WHO GUIDELINES

for malaria

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World Health Organization

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4 - PREVENTION

4.1 - Vector control

4.1.1 - Interventions recommended for large-scale deployment

Insecticide-treated nets (2019)

Pyrethroid-only nets

Pyrethroid-only long-lasting insecticidal nets (LLINs) prequalified by WHO are recommended for deployment in all malaria-endemic settings.

Strong recommendation, high-certainty evidence

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).

Pyrethroid-PBO nets (2019)

Pyrethroid-PBO nets prequalified by WHO are conditionally recommended for deployment instead of pyrethroid-only ITNs 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.

Conditional recommendation, moderate certainty evidence

Remark: WHO recommends pyrethroid-PBO nets that have been prequalified by WHO for areas where resistance in the principal malaria vector(s) 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.

Pyrethroid-PBO nets combine pyrethroids and a synergist, which acts by inhibiting certain metabolic enzymes within the mosquito before they can have a toxic effect . 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.

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

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 such as through antenatal care clinics (ANC) and the expanded programme on immunization (EPI).

Recipients of ITNs should be advised (through appropriate communication strategies) to continue using their nets beyond the 3-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)

Old ITNs should only be collected where there is assurance that: i) communities are not left uncovered, 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.

Recipients of ITNs should 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).

Good practice statement

Indoor residual spraying (2019)

IRS deploying a product prequalified by WHO is recommended in most malaria-endemic settings. DDT has not been prequalified; it 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.

Strong recommendation, low-certainty evidence

Remark: WHO recommends IRS with a product that has been prequalified by WHO for 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 considered an appropriate intervention where:

- the majority of the vector population feeds and rests inside houses;
- 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.

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.

Good practice statement

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4.1.2 - Combining ITNs and IRS

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

Priority should 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.

Conditional recommendation against combining the core interventions to reduce morbidity and mortality, moderate-certainty evidence

Remark: In settings where there is optimal ITN coverage as specified in the strategic plan has been achieved and where these 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.

Considering combination once optimal coverage has been achieved (2019)

Once optimal coverage with either ITNs or IRS has been achieved, programmes may consider deploying the other intervention as an approach to prevent, manage and mitigate insecticide resistance. The ITN and IRS products selected for co-deployment must not contain the same insecticide class(es). For instance, IRS with a pyrethroid should not be deployed in the same households or areas as ITNs. The decision to deploy a second vector control intervention should only be taken after conducting a prioritization analysis across malaria interventions, not just vector control, to ensure maximum impact of any additional resources.

Good practice statement

Considering supplementary interventions once optimal coverage of ITNs or IRS has been achieved (2019)

Once optimal coverage with either ITNs or IRS has been achieved, recommended supplementary interventions with proven public health value may be deployed in specific settings and circumstances.

Good practice statement

Remark: The decision to deploy a supplementary vector control intervention should only be taken after conducting a prioritization analysis across malaria interventions, not just vector control, to ensure maximum impact of any additional resources.

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

In areas with ongoing local malaria transmission (irrespective of both the preintervention and current level of transmission), 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.

Good practice statement

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Scale-back in areas where transmission has been interrupted (2019)

Countries and partners should invest in health systems, particularly in the strengthening of disease and entomological surveillance, to be able to identify potential areas for geographical scale-back as well as having the capacity for timely detection and appropriate response to a potential resurgence of malaria.

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

Good practice statement

4.1.3 - Supplementary interventions

Larviciding (2019)

The regular application of biological or chemical insecticides to water bodies (larviciding) is recommended for malaria prevention and control 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.

Conditional recommendation, low-certainty evidence

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 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.

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.

Larvivorous fish (2019)

No recommendation can be made because evidence on the effectiveness (or harms) of larvivorous fish was not identified.

Topical repellents (2019)

Deployment of topical repellents for malaria prevention at the community level is not recommended; however, topical repellents may be beneficial as an intervention to provide personal protection against mosquito bites.

Conditional recommendation against deployment, low-certainty evidence

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 there is no significant impact on malaria when the intervention is deployed at community-level due to the high level of individual compliance needed.

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Insecticide-treated clothing (2019)

Deployment of insecticide-treated clothing for malaria prevention at the community level is not recommended; however, insecticide-treated clothing may be beneficial as an intervention to provide protection against malaria in specific population groups.

Conditional recommendation against deployment, low-certainty evidence

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 on the deployment of spatial/airborne repellents in the prevention and control of malaria can be made until ongoing studies assessing malaria epidemiological outcomes have been completed.

Space spraying (2019)

Space spraying should not be undertaken for malaria control, and IRS or ITNs should be prioritized instead.

Conditional recommendation against deployment, very low-certainty evidence

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)

Intermittent preventive treatment in pregnancy (2015)

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.

