted by sections

1. ABBREVIATIONS

2. EXECUTIVE SUMMARY

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: Insecticide-treated nets or curtains
Comparator: No nets

Summary

Summary of evidence from systematic review
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, Cote 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) and four in South-East Asia (India, Myanmar, Thailand (two studies)) and one in the Eastern Mediterranean (Pakistan).

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

Outcome Timeframe	**Study results and measurements**	**Comparator** No nets	**Intervention** Insecticide-treated nets or curtains	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality	Relative risk 0.83 (CI 95% 0.77 — 0.89) Based on data from	33 per 1000	27 per 1000	High	ITNs or curtains reduce the child mortality from all causes.

Outcome Timeframe	**Study results and measurements**	**Comparator** No nets	**Intervention** Insecticide-treated nets or curtains	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	129,714 participants in 5 studies. (Randomized controlled)	Difference:	**6 fewer per 1000** (CI 95% 8 fewer — 4 fewer)		
P. falciparum uncomplicated episodes	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**	ITNs or curtains reduce the incidence of uncomplicated episodes of P falciparum malaria compared to no nets.
P. falciparum uncomplicated episodes (cumulative incidence)	Relative risk 0.44 (CI 95% 0.31 — 0.62) Based on data from 10,964 participants in 2 studies. (Randomized controlled)	137 per 1000 Difference:	60 per 1000 **77 fewer per 1000** (CI 95% 95 fewer — 52 fewer)	**Moderate** Due to serious indirectness [1]	ITNs or curtains probably reduce the incidence of uncomplicated episodes of P falciparum malaria compared to no nets.
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**	ITNs or curtains reduce the prevalence of P falciparum malaria compared to no nets.
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]	ITNs or curtains probably reduce the incidence of uncomplicated episodes of P vivax malaria compared to no nets.
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, Due to serious imprecision [3]	ITNs or curtains may have little or no effect on the prevalence of P vivax malaria compared to no nets.
Any Plasmodium spp. uncomplicated	Relative risk 0.5 (CI 95% 0.28 — 0.9) Based on data from 5,512 participants in 1	256 per 1000	128 per 1000	**Low** Due to very serious indirectness [4]	ITNs or curtains may reduce the incidence of uncomplicated episodes of any Plasmodium

Outcome Timeframe	**Study results and measurements**	**Comparator** No nets	**Intervention** Insecticide-treated nets or curtains	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
episodes	studies. (Randomized controlled)	Difference:	**128 fewer per 1000** (CI 95% 184 fewer — 26 fewer)		species compared to no nets.
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	ITNs or curtains reduce the incidence of severe malaria episodes compared to no nets.

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

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Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Insecticide-treated nets or curtains
Comparator: Untreated nets

Summary

Summary of evidence from systematic review
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, Cote 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) and four in South-East Asia (India, Myanmar, Thailand (two studies)) and one in the Eastern Mediterranean (Pakistan).

ITNs versus untreated nets:
ITNs probably reduce the rate of all-cause child mortality compared to untreated nets
(Rate Ratio: 0.67; 95% CI (0.36–1.23); two studies; moderate certainty evidence)
ITNs reduce the rate of uncomplicated episodes of *P. falciparum* compared to untreated nets
(Rate Ratio: 0.58; 95% CI (0.43–0.79); five studies; high certainty evidence)
ITNs reduce the prevalence of *P. falciparum* compared to untreated nets
(Risk Ratio: 0.81; 95% CI (0.68–0.97); four studies; high certainty evidence)
ITNs may reduce the rate of uncomplicated episodes of *P. vivax* compared to untreated nets
(Rate Ratio: 0.73; 95% CI (0.51–1.05); three studies; low certainty evidence)
The effect of ITNs on the prevalence of *P. vivax*, compared to untreated nets, is unknown
(Risk Ratio: 0.52; 95% CI (0.13–2.04); two studies; very low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** Untreated nets	**Intervention** Insecticide-treated nets or curtains	**Certainty of the Evidence** (Quality of evidence)	**Plain language 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]	ITNs or curtains probably reduce all-cause child mortality compared to untreated nets.
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	ITNs or curtains reduce the incidence of uncomplicated P falciparum malaria episodes compared to untreated nets.
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	ITNs or curtains reduce the prevalence of P falciparum malaria compared to untreated nets.
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]	ITNs or curtains may reduce the incidence of uncomplicated P vivax malaria episodes compared to untreated nets.
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]	ITNs or curtains may reduce the incidence of uncomplicated P vivax malaria episodes compared to untreated nets.
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]	it is unclear if the proportion of people infected with P vivax parasites is any lower in those using an ITN than those using an untreated net.
Any	Relative risk 0.47	69	32	Moderate	ITNs or curtains

Outcome Timeframe	**Study results and measurements**	**Comparator** Untreated nets	**Intervention** Insecticide-treated nets or curtains	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Plasmodium spp. uncomplicated episodes (cumulative incidence)	(CI 95% 0.17 — 1.28) Based on data from 7,082 participants in 2 studies. (Randomized controlled)	per 1000 Difference:	per 1000 **37 fewer per 1000** (CI 95% 57 fewer — 19 more)	Due to serious imprecision [5]	probably reduce the incidence of uncomplicated malaria episodes of any species compared to untreated nets.
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]	It is unclear if ITNs reduce the prevalence of malaria, regardless of species, compared to untreated nets.

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

References

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Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Pyrethroid-PBO nets
Comparator: LLIN

Summary

Summary of evidence from systematic review
Fifteen trials met the inclusion criteria: two laboratory trials, eight experimental hut trials, and five cluster-randomized controlled village trials.

One village trial examined the effect of pyrethroid-PBO nets on malaria infection prevalence in an area with highly pyrethroid-resistant mosquitoes. The latest endpoint at 21 months post-intervention showed that malaria prevalence probably decreased in the intervention arm (OR 0.40, 95% CI 0.20 to 0.80; 1 trial, 1 comparison, moderate-certainty evidence).

Other trials reported entomological outcomes (not included here).

Outcome Timeframe	Study results and measurements	Comparator LLIN	Intervention PBO	Certainty of the Evidence (Quality of evidence)	Plain language summary
Prevalence of malaria	Odds Ratio 0.4 (CI 95% 0.2 — 0.8) Based on data from 3,966 participants in 1 studies.	527 per 1000 Difference:	211 per 1000 **316 fewer per 1000** (CI 95% 422 fewer — 105 fewer)	Moderate Due to serious indirectness [1]	Prevalence of malaria is probably decreased with pyrethroid-PBO nets compared to standard LLINs in areas of high insecticide resistance.

1. **Indirectness: serious.**

References

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Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: IRS
Comparator: no IRS

Summary

IRS versus no IRS in areas with unstable transmission: IRS may reduce malaria incidence compared to no IRS (Risk Ratio: 0.12; 95% CI (0.04–0.31); one study; low certainty evidence)

IRS may reduce parasite prevalence compared to no IRS (Risk Ratio: 0.24; 95% CI (0.17–0.34); one study; low certainty evidence)

Outcome Timeframe	Study results and measurements	Comparator no IRS	Intervention IRS	Certainty of the Evidence (Quality of evidence)	Plain language summary
Incidence of malaria in children under 5 years in areas of intense malaria transmission	Relative risk 0.86 (CI 95% 0.77 — 0.95) Based on data from 884 participants in 1 studies. (Randomized controlled)	650 per 1000 Difference:	560 per 1000 **90 fewer per 1000** (CI 95% 150 fewer — 40 fewer)	Low Due to serious indirectness, Due to serious imprecision [1]	

Outcome Timeframe	Study results and measurements	Comparator no IRS	Intervention IRS	Certainty of the Evidence (Quality of evidence)	Plain language summary
Parasite prevalence in children under 5 years in areas of intense malaria transmission	Relative risk 0.94 (CI 95% 0.82 — 1.08) Based on data from 452 participants in 1 studies. (Randomized controlled)	680 per 1000 Difference:	630 per 1000 **50 fewer per 1000** (CI 95% 130 fewer — 50 more)	Low Due to serious indirectness, Due to serious imprecision [2]	
Incidence of malaria in all ages in areas of unstable malaria	Relative risk 0.12 (CI 95% 0.04 — 0.31) Based on data from 18,261 participants in 1 studies. (Randomized controlled)	50 per 1000 Difference:	10 per 1000 **40 fewer per 1000** (CI 95% 50 fewer — 40 fewer)	Low Due to serious indirectness, Due to serious imprecision [3]	
Parasite prevalence in children aged 5–15 years in areas of unstable malaria	Relative risk 0.24 (CI 95% 0.17 — 0.34) Based on data from 2,359 participants in 1 studies. (Randomized controlled)	110 per 1000 Difference:	30 per 1000 **80 fewer per 1000** (CI 95% 90 fewer — 70 fewer)	Low Due to serious indirectness, Due to serious imprecision [4]	

1. **Indirectness: serious. Imprecision: serious.**
2. **Indirectness: serious. Imprecision: serious.**
3. **Indirectness: serious. Imprecision: serious.**
4. **Indirectness: serious. Imprecision: serious.**

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: IRS
Comparator: ITNs

Summary

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)	**Plain language 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]	
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]	
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]	
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)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**Low** Due to serious indirectness, Due to serious imprecision [4]	

1. **Indirectness: serious. Imprecision: serious.**
2. **Indirectness: serious. Imprecision: serious.**
3. **Indirectness: serious. Imprecision: serious.**
4. **Indirectness: serious. Imprecision: serious.**

4.1.2. Combining 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

IRS in addition to ITNs:
Four RCTs were included in the systematic review.
Studies were conducted in Benin, Eritrea, Gambia and United Republic of Tanzania.
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)

A review conducted in 2014 on the deployment of IRS in combination with ITNs (specifically pyrethroid-only LLINs) provided evidence that, in settings where there is high coverage with ITNs and where these remain effective, IRS may have limited utility in reducing malaria morbidity and mortality.

WHO guidance was developed accordingly to emphasize the need for good-quality implementation of either ITNs or IRS, rather than deploying both in the same area *(54)*.

Outcome Timeframe	**Study results and measurements**	**Comparator** ITNs	**Intervention** Pyrethroid-like IRS plus ITNs	**Certainty of the Evidence** (Quality of evidence)	**Plain language 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]	We did not know if there was an effect on the EIR of IRS using pyrethroid-like insecticides in addition to pyrethroid ITNs 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	50 per 1000	50 per 1000	Moderate Due to serious imprecision [4]	IRS using pyrethroid-like insecticides in addition to pyrethroid ITNs probably has little or no

Outcome Timeframe	**Study results and measurements**	**Comparator** ITNs	**Intervention** Pyrethroid-like IRS plus ITNs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	studies. (Randomized controlled)	Difference:	**0 fewer per 1000** (CI 95% 10 fewer — 10 more)		effect on anaemia prevalence compared to pyrethroid ITNs alone

1. **Imprecision: serious.**
2. **Inconsistency: serious. Imprecision: serious.**
3. **Inconsistency: serious. Imprecision: very serious.**
4. **Imprecision: serious.**

References

53. Choi L, Pryce J, Garner P : Indoor residual spraying for preventing malaria in communities using insecticide-treated nets. Cochrane Database of Systematic Reviews 2019;(5): Pubmed Journal Website

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

Larviciding versus no larviciding:
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)	**Plain language 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]	We are uncertain of the effects on malaria incidence in area where mosquito aquatic habitats are more than 1 km².
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]	We are uncertain of the effects on parasite prevalence in area where mosquito aquatic habitats are more than 1 km².
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 compared to no larviciding in area where mosquito aquatic habitats are less than 1 km².
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 decrease parasite prevalence compared to no larviciding in area where mosquito aquatic habitats are less than 1 km²

1. **Inconsistency: serious. Imprecision: serious.**
2. **Inconsistency: serious. Imprecision: very serious.**
3. **Imprecision: serious.**

References

59. Choi L, Majambere S, Wilson AL : Larviciding to prevent malaria transmission. Cochrane Database of Systematic Reviews 2019;(8): 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

Outcome Timeframe	**Study results and measurements**	**Comparator** No larval habitat manipulation	**Intervention** Larval habitat manipulation	**Certainty of the Evidence** (Quality of evidence)	**Plain language 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]	We are uncertain whether using spillways as a habitat manipulation water management approach compared to no intervention across streams reduces malaria parasite prevalence

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

Outcome Timeframe	**Study results and measurements**	**Comparator** IRS	**Intervention** Larval habitat manipulation and IRS	**Certainty of the Evidence** (Quality of evidence)	**Plain language 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]	We are uncertain whether using floodgates on a dam as a habitat manipulation water management across streams approach compared to no habitat manipulation in areas with IRS reduced clinical malaria incidence
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		**Very low** Due to serious risk of bias, due to very serious imprecision [2]	We are uncertain whether flushing of dams through sluice gates in areas with IRS has an effect on malaria parasite prevalence compared to no flushing

Outcome Timeframe	**Study results and measurements**	**Comparator** IRS	**Intervention** Larval habitat manipulation and IRS	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		decline in parasite rate (P < 0.01) in intervention villages. (Data on numbers of participants at follow-up not provided)			

1. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
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

Larvivorous fish versus no larvivorous fish:
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)	**Plain language 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)	**Plain language 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]	No clear evidence whether or not larvivorous fish reduce the density of immature anopheline mosquitoes in water bodies.
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		**Very low**	Larvivorous fish may reduce the number of larval sites positive for immature anopheline mosquitoes.