Strong recommendation, high-certainty evidence

4.2.2 - Intermittent preventive treatment of malaria in infants (IPTi)

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Intermittent preventive treatment in infants (2015)

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.

*Strong recommendation**

*unGRADEd recommendation, anticipated to be updated in 2021

4.2.3 - Seasonal malaria chemoprevention (SMC)

Seasonal malaria chemoprevention (2015)

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.

Strong recommendation, high-certainty evidence

5 - CASE MANAGEMENT

5.1 - Diagnosing malaria (2015)

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.

Good practice statement

5.2 - Treating uncomplicated malaria

5.2.1 - Artemisinin-based combination therapy

Treating uncomplicated *P. falciparum* malaria (2015)

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).

Strong recommendation, high-certainty evidence

- artesunate + pyronaridine (currently unGRADEd)

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 *[99]* 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

Treating uncomplicated *P. falciparum* malaria (2015)

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

Strong recommendation, high-certainty evidence

5.2.3 - Dosing of ACTS

Treating uncomplicated *P. falciparum* malaria (2015)

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.

Strong recommendation*

*unGRADEd recommendation, anticipated to be updated in 2021

5.2.4 - Recurrent falciparum malaria

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

Treating uncomplicated *P. falciparum* malaria (2015)

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.

Strong recommendation, low-certainty evidence

5.3 - Treating special risk groups

5.3.1 - Pregnant and lactating women

First trimester of pregnancy (2015)

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

*Strong recommendation**

*unGRADEd recommendation, anticipated to be updated in 2021

5.3.2 - Young children and infants

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.

*Strong recommendation**

*unGRADEd recommendation, anticipated to be updated in 2021

5.3.3 - Patients co-infected with HIV

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.

Good practice statement

5.3.4 - Non-immune travellers

Non-immune travellers (2015)

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

Strong recommendation, high-certainty evidence

5.3.5 - Uncomplicated hyperparasitaemia

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.

Good practice statement

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

Blood stage infection (2015)

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

Good practice statement

Blood stage infection (2015)

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, high-certainty evidence

Blood stage infection (2015)

Treat pregnant women in their first trimester who have chloroquine-resistant *P. vivax* malaria with quinine.

Strong recommendation, very low-quality evidence

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

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

Good practice statement

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

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.

Strong recommendation, high-certainty evidence

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

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.

Conditional recommendation, very low-certainty evidence

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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.

Good practice statement

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

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.

Conditional recommendation, moderate-certainty evidence

5.5 - Treating severe malaria

5.5.1 - Artesunate

Treating severe malaria (2015)

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, high-certainty evidence

Revised dose recommendation for parenteral artesunate in young children (2015)

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.

Strong recommendation based on pharmacokinetic modelling*

*unGRADEd recommendation, anticipated to be updated in 2021

5.5.2 - Parenteral alternatives when artesunate is not available

Parenteral alternatives where artesunate is not available (2015)

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

Conditional recommendation, low-certainty evidence

5.5.3 - Pre-referral treatment options

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Treating cases of suspected severe malaria pending transfer to a higher- level facility (pre-referral treatment) (2015)

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.

Strong recommendation, moderate-certainty evidence

5.6 - Chemoprevention in special risk groups

5.7 - Other considerations in treating malaria

5.7.1 - Management of malaria cases in special situations

5.7.2 - Quality of antimalarial drugs

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.

Good practice statement

5.7.3 - Monitoring efficacy and safety of antimalarial drugs and resistance

Monitoring the efficacy of antimalarial drugs (2015)

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

Good practice statement

5.8 - National adaptation and implementation

National adaptation and implementation (2015)

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

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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.

Good practice statement

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1 - 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 normative processes *[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 policy makers to adopt and adapt strategies which 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 following the availability of new evidence. Users can access the research evidence and evidence to decision tables that informed the recommendation by using the tabs below each 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.

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

In certain situations, good practice statements may be provided. These statements reflect consensus of the guidelines development group that the benefits of adherence to the statement are large and unequivocal, and may not necessarily be supported by a systematic evidence review.

The primary purpose for these WHO guidelines is to support the 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, 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 UN and other procurement agencies in 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.

Use of strategic information to drive impact
Clear evidence-informed recommendations are a critical component to support the development of national malaria strategic plans, and 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 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 to inform global knowledge.

WHO also develops implementation guidance such as operational and field manuals to support the "how" to deliver the recommended tools and strategies. Operational manuals and other guidance are practical information to increase access of interventions to the target population and will be linked to these Guidelines moving forward. 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 this 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 is done.

Evidence base
These Guidelines are based on analyses and grading of available

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evidence. Systematic reviews and the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach enable development of the evidence to decision framework for each recommendation *[2]*. The strength of each recommendation reflects the quality of the evidence, as well as additional factors relating to the harms and benefits of the intervention.

For areas where evidence is currently weak or absent, the development of guidance may rely on expert opinion. 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 Guidelines Development Group 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 Guidelines are presented in Section 10: Contributors and interests.

Updating evidence-based guidance

The first iteration of this consolidated guideline was released in early 2021 as a compilation of the existing recommendations. At the same time, a set of parallel processes of reviewing and, where appropriate, updating the evidence syntheses and recommendations based upon them has been ongoing, ensuring that the guidelines remain up to date and incorporate the latest evidence.

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. From this point forward, 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 will be translated into three languages (French, 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 labeled 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 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.

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2 - 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 229 000 cases and 409 000 deaths globally in 2019. 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 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, the strategy defines goals, milestones and targets on the path to a world free of malaria (Table 1). The goals focus attention both on the need to reduce morbidity and mortality, as well as to progressively eliminate malaria from countries that had malaria transmission in 2015. The GTS presents a framework through which the goals can be achieved (Figure 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 *Global technical strategy for malaria 2016 - 2030* [4] states that it is essential for malaria programmes to 'ensure access to malaria prevention, diagnosis and treatment as part of universal health coverage' (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 communitieis are covered by the appropriate mix of these interventions, based on local context, to control and ultimately, eliminate malaria.

The principal objective of national malaria programmes 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.

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

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", 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 ensuring continued progress with 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 recommendations on the appropriate choice(s) for malaria prevention (vector control and chemotherapies) and case management (diagnosis and

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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.

Target audience

The primary audience for these guidelines is the policy makers in ministries of health and the managers of national malaria control programmes 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 in support of interventions and procurement of appropriate malaria control products. They are also 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.

Scope

The consolidated *WHO Guidelines for malaria* bring together all recommendations for malaria, including prevention using vector control and preventive chemotherapy, 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 *[6]*.

Structure of the Guidelines

The guidelines are organized around the major interventions available for malaria: prevention (vector control and preventive chemotherapies), case management (diagnosis and treatment), and strategies to be used in elimination settings. Although guidance on surveillance, monitoring and evaluation is not generated using the same methodology as other recommendations, it is an important source of information on approaches to optimize implementation and can be accessed through links for ease of reference. The Guidelines are structured as follows:

- Section 1. Executive Summary
- Section 2. Introduction
- Section 3. Abbreviations
- Section 4. Prevention: recommendations and practice statements for prevention strategies including vector control and preventive chemotherapies.
- Section 5. Case Management: recommendations and practice statements for diagnosing malaria; treating uncomplicated malaria; treating special risk groups; treating uncomplicated malaria caused by *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi*; and treating severe malaria. Also included is information for treating malaria in special situations (e.g. epidemics and humanitarian emergencies and elimination settings) and other considerations in treating malaria.
- Section 6. Elimination: recommendations and practice statements for implementation in elimination settings (currently in development and anticipated to be published in 2021. Also includes links to the framework for malaria elimination
- Section 7. Surveillance: high level overview on surveillance and presents information on the strategic use of information for subnational stratification to drive impact and links to further resources.
- Section 8. Methods: describes the methods used to develop the recommendations and practice statements.
- Section 9. Glossary: defines commonly used terms for malaria control and elimination and links to the WHO publication on malaria terminology.
- Section 10. Contributors and interests: presents the many contributors to the development of this guideline and their declared interests.

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 > 0 but < 1%.

The relation between parasite incidence, parasite prevalence and the number of cases presenting to a health facility per week can be estimated in models *[9]*. Differences in transmission from one

area to another may be due to geographical characteristics, such as altitude, temperature and 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 seen, 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 3- or 4-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. In contrast, in these settings adolescents and adults are partially immune and suffer clinical disease much less frequently, although they often are 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.

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 program decisions about 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 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 which every program 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, that define strata-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 national malaria programmes 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 program 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.