1. **Inconsistency: serious.**

References

61. Walshe DP, Garner P, Adeel AA, Pyke GH, Burkot TR : Larvivorous fish for preventing malaria transmission. Cochrane Database of Systematic Reviews 2017;(12): 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

Topical repellent versus placebo or no topical repellent:
A total of six RCTs were included in the review. Studies were conducted among residents in Plurinational State of Bolivia, Cambodia, Lao People's Democratic Republic and United Republic of Tanzania, and in specific populations in Pakistan (refugees) and Thailand (pregnant women).

It is unknown whether topical repellents have an effect on clinical malaria caused by *P. falciparum*
(Risk Ratio: 0.65; 95% CI (0.40–1.07); three studies; very low certainty evidence)
Topical repellents may or may not have a protective effect against *P. falciparum* parasitaemia
(Risk Ratio: 0.84; 95% CI (0.64–1.12); four studies; low

certainty evidence)
Topical repellents may increase the number of clinical cases caused by *P. vivax*
(Risk Ratio: 1.32; 95% CI (0.99–1.76); two studies; low certainty evidence)

Topical repellents may or may not have a protective effect against *P. vivax* parasitaemia
(Risk Ratio: 1.07; 95% CI (0.80–1.41); three 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)	**Plain language summary**
Clinical malaria (P. falciparum)	Relative risk 0.65 (CI 95% 0.4 — 1.07) Based on data from 4,450 participants in 3 studies.	39 per 1000 Difference:	25 per 1000 **14 fewer per 1000** (CI 95% 24 fewer — 2 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency [1]	We do not know if topical repellents have an effect on malaria cases caused by P. falciparum. We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
Parasitaemia (P. falciparum)	Relative risk 0.84 (CI 95% 0.64 — 1.12) Based on data from 13,310 participants in 4 studies.	15 per 1000 Difference:	12 per 1000 **3 fewer per 1000** (CI 95% 6 fewer — 2 more)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	Topical repellents may or may not have a protective effect against P. falciparum parasitaemia. Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimation of the effect.
Clinical malaria (P. vivax)	Relative risk 1.32 (CI 95% 0.99 — 1.76) Based on data from 3,996 participants in 2 studies.	36 per 1000 Difference:	48 per 1000 **12 more per 1000** (CI 95% 0 more — 28 more)	**Low** Due to serious risk of bias, Due to serious imprecision [3]	Topical repellents may increase the number of clinical cases caused by P. vivax. Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimation of the effect.
Parasitaemia (P. vivax)	Relative risk 1.07 (CI 95% 0.8 — 1.41) Based on data from 9,434 participants in 3 studies.	18 per 1000 Difference:	19 per 1000 **1 more per 1000** (CI 95% 4 fewer — 7 more)	**Low** Due to serious risk of bias, Due to serious imprecision [4]	Topical repellents may or may not have a protective effect against P. vivax parasitaemia Our confidence in the effect estimation is limited. The true effect may be substantially different from the estimation of the effect.

1. **Risk of Bias: serious. Inconsistency: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Imprecision: serious.**
3. **Risk of Bias: serious. Imprecision: serious.**
4. **Risk of Bias: serious. Imprecision: serious.**

References

62. Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ : Mosquito repellents for malaria prevention. Cochrane Database of Systematic Reviews 2018;(2): Pubmed Journal Website

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Insecticide-treated clothing
Comparator: placebo or untreated clothing

Summary

Insecticide-treated clothing versus placebo or untreated clothing:
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)	**Plain language 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 have a protective effect against malaria caused by P. falciparum. Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
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-treated clothing may have a protective effect against malaria caused by P. vivax. Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

1. **Risk of Bias: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Imprecision: serious.**

References

62. Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ : Mosquito repellents for malaria prevention. Cochrane Database of Systematic Reviews 2018;(2): 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

Spatial/airborne repellents versus placebo or no malaria prevention intervention:
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)	**Plain language 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]	We do not know if spatial repellents protect against malaria. We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

1. **Risk of Bias: serious. Inconsistency: serious. Imprecision: serious.**

References

62. Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ : Mosquito repellents for malaria prevention. Cochrane Database of Systematic Reviews 2018;(2): 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

Summary of evidence from systematic review
After searching for relevant trials up to 18 April 2018, we identified four studies conducted between 1972 and 2000. Across the four studies, a range of insecticide delivery methods were used, including handheld, vehicle-mounted, and aircraft-mounted spraying equipment. A variety of different insecticides, doses, and spraying times were also used to suit the local environment and the behaviour of the targeted mosquito species.

In three studies, the evidence was considered to be unsuitable for reliably assessing the impact of space spraying on the number of cases of malaria. The remaining study, which took place in a single state in India and covered a combined population of 18,460 people, reported the number of malaria cases in the years preceding and following the introduction of space spraying. The evidence suggested that space spraying led to a decrease in the number of cases of malaria, but as the trial was conducted over 30 years ago and within one state in India, we cannot be certain that these findings are applicable in other areas where malaria occurs. Reliable research in a variety of settings will help to establish whether and when this intervention may be worthwhile.

Across the included studies, the incidence of malaria was the only outcome reported with a valid comparator that could be used to estimate the impact of space spraying. One study reported the monthly incidence of malaria over a four-year period, with at least one year prior and at least two years post-intervention reported (Tewari 1990). The findings of the study suggest that space spraying had an effect on the incidence of malaria. However, the certainty of the evidence is very low, and we cannot be certain that the evidence provided is indicative of the true impact of space spraying on malaria incidence. We do not know 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). In addition, we do not know if space spraying causes a change in the slope of malaria incidence over time (RR 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)	**Plain language 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-randomized))	6 per 1000 Difference:	6 per 1000 **0 more per 1000** (CI 95% 3 fewer — 6 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [1]	We do not know if space spraying causes an immediate shift in the trend of malaria incidence.
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]	We do not know if space spraying causes a change in the slope of malaria incidence over time.

1. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**

References

63. Pryce J, Choi L, Richardson M, Malone D : Insecticide space spraying for preventing malaria transmission. 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: Screening of windows, ceilings, doors and eaves with untreated material
Comparator: No house screening

Summary

House screening versus no house screening in areas with risk of malaria:
Six cRCTs met the inclusion criteria, all conducted in sub-Saharan Africa; three randomized by household, two by village, and one by communities. At the time of publishing the review (January 2021), two of the six trials had published results, both of which compared screened houses (without insecticide) to unscreened houses. One trial in Ethiopia assessed screening of windows and doors. Another trial in The 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, 184 participants, 219.3 person-years; low-certainty evidence; Ethiopian study). For malaria parasite prevalence, the point estimate, derived from The Gambia study, was smaller (RR 0.84, 95% CI 0.60 to 1.17; 713 participants, 1 trial; low-certainty evidence), and showed an effect on 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): both trials showed lower estimates in the intervention arm. In the Gambian trial, 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), depending on the study year and treatment arm. The Ethiopian trial reported a mean difference in EIR of 4.57, favouring screening (95% CI 3.81 to 5.33; low-certainty evidence).

Pooled analysis of the trials showed that individuals living in fully screened houses were slightly less likely to sleep under a bed net (RR 0.84, 95% CI 0.65 to 1.09; 2 trials, 203 participants). In one trial, bed net usage was also lower in individuals living in houses with screened ceilings (RR 0.69, 95% CI 0.50 to 0.95; 1 trial, 135 participants).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening	**Intervention** Screening	**Certainty of the Evidence** (Quality of evidence)	**Plain language 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. (Randomized controlled) Follow up: 6 months.	91 per 1000 Difference:	35 per 1000 **56 fewer per 1000** (CI 95% 75 fewer — 21 fewer)	Low Due to serious risk of bias, Due to serious imprecision [1]	Screening may reduce clinical P falciparum malaria.
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 may have a small effect on malaria parasite prevalence.
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 probably reduces anaemia prevalence.

Outcome Timeframe	Study results and measurements	Comparator No screening	Intervention Screening	Certainty of the Evidence (Quality of evidence)	Plain language summary
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 may reduce EIR.

1. **Risk of Bias: serious. Imprecision: serious.**
2. Systematic reviewwith included studies: Kirby 2009. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Imprecision: serious.**
4. Systematic reviewwith included studies: Kirby 2009. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Imprecision: serious.**
6. **Imprecision: very serious.** the CIs around the mean estimates are very wide..

4.1.4. Other considerations for vector control

4.1.4.1. Special situations

4.1.4.2. Implementation challenges

4.1.4.3. Monitoring and evaluation of vector control

4.1.5. Research needs

4.2. Preventive chemotherapies & Mass drug administration

4.2.1. Intermittent preventive treatment of malaria in pregnancy (IPTp)

Clinical Question/ PICO

Population: Malaria-endemic areas
Intervention: Three or more doses of sulfadoxine–pyrimethamine
Comparator: Two doses of sulfadoxine–pyrimethamine

Outcome Timeframe	**Study results and measurements**	**Comparator** Sulfadoxine–pyrimethamine (2 doses)	**Intervention** Sulfadoxine–pyrimethamine (≥ 3 doses)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Severe anaemia in 3rd trimester	Relative risk 0.73 (CI 95% 0.48 — 1.11) Based on data from 2,196 participants in 6 studies. (Randomized controlled)	34 per 1000 Difference:	25 per 1000 **9 fewer per 1000** (CI 95% 18 fewer — 4 more)	Low Due to serious risk of bias and serious imprecision [1]	
Anaemia in 3rd trimester	Relative risk 0.95 (CI 95% 0.9 — 1.01) Based on data from 2,088 participants in 7 studies. (Randomized controlled)	509 per 1000 Difference:	484 per 1000 **25 fewer per 1000** (CI 95% 51 fewer — 5 more)	Moderate Due to serious risk of bias [2]	
Parasitaemia at delivery	Relative risk 0.68 (CI 95% 0.52 — 0.89) Based on data from 2,096 participants in 7 studies. (Randomized controlled)	92 per 1000 Difference:	63 per 1000 **29 fewer per 1000** (CI 95% 44 fewer — 10 fewer)	Moderate Due to serious risk of bias [3]	

1. **Risk of Bias: serious.** The strongest effect was seen in a trial at high risk of selection bias; removal of this trial removes the statistical significance. None of the three trials was blinded, and all had a high attrition rate.. **Inconsistency: no serious.** Statistical heterogeneity is low. **Indirectness: no serious.** These three studies were conducted in Kenya (1996), Burkina Faso (2005) and Malawi (2005) in women in their first or second pregnancy. **Imprecision: serious.** These trials had inadequate power. To detect a 25% relative reduction in severe anaemia confidently would require a sample size of over 12 000.
2. **Risk of Bias: serious.** Two trials were at high risk of selection bias, three were unblinded and four had a high attrition rate. **Inconsistency: no serious.** Statistical heterogeneity is low. **Indirectness: no serious.** The four studies were conducted in Kenya (1996), Zambia (2004), Burkina Faso (2005) and Malawi (2005) in women in their first or second pregnancy. **Imprecision: no serious.** This meta-analysis has adequate power to detect an effect.
3. **Risk of Bias: serious.** Two of the three studies were at high risk of selection bias. All three had a high attrition rate. **Inconsistency: no serious.** A subgroup analysis suggests that the effect may be larger in women infected with HIV. **Indirectness: no serious.** These three trials were conducted in Kenya (1996), Zambia (2004) and Malawi (2005) in women in their first or second pregnancy. In two trials, the analysis was stratified by HIV status. **Imprecision: no serious.** This meta-analysis has adequate power to detect an effect.

Clinical Question/ PICO

Population: Malaria-endemic areas
Intervention: Three or more doses of sulfadoxine–pyrimethamine
Comparator: Two doses of sulfadoxine–pyrimethamine

Outcome Timeframe	**Study results and measurements**	**Comparator** Sulfadoxine–pyrimethamine (2 doses)	**Intervention** Sulfadoxine–pyrimethamine (≥ 3 doses)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Miscarriage	Relative risk 1.43 (CI 95% 0.88 — 2.33) Based on data from 2,471 participants in 6 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 risk of bias and very serious imprecision [1]	
Stillbirth	Relative risk 1.14 (CI 95% 0.85 — 1.55) Based on data from 2,676 participants in 7 studies. (Randomized controlled)	30 per 1000 Difference:	34 per 1000 **4 more per 1000** (CI 95% 4 fewer — 17 more)	Very low Due to serious risk of bias and very serious imprecision [2]	
Neonatal mortality	Relative risk 0.88 (CI 95% 0.57 — 1.35) Based on data from 2,405 participants in 6 studies. (Randomized controlled)	21 per 1000 Difference:	18 per 1000 **3 fewer per 1000** (CI 95% 9 fewer — 7 more)	Very low Due to serious risk of bias and very serious imprecision [3]	
Preterm birth	Relative risk 1.28 (CI 95% 0.9 — 1.82) Based on data from 2,579 participants in 7 studies. (Randomized controlled)	122 per 1000 Difference:	116 per 1000 **6 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [4]	
Low birth weight	Relative risk 0.8 (CI 95% 0.69 — 0.94) Based on data from 2,190 participants in 7 studies. (Randomized controlled)	167 per 1000 Difference:	134 per 1000 **33 fewer per 1000** (CI 95% 52 fewer — 10 fewer)	High [5]	
Placental parasitaemia	Relative risk 0.51 (CI 95% 0.38 — 0.68) Based on data from 1,436 participants in 6 studies. (Randomized controlled)	63 per 1000 Difference:	32 per 1000 **31 fewer per 1000** (CI 95% 39 fewer — 20 fewer)	High [6]	
Cord blood haemoglobin	Relative risk		CI 95%		

Outcome Timeframe	**Study results and measurements**	**Comparator** Sulfadoxine–pyrimethamine (2 doses)	**Intervention** Sulfadoxine–pyrimethamine (≥ 3 doses)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mean birth weight	Based on data from: 2,190 participants in 7 studies. (Randomized controlled)	Sulfadoxine–pyrimethamine (2 doses): Mean birth weight in the control groups ranged from 2722 g to 3239 g. Sulfadoxine–pyrimethamine (≥ 3 doses): Mean birth weight in the intervention groups was 56 g higher (29 to 83 g higher).		High [7]	

1. **Risk of Bias: serious.** Two studies were at high risk of selection bias, and all three were unblinded and at high risk of attrition bias. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: no serious.** The three studies were conducted in Kenya (1996), Malawi (2005) and Burkina Faso (2008) in women in their first or second pregnancy. **Imprecision: very serious.** The trials had inadequate power to detect an effect. Confident detection of a 25% reduction in mortality would require a sample size of over 25 000.
2. **Risk of Bias: serious.** Two studies were at high risk of selection bias, and all three were unblinded and at high risk of attrition bias. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: no serious.** The three studies were conducted in Kenya (1996), Malawi (2005) and Burkina Faso (2008) in women in their first or second pregnancy. **Imprecision: very serious.** The trials had inadequate power to detect an effect. Confident detection of a 25% reduction in mortality would require a sample size of over 14 000.
3. **Risk of Bias: serious.** Two studies were at high risk of selection bias, and all three were unblinded and at high risk of attrition bias. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: no serious.** The three studies were conducted in Kenya (1996), Malawi (2005) and Burkina Faso (2008) in women in their first or second pregnancy. **Imprecision: very serious.** The trials had inadequate power to detect an effect. Confident detection of a 25% reduction in mortality would require a sample size of over 14 000.
4. **Risk of Bias: serious.** Two of the four studies were at high risk of selection bias and three at high risk of attrition bias. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: no serious.** These four studies were conducted in Kenya (1996), Zambia (2004), Malawi (2005) and Burkina Faso (2008) in women in their first or second pregnancy. **Imprecision: serious.** The 95% CI does not exclude what may be clinically important effects. Confident detection of a 25% reduction in pre-term birth would require a sample size of > 2500.
5. **Risk of Bias: no serious.** Two studies are at low risk of bias. Removal of the trials with high risk of bias did not influence the effect estimate. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: no serious.** These studies were conducted in Kenya (1996), Zambia (2004), Malawi (2005 and 2006), Mali (2008) and Burkina Faso (2008) in women in their first or second pregnancy. **Imprecision: no serious.** The sample size is sufficiently large to detect a difference between the two drug regimens, and the result is statistically significant.
6. **Risk of Bias: no serious.** Two studies are at low risk of bias. Removal of the trials with high risk of bias did not influence the effect estimate. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: no serious.** These studies were conducted in Kenya (1996), Zambia (2004), Malawi (2005) and Mali (2008) in women in their first or second pregnancy. **Imprecision: no serious.** The sample size is sufficiently large to detect a difference between the two drug regimens, and the result is statistically significant.
7. **Risk of Bias: no serious.** Two studies are at low risk of bias. Removal of the trials with high risk of bias did not influence the effect estimate. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: no serious.** These studies were conducted in Kenya (1996), Zambia (2004), Malawi (2005 and 2006), Mali (2008) and Burkina Faso (2008) in women in their first or second pregnancy. **Imprecision: no serious.** The sample size is sufficiently large to detect a difference between the two drug regimens, and the result is statistically significant.

4.2.2. Intermittent preventive treatment of malaria in infants (IPTi)

4.2.3. Seasonal malaria chemoprevention (SMC)

Clinical Question/ PICO

Population: Children aged < 5 years (areas with seasonal transmission)

Intervention: Regular full treatment doses of antimalarial medicines (amodiaquine + sulfadoxine–pyrimethamine, artesunate + sulfadoxine–pyrimethamine or sulfadoxine–pyrimethamine alone) every 1–2 months during the malaria transmission season

Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** SMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death from any cause (per 1000 per year)	Relative risk 0.66 (CI 95% 0.31 — 1.39) Based on data from 9,533 participants in 6 studies. (Randomized controlled)	3 per 1000 Difference:	2 per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 1 more)	Moderate Due to serious imprecision [1]	
Moderately severe anaemia (per 1000 per year)	Relative risk 0.71 (CI 95% 0.52 — 0.98) Based on data from 8,805 participants in 5 studies. (Randomized controlled)	67 per 1000 Difference:	48 per 1000 **19 fewer per 1000** (CI 95% 32 fewer — 1 fewer)	Moderate Due to serious inconsistency [2]	
Serious drug-related adverse events	Relative risk Based on data from 9,533 participants in 6 studies. (Randomized controlled)		CI 95%	Moderate Due to serious imprecision [3]	
Non-serious adverse events	Relative risk Based on data from 9,533 participants in 6 studies. (Randomized controlled)		CI 95%	Moderate Due to serious risk of bias [4]	
Clinical malaria	Based on data from: 9,321 participants in 6 studies. (Randomized controlled)	Placebo: 2.5 episodes per child per year (The incidence of malaria in the control groups was 2.88 episodes per child per year in Burkina Faso, 2.4 in Mali and 2.25 in Senegal). SMC: 0.7 episodes per child per year (0.4 to 1.0). Rate ratio: 0.26 (0.17 to 0.38).		High [5]	
Severe malaria	Based on data from: 5,964 participants in 2 studies. (Randomized controlled)	Placebo: 35 episodes per 1000 children per year (The incidence of severe malaria in the control groups was 32 per 1000 children per year in Burkina Faso and 37 per 1000 children per year in Mali). SMC: 9 episodes per 1000 children per year (4 to 27). Rate ratio 0.27 (0.1 to		High [6]	

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention SMC	Certainty of the Evidence (Quality of evidence)	Plain language summary
		0.76).			

1. **Imprecision: serious.** There were very few deaths in these trials, and none of the trials had adequate power to detect an effect on mortality. Larger trials are necessary for this effect to be established confidently. A reduction in the number of deaths would be consistent with the high-quality evidence of a reduction in severe malaria..
2. **Risk of Bias: no serious.** There was no reason to downgrade for study limitations, directness or precision. **Inconsistency: serious.** There was substantial heterogeneity among these five trials, and the trials in the Gambia and Ghana did not show an effect. Downgraded by 1 for inconsistency. **Indirectness: no serious.** There was no reason to downgrade for study limitations, directness or precision. **Imprecision: no serious.** There was no reason to downgrade for study limitations, directness or precision.
3. **Imprecision: serious.** No drug-related serious adverse events were reported. Downgraded by 1 for precision, as trials of this size have inadequate power to fully detect or exclude rare, serious adverse events.
4. **Risk of Bias: serious.** Downgraded by 1 for study limitations. All seven trials reported observed adverse events; however, the adequacy of the methods used to collect these data is unclear in some trials. The only adverse event found to be statistically more common with SMC was vomiting after amodiaquine + sulfadoxine–pyrimethamine.
5. **Risk of Bias: no serious.** The trials were conducted in children aged < 5 years in Burkina Faso, the Gambia, Ghana, Mali (two) and Senegal. In three studies, amodiaquine + sulfadoxine–pyrimethamine administered monthly, in two studies sulfadoxine–pyrimethamine was given every 2 months, and in one study sulfadoxine–pyrimethamine + artesunate was given monthly. Two studies, in which insecticide-treated nets were also distributed, showed that the benefits remained even when use of mosquito nets was > 90%. There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision. **Inconsistency: no serious.** There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision. **Indirectness: no serious.** There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision. **Imprecision: no serious.** There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.
6. **Risk of Bias: no serious.** The trials were conducted in children aged < 5 years in Burkina Faso, the Gambia, Ghana, Mali (two) and Senegal. In three studies, amodiaquine + sulfadoxine–pyrimethamine administered monthly, in two studies sulfadoxine–pyrimethamine was given every 2 months, and in one study sulfadoxine–pyrimethamine + artesunate was given monthly. Two studies, in which insecticide-treated nets were also distributed, showed that the benefits remained even when use of mosquito nets was > 90%. There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision. **Inconsistency: no serious.** There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision. **Indirectness: no serious.** There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision. **Imprecision: no serious.** There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.

4.3. Vaccine

Clinical Question/ PICO

Population: Children ≥5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission

Intervention: A minimum of four doses of RTS,S/AS01 (given as a three-dose initial series; first dose should be provided between 5 and 17 months of age) with a minimal interval between doses of four weeks

Comparator: Malaria interventions currently in place without malaria vaccination

Summary

Systematic review summary Three studies form the basis of these recommendations:

two were individual randomized controlled trials (RCTs) and one was an open-label extension study of an included RCT. One was a multicentre study comparing three or four doses of the RTS,S/AS01 malaria vaccine to no malaria vaccination. The other RCT compared the RTS,S/AS01 malaria vaccine alone to SMC alone, and also compared a combination of malaria vaccine and SMC to the malaria vaccine alone or SMC alone. Based on WHO regions, all three studies were conducted in Africa, specifically: Burkina Faso (three studies), Gabon, Ghana, Kenya (two studies), Malawi, Mali, Mozambique, and the United Republic of Tanzania (two studies).

In addition, data from the observational evaluation of the first 24 months of pilot implementation in Ghana, Malawi, and Kenya were considered by MPAG/SAGE and included in the evidence summary.

The RCTs showed that RTS,S/AS01 reduces clinical malaria, 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 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Protective efficacy (%) against clinical malaria episodes; 4-doses of RTS,S/AS01 versus control [1] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 6 Important	36.3 (CI 95% 31.8 — 40.5) Based on data from 5,950 participants in 1 studies. [2] (Randomized controlled) Follow up: 48 months.	Difference:	**1,774 fewer per 1000** (CI 95% 1,387 fewer — 2,186 fewer)	**High**	RTS,S/AS01 vaccination reduces clinical malaria.
Protective efficacy (%) against clinical malaria of vaccine alone versus SMC alone [3] Phase 3b randomized study 2017–2020; 3 years' follow-up	7.9 (CI 99% -1 — 16) Based on data from 3,953 participants in 1 studies. [4] (Randomized controlled)	305 per 1000 Difference:	278 per 1000 **27 fewer per 1000** (CI 95% 13 fewer — 40 fewer)	**High**	RTS,S/AS01 vaccination is non inferior to SMC in reducing clinical malaria.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important **Protective efficacy (%) against clinical malaria of vaccine + SMC combination versus SMC alone** [5] Phase 3b randomized study 2017–2020; 3 years' follow-up	62.8 (CI 95% 58.4 — 66.8) Based on data from 3,932 participants in 1 studies. [6] (Randomized controlled)	305 per 1000 Difference:	113 per 1000 **192 fewer per 1000** (CI 95% 182 fewer — 200 fewer)	**High**	The combination of RTS,S/AS01 vaccination with SMC is superior to SMC alone in reducing clinical malaria.
6 Important **Protective efficacy (%) against severe malaria episodes; 4 vaccine doses versus control** [7] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up	32.2 (CI 95% 13.7 — 46.9) Based on data from 5,950 participants in 1 studies. [8] (Randomized controlled) Follow up: 48 months.	Difference:	**19 fewer per 1000** (CI 95% 4 fewer — 35 fewer)	**High** [9]	RTS,S/AS01 vaccination reduces severe malaria.
9 Critical **Protective efficacy (%) against hospitalization due to severe malaria of vaccine alone versus SMC alone** [10] Phase 3b randomized study 2017–2020; 3 years' follow-up	-0.4 (CI 95% -60.2 — 37.1) Based on data from 3,953 participants in 1 studies. [11] (Randomized controlled)	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 [12]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing hospitalization with severe malaria.
9 Critical **Protective efficacy (%) against hospitalization**	70.5 (CI 95% 41.9 — 85) Based on data from 3,932 participants in 1	6.8 per 1000	2 per 1000	**Moderate** Due to serious imprecision [15]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
due to severe malaria of vaccine + SMC combination versus SMC alone [13] Phase 3b randomized study 2017–2020, 3 years' follow-up 9 Critical	studies. [14] (Randomized controlled)	Difference:	**4.8 fewer per 1000** (CI 95% 3.2 fewer — 5.7 fewer)		reducing hospitalization with severe malaria.
Incidence rate ratio for impact of routine RTS,S/AS01 vaccination on hospitalization with severe malaria in implementing versus comparison areas [16] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	0.7 (CI 95% 0.54 — 0.92) Based on data from 27,678 participants in 1 studies. [17]			Moderate Due to serious imprecision [18]	RTS,S/AS01 vaccine introduction is probably associated with a reduction in incidence of hospital admissions with severe malaria.
Protective efficacy (%) against severe malaria anaemia; 4 vaccine doses versus control [19] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 6 Important	47.8 (CI 95% 11.6 — 69.9) Based on data from 5,950 participants in 1 studies. [20] (Randomized controlled) Follow up: 48 months.	Difference:	**11 fewer per 1000** (CI 95% 1 fewer — 24 fewer)	Moderate Due to serious imprecision [21]	RTS,S/AS01 vaccination probably reduces severe malaria anaemia.
Protective efficacy (%) against severe malaria anaemia of vaccine alone versus SMC alone [22] Phase 3b	18.4 (CI 95% -39.3 — 52.2) Based on data from 3,953 participants in 1 studies. [23] (Randomized controlled)	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 [24]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing severe malaria anaemia.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
randomized study 2017–2020, 3 years' follow-up 6 Important					
Protective efficacy (%) against severe malaria anaemia of vaccine + SMC combination versus SMC alone [25] Phase 3b randomized study 2017–2020, 3 years' follow-up 6 Important	67.9 (CI 95% 34.1 — 84.3) Based on data from 3,932 participants in 1 studies. [26] (Randomized controlled)	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 [27]	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 vaccine doses versus control [28] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 6 Important	28.5 (CI 95% 3.5 — 47.2) Based on data from 5,950 participants in 1 studies. [29] (Randomized controlled)	Difference:	**15 fewer per 1000** (CI 95% 1 fewer — 31 fewer)	**Moderate** Due to serious imprecision [30]	RTS,S/AS01 vaccination probably reduces the need for blood transfusions.
Protective efficacy (%) against blood transfusion of vaccine alone versus SMC alone [31] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	8.27 (CI 95% -67.6 — 49.8) Based on data from 3,953 participants in 1 studies. [32] (Randomized controlled)	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 [33]	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	65.4 (CI 95% 22.9 — 84.5) Based on data from	4.22 per 1000	1.45 per 1000	**Low** Due to very serious	The combination of RTS,S/AS01 vaccination with SMC may be

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
transfusions of vaccine + SMC combination versus SMC alone [34] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	3,932 participants in 1 studies. [35] (Randomized controlled)	Difference:	**2.77 fewer per 1000** (CI 95% 1.32 fewer — 3.49 fewer)	imprecision [36]	superior to SMC alone in reducing the need for blood transfusions.
Protective efficacy (%) against all-cause hospital admissions; 4 vaccine doses versus control [37] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 9 Critical	16.5 (CI 95% 7.2 — 24.9) Based on data from 5,950 participants in 1 studies. [38] (Randomized controlled)	Difference:	**59 fewer per 1000** (CI 95% 18 fewer — 103 fewer)	**High** [39]	RTS,S/AS01 vaccination reduces all-cause hospital admissions.
Protective efficacy (%) against all-cause hospital admissions of vaccine alone versus SMC alone [40] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	-22.3 (CI 95% -74.4 — 14.3) Based on data from 3,953 participants in 1 studies. [41] (Randomized controlled)	**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 [42]	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 of vaccine + SMC combination versus SMC alone [43] Phase 3b randomized study 2017–2020; 3 years' follow-up	18.7 (CI 95% -19.4 — 44.7) Based on data from 3,932 participants in 1 studies. [44] (Randomized controlled)	**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 [45]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in reducing all-cause hospital admissions.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical **Incidence rate ratio for impact of routine RTS,S/AS01 vaccination on all-cause hospital admissions in implementing versus comparison areas** [46] Pilot implementation study 2019–2021 (month 0 to month 24)	0.92 (CI 95% 0.83 — 1.03) Based on data from 27,678 participants in 1 studies. [47]			**Moderate** Due to serious imprecision [48]	RTS,S/AS01 vaccine introduction probably has little or no difference on all-cause hospital admissions.
9 Critical **Incidence rate ratio for impact of routine RTS,S/AS01 vaccination on hospital admissions with a positive malaria test in implementing versus comparison areas** [49] Pilot implementation study 2019–2021 (month 0 to month 24)	0.79 (CI 95% 0.68 — 0.93) Based on data from 27,678 participants in 1 studies. [50]			**High** [51]	RTS,S/AS01 vaccine introduction is associated with reduced hospital admissions with a positive malaria test.
9 Critical **Protective efficacy (%) against all-cause mortality; 3 or 4 vaccine doses versus control** [52] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up	Based on data from 8,922 participants in 1 studies. [53] (Randomized controlled)			**Low** Due to very serious imprecision [54]	There were too few deaths to determine the impact of RTS,S/AS01 vaccination on all-cause mortality.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical **Protective efficacy (%) against all-cause mortality; vaccine alone versus SMC alone** [55] Phase 3b randomized study 2017–2020; 3 years' follow-up	12.1 (CI 95% -55.7 — 50.4) Based on data from 3,953 participants in 1 studies. [56] (Randomized controlled)	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 [57]	There may be little or no difference between the impact of RTS,S/AS01 vaccination and SMC administration on all-cause mortality.
9 Critical **Protective efficacy (%) against all-cause mortality of vaccine + SMC combination versus SMC alone** [58] Phase 3b randomized study 2017–2020; 3 years' follow-up	52.3 (CI 95% 4.99 — 76) Based on data from 3,932 participants in 1 studies. [59] (Randomized controlled)	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 [60]	The combination of RTS,S/AS01 vaccination and SMC is probably associated with a reduction in all-cause mortality.
9 Critical **Incidence rate ratio of meningitis; 3 or 4 vaccine doses versus control** [61] Post-hoc analysis of Ph 3 randomized trial 2009–2014	10.5 (CI 95% 1.41 — 78) Based on data from 8,922 participants in 1 studies. [62]			**Low** Due to serious risk of bias, Due to serious imprecision [63]	There were too few meningitis cases to determine an association with RTS,S/AS01 vaccination.
9 Critical **Incidence rate ratio of meningitis in vaccine alone versus SMC alone versus combination of vaccine with SMC** [64] Phase 3b	Based on data from 6,861 participants in 1 studies. [65] (Randomized controlled)			**Low** Due to very serious imprecision [66]	There were no meningitis cases to determine an association with RTS,S/AS01 vaccination.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
randomized study 2017–2020; 3 years' follow-up 9 Critical					
Incidence rate ratio of hospital admissions with meningitis; vaccine implementing versus comparison areas [67] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	0.81 (CI 95% 0.43 — 1.55) Based on data from 27,678 participants in 1 studies. [68]			**Moderate** Due to serious imprecision [69]	There is probably no evidence that RTS,S/AS01 vaccine introduction is associated with an increase in hospital admissions with meningitis.
Incidence rate ratio of possible cerebral malaria; 4-dose + 3-dose versus control groups [70] Post-hoc analysis of Ph 3 randomized trial 2009–2014 9 Critical	2.15 (CI 95% 1.1 — 4.3) Based on data from 8,922 participants in 1 studies. [71]			**Very low** Due to very serious risk of bias and serious imprecision [72]	There is uncertainty whether RTS,S/AS01 vaccination is associated with an increase in cerebral malaria cases.
Incidence rate ratio of cerebral malaria in vaccine alone versus SMC alone vs combination of vaccine with SMC [73] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	Based on data from 5,920 participants in 1 studies. [74] (Randomized controlled)			**Low** Due to very serious imprecision [75]	There were too few cerebral malaria cases to determine an association with RTS,S/AS01 vaccination.
Incidence rate ratio of hospital	0.77 (CI 95% 0.44 — 1.35)			**Moderate** Due to serious	There is probably no evidence that RTS,S/

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
admissions with cerebral malaria; vaccine implementing versus comparison areas [76] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	Based on data from 27,678 participants in 1 studies. [77]			inconsistency and serious imprecision [78]	AS01 vaccine introduction is associated with an increase in hospital admissions with cerebral malaria.
Female:male risk ratio of vaccine impact on all-cause mortality; 4-dose + 3-dose versus control groups [79] Post-hoc analysis of Ph 3 randomized trial 2009–2014 9 Critical	1.5 (CI 95% 1.03 — 2.08) Based on data from 8,922 participants in 1 studies. [80]			**Low** Due to very serious imprecision [81]	RTS,S/AS01 vaccination may be associated with an increase in deaths in girls and a decrease in deaths in boys.
Female:male rate ratio on vaccine impact on all-cause mortality; vaccine alone versus SMC alone [82] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	1.8 (CI 95% 0.56 — 5.79) Based on data from 3,953 participants in 1 studies. [83] (Randomized controlled)			**Low** Due to very serious imprecision [84]	There may be no evidence that the effect of RTS,S/AS01 vaccination differs between girls and boys.
Female:male rate ratio for all-cause mortality; combination of vaccine with SMC versus SMC alone [85] Phase 3b randomized study 2017–2020; 3 years' follow-up	0.35 (CI 95% 0.06 — 1.98) Based on data from 3,932 participants in 1 studies. [86] (Randomized controlled)			**Low** Due to very serious imprecision [87]	There may be no evidence that the effect of RTS,S/AS01 vaccination differs between girls and boys.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical **Female:male rate ratio of all-cause mortality ratio; vaccine implementing versus comparison areas** [88] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	1.08 (CI 95% 0.93 — 1.25) Based on data from 13,682 participants in 1 studies. [89]			**Moderate** Due to serious imprecision because not yet powered to assess overall impact on all-cause mortality, however well powered to detect gender imbalance in all-cause mortality [90]	There is probably no evidence that the effect of RTS,S/AS01 vaccine introduction on all-cause mortality differs between girls and boys.

1. Clinical malaria episodes (from month 0 to end of study; median follow-up: 48 months) (modified ITT analysis) 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. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration); four-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; Control group received comparator vaccine at months 0, 1, 2, and 20; Protective efficacy = (1-hazard ratio); Per Protocol analysis: VE 28.5% (95% CI 6.3 to 45.7)
2. Primary study[89]. 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 booster dose and R3R and R3C separately after the booster dose) and expressed per 1000 participants vaccinated. Among the older children, in the 12 months following administration of the first three doses, vaccine efficacy against clinical (uncomplicated and severe) malaria was 51% (95% CI 47-55) (per protocol analysis). **Baseline/comparator:** . **Supporting references:** [89],
3. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
4. Primary study[91]. 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;. **Baseline/comparator:** . **Supporting references:** [91], The 90, 95, and 99% CIs for the hazard ratio (HR) all excluded the pre-specified non-inferiority margin of 1.20..
5. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
6. Primary study[91]. 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;. **Baseline/comparator:** . **Supporting references:** [91],

7. 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 acoexisting 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. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration). 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio). Per Protocol analysis: VE 28.5% (95%CI: 6.3 to 45.7)
8. Primary study[89]. Among the older children, in the 12 months following administration of the first three doses, vaccine efficacy against severe malaria was 45% (95% CI 22-60) (per protocol analysis).. **Baseline/comparator:** . **Supporting references:** [89], PP analysis VE: 28.5% (95% CI: 6.3 to 45.7); The number of cases averted overtime 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 booster dose and R3R and R3C separately after the booster dose) and expressed per 1000 participants vaccinated..
9. **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.**
10. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
11. Primary study[91]. 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;. **Baseline/comparator:** . **Supporting references:** [91], Most cases of severe malaria were severe malaria anaemia (vaccine: 25/37; SMC: 31/37).
12. **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.**
13. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
14. Primary study[91]. Combination group of RTS,S + SMC 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;. **Baseline/comparator:** . **Supporting references:** [91],
15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI. **Publication bias: no serious.**
16. Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries, there was a total of 27 678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementating areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas
17. [101]. Among children eligible to have received all three primary doses of RTS,S/AS01, there was a total of 1107 admissions with severe malaria (out of 9,994 total age-eligible admissions), 418 from implementation areas and 689 from comparison areas. Among children who were not eligible there were 2,703 total admissions with severe malaria (out of 17,684 total age-ineligible admissions) to have received any doses of RTS,S/AS01: 1313 from implementation areas and 1390 from comparison areas. The incidence rate ratio comparing incidence of admission with severe malaria between implementing and comparison areas was 0.70 (95%CI 0.54 to 0.92), a reduction of 30% (95%CI 8% to 46%); there was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria. **Baseline/comparator:** .
18. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggestthere is no evidence that the introduction of RTS,S/AS01 had a negative effect on the 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.**
19. Assessed with: a documented 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 group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio).
20. Primary study[89]. **Baseline/comparator:** .
21. **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.**
22. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
23. Primary study[91]. The RTS,S vaccine group had 25 severe malaria anemia cases over 5535.7 total 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;. **Baseline/comparator:** . **Supporting references:** [91],
24. **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.**
25. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
26. Primary study[91]. The RTS,S vaccine and SMC combination group had 10 severe malaria anaemia cases over 5508 total 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;. **Baseline/comparator:** . **Supporting references:** [91],
27. **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.**
28. 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio).
29. Primary study[89]. **Baseline/comparator:** .
30. **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.**
31. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
32. Primary study[91]. 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;. **Baseline/comparator:** . **Supporting references:** [91],
33. **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.**
34. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
35. Primary study[91]. 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;. **Baseline/comparator:** . **Supporting references:** [91],
36. **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.**
37. 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio).
38. Primary study[89]. **Baseline/comparator:** .
39. **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.
40. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
41. Primary study[91]. 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;. **Baseline/comparator:** .
42. **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.**
43. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
44. Primary study[91]. 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;. **Baseline/comparator:** . **Supporting references:** [91],
45. **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.**
46. Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries, there was a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementating areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas
47. [101]. Severe malaria represented 19% 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 3196 admissions to sentinel hospitals in implementation areas and 3569 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 0.83 to 1.03), a reduction of 8% (95%CI -3% to 17%).. **Baseline/comparator:** .
48. **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.**
49. Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries, there were a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementing areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas.
50. [101]. Patients admitted to sentinel hospitals were routinely tested for malaria infection by rapid diagnostic test (RDT) or microscopy. Out of a total of 27,678 patients admitted, test results were available for 88%. Among children eligible to have received three vaccine doses, the number of patients admitted with a positive malaria test was 2630-- 1075 from implementation areas and 1555 from comparison areas. The rate ratio comparing the incidence of hospital admission with a positive malaria test between implementation and comparison areas was 0.79 (95%CI 0.68 to 0.93), a reduction of 21% (95%CI 7% to 32%).. **Baseline/comparator:** .
51. **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.**
52. 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; 3-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a comparator vaccine at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio).
53. [89]. Four dose group: 61 deaths (13 malaria)/2976 children + Three dose group: 51 deaths (17 malaria) / 2972 children vs Control group: 46 deaths (13 malaria) / 2974 children.. **Baseline/comparator:** .
54. **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.**

55. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).

56. Primary study[91]. 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.. **Baseline/comparator:** .

57. **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.**

58. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).

59. Primary study[91]. 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.. **Baseline/comparator:** .

60. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI.. **Publication bias: no serious.**

61. mITT analysis; 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; 3-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a comparator vaccine at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio).

62. [89]. 4-dose group 11/2976 + 3-dose group 10/2972 vs Control group 1/2974. **Baseline/comparator:** .

63. **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.**

64. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).

65. Primary study[91]. Eight cases of clinically suspected meningitis (four in the SMC-alone group, three in the RTS,S vaccine-alone group, and one in the RTS,S + SMC combined group) were investigated with the use of lumbar puncture, but none showed proven meningitis.. **Baseline/comparator:** .

66. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels for imprecision: no events reported in any groups. **Publication bias: no serious.**

67. Pilot implementation study designed to be analysed using cluster randomized control methodology; to be able to rule out an association with meningitis of the magnitude seen in the Phase 3 trial it would therefore be necessary to exclude rate ratios of about 10.5 (4.5 allowing for coverage and contamination) or more. Across the three countries, there was a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementing areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas

68. Primary study[101]. A total of 4,311 suspected cases of meningitis were investigated. Lumbar punctures were performed in 2,652 (62%) of these patients, and PCR analysis of samples of cerebrospinal fluid (CSF) was available for 2,249 patients (52%). A total of 51 cases of probable or confirmed meningitis were seen in sentinel hospitals among age groups of children eligible for the malaria vaccine: 27 from implementation areas and 24 from comparison areas. Among the age groups that were not eligible for the malaria vaccine, there were 79 probable or confirmed cases of meningitis: 44 from implementation areas and 35 from comparison areas. The incidence rate ratio comparing rates of admission with meningitis in implementation and comparison areas, among vaccine-eligible children, was 0.81 (95%CI 0.43 to 1.55). 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 sufficient 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, 41% (11/27) had received the RTS,S/AS01 vaccine, compared to 53% (2491/4672) of all other hospital admissions in this age group from implementation areas (odds ratio, adjusted for country and age: 0.73 (95%CI 0.31,1.71). The PCR results showed that only 15% (8/55) 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).. **Baseline/comparator:** .
69. **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.**
70. Unplanned sub-group analysis of participant groups: 4-dose group received three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; 3-dose group received three 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).
71. [89]. 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. **Baseline/comparator:** .
72. **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.**
73. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
74. Primary study[91]. 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).. **Baseline/comparator:** .
75. **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.**
76. 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, there was a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementing areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas
77. [101]. There were 55 cases of cerebral malaria, in whom lumbar puncture was performed to exclude cases with probable meningitis): 25 from implementation areas and 30 from comparison areas. Among age groups of children not eligible to receive the malaria vaccine, there were 241 cases of cerebral malaria, 115 from implementation areas and 126 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 0.77 (95%CI 0.44 to 1.35). The incidence rate ratio for admission with other forms of severe malaria excluding cerebral malaria was 0.70 (95%CI 0.54 to 0.89). There was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria (relative rate ratio 0.94 (95%CI 0.57 to 1.56; and test of interaction p-value: 0.808). When the analysis was broadened to include cases meeting the criteria for cerebral malaria but in whom lumbar puncture was not performed, there was a total of 103 cases in age-groups eligible to have received at least one dose of the malaria vaccine: 49 from implementation areas and 54 from comparison areas. There were 455 cases in non-eligible age groups: 230 from implementing areas and 225 from comparison areas. The incidence rate ratio comparing rates of admission to hospital with cerebral malaria (with the broader case definition) in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.96 (95%CI 0.61 to 1.52). Again there was no evidence that impact differed between cerebral malaria and other forms of severe malaria (test of interaction p-value: 0.470). Similar results were obtained when cerebral malaria was limited to cases defined as U (unresponsive) on the AVPU score. Among children eligible tohave received the vaccine, 20 of the cases from implementation areas and 25 from comparison areas met this stricter criterion, and the estimate of the rate ratio was 0.66 (95%CI: 0.31 to 1.43). Of the patients with cerebral malaria in vaccine-eligible age groups from implementation areas, 47% (23/49) had received RTS,S/AS01 vaccine, compared to 53% (2479/4650) of all other admissions in this age group from

implementation areas (odds ratio, adjusted for country and age,1.03, 95%CI 0.56,1.90; the odds ratio among cases meeting the stricter definition requiring a lumbar puncture was 1.58; 95%CI: 0.66 to 3.80). 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. **Baseline/comparator:** .

78. **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; .

79. All-cause mortality (month 0 to study end) (modified ITT analysis); 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; 3-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a comparator vaccine at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20.

80. [89]. 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. **Baseline/comparator:** .

81. **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.**

82. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).

83. Primary study[91]. 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. **Baseline/comparator:** .

84. **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.**

85. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).

86. Primary study[91]. 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.. **Baseline/comparator:** .

87. **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.**

88. 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 13682 deaths among children 1-59 months of age were reported via community-based mortality surveillance across the three countries from the start of vaccinations on 23 April 2019 to 31 March 2021 (deaths in April 2021 were excluded because verbal autopsies have not all been completed).

89. [101]. 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 three doses of RTS,S/AS01, there was a total of 2864 deaths reported, 1421 from implementing regions and 1443 from comparison regions. In children who were not eligible to have received the vaccine there were 4218 deaths in implementing regions and 3874 in comparison regions. The mortality ratio in the vaccine-eligible age group (eligible for three doses) between implementing and comparison regions, was 0.93 (95%CI: 0.84 to 1.03), a 7% reduction (95%CI: -3% to 16%). There was no evidence that the mortality ratio differed between girls and boys, the p-value for this interaction was 0.343. The mortality ratio in girls was 0.98 and in boys 0.90; the relative mortality ratio (girls:boys) was 1.08 (95%CI: 0.92 to 1.28). 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: 1.08; 95%CI: 0.93 to 1.25; p-value for the interaction: 0.321). Similar results were also obtained when the analysis was repeated for different age groups of eligible children (mortality ratio girls:boys in eligible children under 18 months of age was 1.10 [95%CI: 0.94 to 1.29], and in eligible children aged 18 months and over it was 0.95 [95%CI: 0.70 to 1.31]). The vaccination status of vaccine-eligible children who died in implementation areas was similar in girls and boys (58.9% and 57.0% respectively). According to the household surveys in 12-23 month olds, coverage of the first dose of RTS,S/AS01 was slightly higher in girls than in boys (77.6% in girls and 73.0% in boys in Ghana; 75.1% in girls and 70.1% in boys in Malawi; and 79.0% in girls and 78.2% in boys in Kenya). Coverage was similar for the third dose.. **Baseline/comparator:** .

90. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level because the evaluation was not powered at this time point to assess overall impact of vaccine introduction on mortality. However 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.. **Publication bias: no serious.**

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5. CASE MANAGEMENT

5.1. Diagnosing malaria (2015)

5.2. Treating uncomplicated malaria

5.2.1. 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)	**Plain language summary**
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. PCR unadjusted
2. **Risk of Bias: no serious.** No serious risk of bias: 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.** No serious inconsistency: All the trials had similar results, and statistical heterogeneity was low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** No serious imprecision: The 95% CI implies appreciable benefit, and the meta-analysis is adequately powered to detect this result.. **Publication bias: no serious.**
3. PCR adjusted
4. **Risk of Bias: no serious.** No serious risk of bias: 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.** No serious inconsistency: All the trials had similar results, and statistical heterogeneity was low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** No serious imprecision: 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.**
5. PCR unadjusted
6. **Risk of Bias: no serious.** No serious risk of bias: 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.** No serious inconsistency: 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.** No serious indirectness: The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** No serious imprecision: The 95% CI implies appreciable benefit, and the meta-analysis is adequately powered to detect this result.. **Publication bias: no serious.**

7. PCR adjusted
8. **Risk of Bias: no serious.** No serious risk of bias: 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.** No serious inconsistency: The treatment failure rate with dihydroartemisinin + piperaquine was < 5% in both trials.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** No serious imprecision: 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)	**Plain language summary**
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 participants in 5 studies. (Randomized	30 per 1000 Difference:	15 per 1000 **15 fewer per**	**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)	**Plain language summary**
	controlled)		**1000** (CI 95% 21 fewer — 5 fewer)		

1. PCR unadjusted
2. **Risk of Bias: no serious.** No serious risk of bias: 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.** Downgraded by 1 for serious inconsistency: 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.** No serious indirectness: 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.** No serious imprecision: Overall, no significant difference between treatments; however, dihydroartemisinin + piperaquine may be superior where P. falciparum is resistant to mefloquine.. **Publication bias: no serious.**
3. PCR adjusted
4. **Risk of Bias: no serious.** No serious risk of bias: 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.** Downgraded by 1 for serious inconsistency: 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.** No serious indirectness: 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.** No serious imprecision: 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.**
5. PCR unadjusted
6. **Risk of Bias: no serious.** No serious risk of bias: 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.** Downgraded by 1 for serious inconsistency: 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.** No serious indirectness: The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar and Thailand.. **Imprecision: no serious.** No serious imprecision: Overall, no significant difference between treatments. Although some trials found statistically significant differences, these may not be clinically important.. **Publication bias: no serious.**
7. PCR adjusted
8. **Risk of Bias: no serious.** No serious risk of bias: 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.** Downgraded by 1 for serious inconsistency: Slight variation among trials, only one showing a statistically significant benefit with dihydroartemisinin + piperaquine.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar and Thailand.. **Imprecision: no serious.** No serious imprecision: 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)	**Plain language summary**
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** CI 95%	Moderate Due to serious imprecision [1]	
Early vomiting	Relative risk Based on data from 2,695 participants in 3 studies. (Randomized controlled)	20 per 1000 Difference:	30 per 1000 **10 more per 1000** CI 95% 0 fewer –	Moderate Due to serious risk of bias [2]	
Vomiting	Relative risk Based on data from 6,761 participants in 9 studies. (Randomized controlled)	90 per 1000 Difference:	90 per 1000 **0 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [3]	
Nausea	Relative risk Based on data from 547 participants in 2 studies. (Randomized controlled)	20 per 1000 Difference:	20 per 1000 **0 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [4]	
Diarrhoea	Relative risk Based on data from 4,889 participants in 7 studies. (Randomized controlled)	120 per 1000 Difference:	120 per 1000 **0 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [5]	
Abdominal pain	Relative risk Based on data from 911 participants in 5 studies. (Randomized controlled)	190 per 1000 Difference:	160 per 1000 **30 fewer per 1000** CI 95% 0 fewer –	Low Due to serious risk of bias and serious imprecision [6]	
Anorexia	Relative risk Based on data from 3,834 participants in 5 studies. (Randomized controlled)	150 per 1000 Difference:	140 per 1000 **10 fewer per 1000** CI 95% 0 fewer –	Moderate Due to serious risk of bias [7]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Headache	Relative risk Based on data from 309 participants in 2 studies. (Randomized controlled)	270 per 1000 Difference:	330 per 1000 **60 more per 1000** CI 95% 0 fewer –	Low Due to serious risk of bias and serious imprecision [8]	
Sleeplessness	Relative risk Based on data from 547 participants in 2 studies. (Randomized controlled)	10 per 1000 Difference:	30 per 1000 **20 more per 1000** CI 95% 0 fewer –	Low Due to serious risk of bias and serious imprecision [9]	
Dizziness	Relative risk Based on data from 547 participants in 2 studies. (Randomized controlled)	30 per 1000 Difference:	40 per 1000 **10 more per 1000** CI 95% 0 fewer –	Low Due to serious risk of bias and serious imprecision [10]	
Sleepiness	Relative risk Based on data from 384 participants in 1 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [11]	
Weakness	Relative risk Based on data from 1,812 participants in 5 studies. (Randomized controlled)	170 per 1000 Difference:	180 per 1000 **10 more per 1000** CI 95% 0 fewer –	Moderate Due to serious risk of bias [12]	
Cough	Relative risk Based on data from 4,342 participants in 5 studies. (Randomized controlled)	420 per 1000 Difference:	420 per 1000 **0 fewer per 1000** CI 95% 0 fewer –	Moderate Due to serious risk of bias [13]	
Coryza	Relative risk Based on data from 832 participants in 2 studies. (Randomized controlled)	680 per 1000 Difference:	660 per 1000 **20 fewer per 1000** CI 95% 0 fewer –	Low Due to serious imprecision [14]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Prolonged QT interval (adverse event)	Relative risk Based on data from 1,548 participants in 1 studies. (Randomized controlled)	30 per 1000 Difference:	20 per 1000 **10 fewer per 1000** CI 95% 0 fewer –	**Low** Due to serious imprecision and serious risk of bias [15]	
Prolonged QT interval (Bazett correction)	Relative risk Based on data from 1,548 participants in 1 studies. (Randomized controlled)	70 per 1000 Difference:	90 per 1000 **20 more per 1000** CI 95% 0 fewer –	**Low** Due to serious imprecision and serious risk of bias [16]	
Prolonged QT interval (Fridericia correction)	Relative risk Based on data from 1,548 participants in 1 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** CI 95%	**Low** Due to serious risk of bias and serious imprecision [17]	
Pruritus	Relative risk Based on data from 2,033 participants in 5 studies. (Randomized controlled)	20 per 1000 Difference:	40 per 1000 **20 more per 1000** CI 95% 0 fewer –	**Moderate** Due to serious risk of bias [18]	
Facial oedema	Relative risk Based on data from 384 participants in 1 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** CI 95%	**Low** Due to serious risk of bias and serious imprecision [19]	

1. **Risk of Bias: no serious.** No serious risk of bias: All but one of the trials were open label; however, we did not downgrade for this outcome.. **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: No statistically significant difference was detected between treatments; however the sample size does not exclude the possibility of rare but clinically important differences..
2. **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: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..
3. **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: no serious. No serious imprecision: 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..
5. **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: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..
6. **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: The result does not reach statistical significance..
7. **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: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..
8. **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: The result does not reach statistical significance..
9. **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..
10. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **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..
11. **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..
12. **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: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..
13. **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: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..
14. **Risk of Bias: no serious.** No serious risk of bias: All but one of the trials were open label; however, we did not downgrade for this outcome.. **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: The result does not reach statistical significance..
15. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: 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.. **Indirectness: no serious.** No serious indirectness: This single trial was conducted in children in Burkina Faso, Kenya, Mozambique, Uganda and Zambia.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: The result does not reach statistical significance..
16. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: 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.. **Indirectness: no serious.** No serious indirectness: This single trial was conducted in children in Burkina Faso, Kenya, Mozambique, Uganda and Zambia.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: The result does not reach statistical significance..
17. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: 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.. **Indirectness: no serious.** No serious indirectness: This single trial was conducted in children in Burkina Faso, Kenya, Mozambique, Uganda and Zambia.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: The result does not reach statistical significance..
18. **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: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..
19. **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..

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)	**Plain language summary**
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** CI 95%	Moderate Due to serious imprecision [1]	
Nausea	Relative risk Based on data from 4,531 participants in 9 studies. (Randomized controlled)	20 per 1000 Difference:	14 per 1000 **6 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [2]	
Early vomiting	Relative risk Based on data from 4,114 participants in 9 studies. (Randomized controlled)	7 per 1000 Difference:	6 per 1000 **1 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [3]	
Vomiting	Relative risk Based on data from	13 per 1000	8 per 1000	Moderate Due to serious risk of bias [4]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	2,744 participants in 5 studies. (Randomized controlled)	Difference:	**5 fewer per 1000** CI 95%		
Anorexia	Relative risk Based on data from 3,497 participants in 6 studies. (Randomized controlled)	15 per 1000 Difference:	13 per 1000 **2 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [5]	
Diarrhoea	Relative risk Based on data from 2,217 participants in 5 studies. (Randomized controlled)	6 per 1000 Difference:	8 per 1000 **2 more per 1000** CI 95%	Moderate Due to serious risk of bias [6]	
Abdominal pain	Relative risk Based on data from 3,887 participants in 7 studies. (Randomized controlled)	11 per 1000 Difference:	11 per 1000 **0 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [7]	
Headache	Relative risk Based on data from 2,039 participants in 4 studies. (Randomized controlled)	12 per 1000 Difference:	10 per 1000 **2 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious inconsistency [8]	
Dizziness	Relative risk Based on data from 4,531 participants in 9 studies. (Randomized controlled)	36 per 1000 Difference:	26 per 1000 **10 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [9]	
Sleeplessness	Relative risk Based on data from 2,551 participants in 6 studies. (Randomized controlled)	21 per 1000 Difference:	10 per 1000 **11 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [10]	
Fatigue	Relative risk Based on data from 872 participants in 2 studies. (Randomized controlled)	8 per 1000 Difference:	3 per 1000 **5 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious indirectness [11]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Nightmares	Relative risk Based on data from 220 participants in 1 studies. (Randomized controlled)	10 per 1000 Difference:	1 per 1000 **9 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious indirectness [12]	
Anxiety	Relative risk Based on data from 522 participants in 1 studies. (Randomized controlled)	11 per 1000 Difference:	1 per 1000 **10 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious indirectness [13]	
Blurred vision	Relative risk Based on data from 464 participants in 1 studies. (Randomized controlled)	9 per 1000 Difference:	4 per 1000 **5 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious indirectness [14]	
Tinnitus	Relative risk Based on data from 220 participants in 1 studies. (Randomized controlled)	9 per 1000 Difference:	4 per 1000 **5 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious indirectness [15]	
Palpitations	Relative risk Based on data from 1,175 participants in 3 studies. (Randomized controlled)	18 per 1000 Difference:	11 per 1000 **7 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [16]	
Cough	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	10 per 1000 Difference:	8 per 1000 **2 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [17]	
Dyspnoea	Relative risk Based on data from 220 participants in 1 studies. (Randomized controlled)	9 per 1000 Difference:	3 per 1000 **6 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [18]	
Prolonged QT interval (adverse event)	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	4 per 1000 Difference:	5 per 1000 **1 more per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [19]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Prolonged QT interval (Bazett correction)	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	4 per 1000 Difference:	9 per 1000 **5 more per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [20]	
Prolonged QT interval (Fridericia correction)	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	5 per 1000 Difference:	4 per 1000 **1 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [21]	
Arthralgia	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	6 per 1000 Difference:	5 per 1000 **1 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [22]	
Myalgia	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	6 per 1000 Difference:	6 per 1000 **0 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [23]	
Urticaria	Relative risk Based on data from 719 participants in 2 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 **1 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [24]	
Pruritus	Relative risk Based on data from 872 participants in 2 studies. (Randomized controlled)	3 per 1000 Difference:	2 per 1000 **1 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [25]	
Rash	Relative risk Based on data from 220 participants in 1 studies. (Randomized controlled)	1 per 1000 Difference:	0 per 1000 **1 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [26]	

1. **Risk of Bias: no serious.** No serious risk of bias: Only eight of the 11 reports made any comment on serious adverse events. None of these eight trials was blinded. . **Inconsistency: no serious.** No serious inconsistency: None of the eight trials found statistically significant differences.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: serious.** Downgraded by 1 for imprecision: These trials do not exclude the possibility of rare but clinically important adverse effects..

2. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
3. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: None of the eight trials found statistically significant differences.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The 95% CI around the absolute effect is narrow and excludes clinically important differences..
4. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
5. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: This result does not reach statistical significance..
6. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
7. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: No difference was found between treatments, and the sample is large enough for detection of any differences..
8. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: serious.** Downgraded by 1 for serious inconsistency: There is moderate heterogeneity among trials.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
9. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
10. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
11. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: serious.** Downgraded by 1 for serious indirectness: Only two trials assessed this outcome.. **Imprecision: no serious.**
12. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: serious.** Downgraded by 1 for serious indirectness: Only two trials assessed this outcome.. **Imprecision: no serious.**
13. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: serious.** Downgraded by 1 for serious indirectness: Only two trials assessed this outcome.. **Imprecision: no serious.**
14. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: serious.** Downgraded by 1 for serious indirectness: Only two trials assessed this outcome.. **Imprecision: no**

serious.
15. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious. Indirectness: serious.** Downgraded by 1 for serious indirectness: Only two trials assessed this outcome.. **Imprecision: no serious.**
16. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
17. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded by 1 for serious imprecision: This result does not reach statistical significance..
18. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded by 1 for imprecision: Limited data available, and the result is not statistically significant..
19. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: 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.** No serious indirectness: This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: This result does not reach statistical significance..
20. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious. Indirectness: no serious.** No serious indirectness: This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: This result does not reach statistical significance..
21. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious. Indirectness: no serious.** No serious indirectness: This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: This result does not reach statistical significance..
22. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label. Downgraded by 1 for serious risk of bias: 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 serious imprecision: No difference was found between treatments, and the sample is large enough for detection of any differences..
23. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label. Downgraded by 1 for serious risk of bias: 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 serious imprecision: No difference was found between treatments, and the sample is large enough for detection of any differences..
24. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded by 1 for imprecision: Limited data available, and the result is not statistically significant..
25. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded by 1 for imprecision: Limited data available, and the result is not statistically significant..
26. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded by 1 for imprecision: Limited data available, and the result is not statistically significant..

Clinical Question/ PICO

Population:	Adults and children with uncomplicated falciparum malaria (malaria-endemic areas in Africa and Asia)
Intervention:	Artesunate + pyronaridine once daily for 3 days
Comparator:	Artemether + lumefantrine twice daily for 3 days

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Artesunate + pyronaridine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Treatment failure on day 28 (PCR-unadjusted)	Relative risk 0.6 (CI 95% 0.4 — 0.9) Based on data from 1,720 participants in 2 studies. (Randomized controlled)	70 per 1000 Difference:	42 per 1000 **28 fewer per 1000** (CI 95% 42 fewer — 7 fewer)	Moderate Due to serious indirectness [1]	
Treatment failure on day 28 (PCR-adjusted)	Relative risk 1.69 (CI 95% 0.56 — 5.1) Based on data from 1,650 participants in 2 studies. (Randomized controlled)	10 per 1000 Difference:	17 per 1000 **7 more per 1000** (CI 95% 4 fewer — 41 more)	Moderate Due to serious indirectness [2]	
Treatment failure on day 42 (PCR-unadjusted)	Relative risk 0.85 (CI 95% 0.53 — 1.36) Based on data from 1,691 participants in 2 studies. (Randomized controlled)	170 per 1000 Difference:	145 per 1000 **25 fewer per 1000** (CI 95% 80 fewer — 61 more)	Moderate Due to serious indirectness [3]	
Treatment failure on day 42 (PCR-adjusted)	Relative risk 1.53 (CI 95% 0.73 — 3.19) Based on data from 1,472 participants in 2 studies. (Randomized controlled)	20 per 1000 Difference:	31 per 1000 **11 more per 1000** (CI 95% 5 fewer — 44 more)	Low Due to serious indirectness and serious inconsistency [4]	

1. **Risk of Bias: no serious.** Both studies were well conducted with low risk of bias. **Inconsistency: no serious.** The trend was towards benefit with artesunate + pyronaridine in both trials but reached statistical significance in only one. **Indirectness: serious.** The two trials were conducted in children aged 3 months–12 years in study sites in Africa and Asia. In both trials, only 152 children aged < 5 years received artesunate + pyronaridine, and only 115 children in total were randomized to artesunate + pyronaridine in Asia. Further, adequately powered studies in children in Africa and adults and children in Asia would be needed to generalize this result. **Imprecision: no serious.** The result is statistically significant and the meta-analysis is adequately powered; however, these multi-centred trials are underpowered to show equivalence at country level. Not downgraded.
2. **Risk of Bias: no serious.** Both studies were well conducted with low risk of bias. **Inconsistency: no serious.** The trend was towards benefit with artesunate + pyronaridine in both trials but reached statistical significance in only one. **Indirectness: serious.** The two trials were conducted in children aged 3 months–12 years in study sites in Africa and Asia. In both trials, only 152 children aged < 5 years received artesunate + pyronaridine, and only 115 children in total were randomized to artesunate + pyronaridine in Asia. Further, adequately powered studies in children in Africa and adults and children in Asia would be needed to generalize this result. **Imprecision: no serious.** No substantial difference found between the two ACTs; however, these multi-centred trials are underpowered to show equivalence at country level. Not downgraded.
3. **Risk of Bias: no serious.** Both studies were well conducted with low risk of bias. **Inconsistency: no serious.** The trend was towards benefit with artesunate + pyronaridine in both trials but reached statistical significance in only one. **Indirectness: serious.** The two trials were conducted in children aged 3 months–12 years in study sites in Africa and

Asia. In both trials, only 152 children aged < 5 years received artesunate + pyronaridine, and only 115 children in total were randomized to artesunate + pyronaridine in Asia. Further, adequately powered studies in children in Africa and adults and children in Asia would be needed to generalize this result. **Imprecision: no serious.** No substantial difference found between the two ACTs; however, these multi-centred trials are underpowered to show equivalence at country level. Not downgraded.

4. **Risk of Bias: no serious.** Both studies were well conducted with low risk of bias. **Inconsistency: serious.** Although statistical heterogeneity was low, PCR-adjusted treatment failure was > 5% in the one study with children aged < 5 years. **Indirectness: serious.** The two trials were conducted in children aged 3 months–12 years in study sites in Africa and Asia. In both trials, only 152 children aged < 5 years received artesunate + pyronaridine, and only 115 children in total were randomized to artesunate + pyronaridine in Asia. Further, adequately powered studies in children in Africa and adults and children in Asia would be needed to generalize this result. **Imprecision: no serious.** No substantial difference found between the two ACTs; however, these multi-centred trials are underpowered to show equivalence at country level. Not downgraded.

Clinical Question/ PICO

Population: People with uncomplicated falciparum malaria (malaria-endemic areas in Africa and Asia)
Intervention: Artesunate + pyronaridine once daily for 3 days
Comparator: Artesunate + mefloquine once daily for 3 days

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Artesunate + pyronaridine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Treatment failure on day 28 (PCR-unadjusted)	Relative risk 0.35 (CI 95% 0.17 — 0.73) Based on data from 1,200 participants in 1 studies. (Randomized controlled)	40 per 1000 Difference:	14 per 1000 **26 fewer per 1000** (CI 95% 33 fewer — 11 fewer)	Moderate Due to serious indirectness [1]	
Treatment failure on day 28 (PCR-adjusted)	Relative risk 0.38 (CI 95% 0.14 — 1.02) Based on data from 1,187 participants in 1 studies. (Randomized controlled)	20 per 1000 Difference:	8 per 1000 **12 fewer per 1000** (CI 95% 17 fewer — 0 fewer)	Moderate Due to serious indirectness [2]	
Treatment failure on day 42 (PCR-unadjusted)	Relative risk 0.86 (CI 95% 0.57 — 1.31) Based on data from 1,146 participants in 1 studies. (Randomized controlled)	80 per 1000 Difference:	69 per 1000 **11 fewer per 1000** (CI 95% 34 fewer — 25 more)	Moderate Due to serious indirectness [3]	
Treatment failure on day	Relative risk 1.64 (CI 95% 0.89 — 3)	40 per 1000	66 per 1000	Low Due to serious	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Artesunate + pyronaridine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
42 (PCR-adjusted)	Based on data from 1,116 participants in 1 studies. (Randomized controlled)	Difference:	**26 more per 1000** (CI 95% 4 fewer — 80 more)	indirectness [4]	

1. **Risk of Bias: no serious.** This study was well conducted with low risk of bias. **Inconsistency: no serious.** Not applicable, as only one trial. **Indirectness: serious.** Of the 1271 children and adults aged > 5 years enrolled in this study, 81.3% (1033) were enrolled and treated in study sites in Asia (Cambodia, India, Thailand, Viet Nam) and only 18.7% (237) in Africa (Burkina Faso, Côte d'Ivoire, United Republic of Tanzania). Further studies in African children are necessary to generalize this result. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis is adequately powered; however, this multi-centred trial is underpowered to show equivalence at country level. Not downgraded.
2. **Risk of Bias: no serious.** This study was well conducted with low risk of bias. **Inconsistency: no serious.** Not applicable, as only one trial. **Indirectness: serious.** Of the 1271 children and adults aged > 5 years enrolled in this study, 81.3% (1033) were enrolled and treated in study sites in Asia (Cambodia, India, Thailand, Viet Nam) and only 18.7% (237) in Africa (Burkina Faso, Côte d'Ivoire, United Republic of Tanzania). Further studies in African children are necessary to generalize this result. **Imprecision: no serious.** No clinically important differences found between ACTs; however, this multi-centred trial is underpowered to show equivalence at country level. Not downgraded.
3. **Risk of Bias: no serious.** This study was well conducted with low risk of bias. **Inconsistency: no serious.** Not applicable, as only one trial. **Indirectness: serious.** Of the 1271 children and adults aged > 5 years enrolled in this study, 81.3% (1033) were enrolled and treated in study sites in Asia (Cambodia, India, Thailand, Viet Nam) and only 18.7% (237) in Africa (Burkina Faso, Côte d'Ivoire, United Republic of Tanzania). Further studies in African children are necessary to generalize this result. **Imprecision: no serious.** No clinically important differences found between ACTs; however, this multi-centred trial is underpowered to show equivalence at country level. Not downgraded.
4. **Risk of Bias: no serious.** This study was well conducted with low risk of bias. **Inconsistency: no serious.** Not applicable, as only one trial. **Indirectness: serious.** Of the 1271 children and adults aged > 5 years enrolled in this study, 81.3% (1033) were enrolled and treated in study sites in Asia (Cambodia, India, Thailand, Viet Nam) and only 18.7% (237) in Africa (Burkina Faso, Côte d'Ivoire, United Republic of Tanzania). Further studies in African children are necessary to generalize this result. **Imprecision: no serious.** No clinically important differences found between ACTs; however, this multi-centred trial is underpowered to show equivalence at country level. Not downgraded.

Clinical Question/ PICO

Population: People with uncomplicated falciparum malaria (high- and low-transmission settings for P. falciparum and P. vivax malaria)

Intervention: Pyronaridine alone or with an artemisinin derivative

Comparator: Another antimalarial drug

Outcome Timeframe	**Study results and measurements**	**Comparator** Comparator antimalarial	**Intervention** Pyronaridine alone or with artesunate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Elevated alanine aminotransaminase activity (Grade 3, 4 toxicity)	Relative risk 4.17 (CI 95% 1.38 — 12.61) Based on data from 3,523 participants in 4 studies. (Randomized controlled)	2 per 1000 Difference:	8 per 1000 **6 more per 1000** (CI 95% 1 more — 23 more)	**Moderate** Due to serious indirectness [1]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Comparator antimalarial	**Intervention** Pyronaridine alone or with artesunate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Elevated aspartate aminotransferase activity (Grade 3, 4 toxicity)	Relative risk 4.08 (CI 95% 1.17 — 14.26) Based on data from 3,528 participants in 4 studies. (Randomized controlled)	2 per 1000 Difference:	8 per 1000 **6 more per 1000** (CI 95% 0 fewer — 27 more)	Moderate Due to serious indirectness [2]	
Elevated alkaline phosphatase activity (Grade 3, 4 toxicity)	Relative risk 0.62 (CI 95% 0.15 — 2.51) Based on data from 2,606 participants in 3 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 3 more)	Moderate Due to serious indirectness [3]	
Elevated bilirubin (Grade 3, 4 toxicity)	Relative risk 1.92 (CI 95% 0.59 — 6.24) Based on data from 3,067 participants in 3 studies. (Randomized controlled)	3 per 1000 Difference:	6 per 1000 **3 more per 1000** (CI 95% 1 fewer — 16 more)	Low Due to serious indirectness and serious imprecision [4]	

1. **Risk of Bias: no serious.** The studies were well conducted, although the data analysis was not clearly independent of the drug manufacturer in three of the studies. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only 232 children aged < 5 years were included in these trials. **Imprecision: no serious.** The 95% CI is wide, and there are few events. Larger trials would be necessary for the group to have full confidence in this result, but it was not downgraded.
2. **Risk of Bias: no serious.** The studies were well conducted, although the data analysis was not clearly independent of the drug manufacturer in three of the studies. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only 232 children aged < 5 years were included in these trials. **Imprecision: no serious.** The 95% CI is wide, and there are few events. Larger trials would be necessary for the group to have full confidence in this result, but it was not downgraded.
3. **Risk of Bias: no serious.** The studies were well conducted, although the data analysis was not clearly independent of the drug manufacturer in three of the studies. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only 232 children aged < 5 years were included in these trials. **Imprecision: no serious.** The 95% CI is narrow and probably excludes clinically important differences.
4. **Risk of Bias: no serious.** The studies were well conducted, although the data analysis was not clearly independent of the drug manufacturer in three of the studies. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only 232 children aged < 5 years were included in these trials. **Imprecision: serious.** The 95% CI is wide and includes no difference in clinically important effects.

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)	**Plain language summary**
Treatment failure on day 28 (PCR-unadjusted)	Relative risk 1.54 (CI 95% 0.27 — 8.96) Based on data from 297 participants in 2 studies. (Randomized controlled)	10 per 1000 Difference:	15 per 1000 **5 more per 1000** (CI 95% 7 fewer — 80 more)	Very low Due to serious indirectness and very 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. **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.
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. **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.
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.

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)	**Plain language summary**
Treatment failure on day 28 (PCR-unadjusted)	Relative risk Based on data from 143 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000 CI 95% 0 fewer —	**Very low** Due to serious indirectness and very serious imprecision [1]	
Treatment failure on day 28 (PCR-adjusted)	Relative risk Based on data from 143 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000 CI 95% 0 fewer —	**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	**Very low** Due to serious indirectness and very serious imprecision [3]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Dihydroartemisinin + piperaquine	**Intervention** Artemisinin + naphthoquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			fewer — 158 more)		
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	Relative risk Based on data from 144 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000 CI 95%	**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 CI 95%	**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. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **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.
2. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **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.
3. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **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.
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. **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. **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. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **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.
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. **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.

5.2.2. 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)	**Plain language 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*

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)	**Plain language summary**
Gametocytaemia 7 days	Relative risk 0.74 (CI 95% 0.58 — 0.93) Based on data from 1,260 participants in 4 studies. (Randomized controlled)	20 per 1000 Difference:	15 per 1000 **5 fewer per 1000** (CI 95% 8 fewer — 1 fewer)	**High** [4]	
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. **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.
2. **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.
3. **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.
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.

5.2.3. Dosing of ACTS

5.2.4. Recurrent falciparum malaria

5.2.5. 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)	**Plain language 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** ACT	**Intervention** ACT + primaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
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 haemoglobin (Hb) [7]	Based on data from: 101 participants in 1 studies. (Randomized controlled)			**Low** Due to very serious indirectness [8]	ACT: 15% mean drop in Hb from baseline in the control group. ACT + primaquine: Mean drop in Hb from baseline in the intervention groups was 3% lower (10% lower to 4% higher).

1. 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.
3. AUC estimates (log10 AUC for days 1–43) are included as footnotes for each dosing stratum.
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.
5. AUC estimates (log10 AUC for days 1–43) are included as footnotes for each dosing stratum.
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.

5.3. Treating special risk groups

5.3.1. Pregnant and lactating women

5.3.2. Young children and infants

5.3.3. Patients co-infected with HIV

5.3.4. Non-immune travellers

5.3.5. Uncomplicated hyperparasitaemia

5.4. Treating 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)	**Plain language summary**
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	290 per 1000	160 per 1000	Moderate Due to serious	

Outcome Timeframe	**Study results and measurements**	**Comparator** Chloroquine	**Intervention** ACT	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	participants in 2 studies. (Randomized controlled)	Difference:	**130 fewer per 1000** (CI 95% 165 fewer — 87 fewer)	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]	
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. **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.
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.

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)	**Plain language summary**
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]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Alternative ACT	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
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.

Clinical Question/ PICO

Population: People with P. vivax malaria
Intervention: Primaquine (0.25 mg/kg bw) for 14 days plus chloroquine (25 mg/kg bw for 3 days)
Comparator: Chloroquine alone (25 mg/kg bw for 3 days)

Outcome Timeframe	**Study results and measurements**	**Comparator** No primaquine	**Intervention** Primaquine 14 days	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
P. vivax relapse defined as reappearance of P. vivax parasitaemia > 30 days after starting primaquine	Relative risk 0.6 (CI 95% 0.48 — 0.75) Based on data from 1,740 participants in 10 studies. (Randomized controlled)	80 per 1000 Difference:	48 per 1000 **32 fewer per 1000** (CI 95% 42 fewer — 20 fewer)	**High** [1]	
Serious adverse events	Based on data from: 1,740 participants in 10 studies. (Randomized controlled)	No adverse events reported in either group. Relative effect cannot be estimated.			
Other adverse events	Based on data from: 1,740 participants in 10 studies. (Randomized controlled)	No adverse events reported in either group. Relative effect cannot be estimated.			

1. **Risk of Bias: no serious.** No serious study limitations: Three studies were at high risk of bias; however, they contributed only 15.5% weight to the pooled effect estimates, and their removal from the sensitivity analysis did not alter the results appreciably. **Inconsistency: no serious.** Results were consistent within subgroups based on duration of follow-up < 6 months or > 6 months and whether treatment was supervised or not; the I2 value for the pooled effect estimate from the 10 trials was 30%. **Indirectness: no serious.** The trials included children and were done in transmission settings and countries representative of the vivax malaria burden. The outcome used was the best estimate currently available in the absence of widely available validated molecular techniques to differentiate relapse from new infections. **Imprecision: no serious.** The upper and lower limits of the 95% CI of the pooled relative risk indicate appreciable benefit with chloroquine + primaquine for 14 days. The total number of events was < 300, but the total sample size was larger than the optimal information size, given the magnitude of risk reduction.

Clinical Question/ PICO

Population: People with P. vivax malaria
Intervention: Primaquine (0.25 mg/kg bw) for 14 days plus chloroquine (25 mg/kg bw for 3 days)
Comparator: Primaquine (0.25 mg/kg bw) for 7 days plus chloroquine alone (25 mg/kg bw for 3 days)

Outcome Timeframe	**Study results and measurements**	**Comparator** 7 days primaquine	**Intervention** 14 days primaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
P. vivax relapse defined as reappearance of	Relative risk 0.45 (CI 95% 0.25 — 0.81) Based on data from 126	420 per 1000	189 per 1000	**Low** Due to serious indirectness and	

Outcome Timeframe	**Study results and measurements**	**Comparator** 7 days primaquine	**Intervention** 14 days primaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
P. vivax parasitaemia > 30 days after starting primaquine	participants in 1 studies. (Randomized controlled)	Difference:	**231 fewer per 1000** (CI 95% 315 fewer — 80 fewer)	serious imprecision [1]	
Severe adverse events	Based on data from: 126 participants in 1 studies. (Randomized controlled)	No adverse events reported in either group. Relative effect cannot be estimated.			
Other adverse events	Based on data from: 126 participants in 1 studies. (Randomized controlled)	No adverse events reported in either group. Relative effect cannot be estimated.			

1. **Indirectness: serious.** The trial authors did not include children < 15 years. Another trial in the same area by the same group of investigators immediately afterwards included children. The results for 3 days of primaquine versus 14 days of primaquine did not differ in children from that in adults. Duration of follow-up was 2 months. While this ensures detection of early relapse, it does not cover relapses after 2 months. The relapse rates at 6 months showed that most relapses occur by 2 months. The effects of 7 days of primaquine were assessed in only one trial. We therefore downgraded the evidence by 1. **Imprecision: serious.** Although the upper and lower limits of the 95% CI of the risk ratio in this trial showed statistically significant, clinically appreciable benefit with 14 days of primaquine over 7 days of primaquine, the total number of events was 38 and the sample size of the trial was 104. This is lower than the optimal information size. We downgraded the evidence by 1.

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)	**Plain language summary**
Clinical malaria	Relative risk		CI 95%		
P. vivax parasitaemia	Relative risk 0.02 (CI 95% 0 — 0.26) Based on data from 951	**70** per 1000	**1** per 1000	**Moderate** Due to serious	

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Chloroquine prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	participants in 1 studies. (Randomized controlled)	Difference:	**69 fewer per 1000** (CI 95% 70 fewer — 52 fewer)	imprecision [1]	
Severe anaemia in third trimester	Relative risk		CI 95%		
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.

5.5. Treating severe malaria

5.5.1. 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)	**Plain language summary**
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]	
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 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 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 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)	**Plain language summary**
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%		

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artesunate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
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.

5.5.2. 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)	**Plain language summary**
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)	**Plain language summary**
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)	**Plain language summary**
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]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
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.

5.5.3. 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)	**Plain language summary**
All-cause mortality (in	Relative risk 0.44 (CI 95% 0.23 — 0.82)	31 per 1000	14 per 1000	**Low** Due to serious	

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Rectal artesunate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Asia) 7-30 days	Based on data from 2,010 participants in 1 studies. (Randomized controlled)	Difference:	**17 fewer per 1000** (CI 95% 24 fewer — 6 fewer)	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)	**Plain language summary**
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.

5.6. Other considerations in treating malaria

5.6.1. Management of malaria cases in special situations

5.6.2. Quality of antimalarial drugs

5.6.3. Monitoring efficacy and safety of antimalarial drugs and resistance

5.7. National adaptation and implementation