3 - ABBREVIATIONS

ACT	artemisinin-based combination therapy		LSM	larval source management
ANC	antenatal care		MPAG	Malaria Policy Advisory Group *(previously Malaria Policy Advisory Committee)*
bw	body weight		NAAT	nucleic acid amplification test
CI	confidence interval		PBO	piperonyl butoxide
CIDG	Cohrane Infectious Diseases Group		PCR	polymerase chain reaction
DPT	diphtheria, tetanus and pertussis (vaccine)		*Pf*HRP2	*Plasmodium falciparum* histidine-rich protein-2
EIR	entomological inoculation rate		PICO	population, participants or patients; intervention or indicator; comparator or control; outcome
EPI	expanded programme on immunization		PQ	prequalification (WHO)
GMP	Global Malaria Programme		*p*LDH	*parasite*-lactate dehydrogenase
GRADE	Grading of Recommendations Assessment, Development and Evaluation		*Pvdhfr*	*Plasmodium vivax* dihydrofolate reductase gene
GTS	*Global technical strategy for malaria (2016 - 2030)*		RCT	randomized controlled trial
G6PD	glucose-6-phosphate dehydrogenase		RDT	rapid diagnostic test
HRP2	histidine-rich protein 2		RR	relative risk, or risk ratio
IPTi	intermittent preventive treatment in infants		SP	sulfadoxine–pyrimethamine
IPTp	intermittent preventive treatment in pregnancy		SP + AQ	sulfadoxine-pyrimethamine + amodiaquine
IRM	insecticide resistance management		SMC	seasonal malaria chemoprevention
IRS	indoor residual spraying		TES	therapeutic efficacy studies
IOS	International Organization for Standardization		VCAG	Vector Control Advisory Group
ITNs	insecticide-treated nets		VCTEG	Technical Expert Group on Malaria Vector Control
ITPS	insectidie-treated plastic sheeting		WHO	World Health Organization
IVM	integrated vector management			
LLIN	long-lasting insecticidal net			

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., proven protective efficacy to reduce or prevention 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 and their behaviour and distribution

Malaria is transmitted through the bites of infective female *Anopheles* mosquitoes. There are more than 400 different species of *Anopheles* mosquito, 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, data collected on behaviour, distribution and infection rates for decision-making by control programmes will have limited use.

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 towards 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 over recent years, largely as a result of population growth and the need to swtich to more expensive tools, increasing 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 *P. falciparum* in endemic Africa was halved and the incidence of clinical disease fell by 40% [14]. Malaria control interventions averted an estimated 663 (credible interval (CI) 542–753) million clinical cases in Africa, with ITNs making the largest contribution (68% of cases averted). IRS contributed an estimated 13% (11–16%), with a larger proportional contribution where intervention coverage was high [13].

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 4 pillars that are underpinned by 2 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

Foundation
- 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), indoor residual spraying (IRS) against malaria and leishmaniasis in India, and larval control for malaria and dengue vectors in cities with particular vector

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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 on 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 eventually 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]. Latest data revealed that almost 90% of malaria endemic countries that report insecticide resistance have detected resistance of their vectors to at least 1 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, being 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 insecticise 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].

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. 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 ITNs.
- IRM principles and methods should be incorporated into all vector control programmes, not as an option, but as a core component of programme design.
- The agricultural sector should try to avoid using classes of insecticide that are widely used for public health and should collaborate with vector control authorities in an intersectoral approach.
- Routine monitoring of insecticide resistance is essential to inform the selection and deployment of insecticides.
- The short-term additional costs of IRM should be balanced against the long-term potential public health impact and potential costs of insecticide resistance.

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.

In the agricultural industry, some success in managing resistance has been through the use of different insecticides over space and time, and 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 their success for malaria vector control and the success of these strategies are likely to depend on mosquito genetics, as well as their behaviour and population dynamics, and the chemical nature of the insecticides and their formulation. These 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 that the presence of resistance to all insecticides in the mixture is rare, so that any individual 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 LLINs. An ITN product

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containing a pyrethroid and a pyrrole insecticide and another containing a pyrethroid and a juvenile hormone mimic have been developed and prequalified by WHO [20]. WHO will require data on the epidemiological impact of these products to enable assessment of their public health value and 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 of 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 will 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 [21]. 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, [22] and to improve understanding of the biological mechanisms that are likely to favour different approaches in different situations [23][24].

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* [25]. Detailed information on insecticide resistance monitoring methods and on how to use the data to inform 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 these are supported by WHO recommendations and have been 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 [26].

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 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 [26]. 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 EIRs and case importation rates, and lower coverage of active case detection and case management [27].

During the pre-elimination and elimination phases, 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 [28].

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 "effective 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 that 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. 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. 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

insecticide-treated nets (ITNs) that are prequalified by WHO, which in many settings continue to be long-lasting insecticidal nets (LLINs); and ii) indoor residual spraying (IRS) with a product prequalified by WHO. Supplementary interventions may be considered for deployment in addition to ITNs or IRS depending on the specifics of the settings.

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 local data available to guide stratification of interventions, the available funding, the relative cost-effectiveness of the available intervention options, the resources that would be 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.

WHO encourages programmes to undertake a resource prioritization exercise to develop context specific intervention mixes and then aim to achieve the optimal coverage levels identified as being financially and programmatically feasible.

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 maximise use, and ensuring timely replacement; or providing these populations with the 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 quantification of commodities to provide full access by the population at risk while realizing that this will not result in either 100% coverage or 100% access due to various systems inefficiences. Being cognisant 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.

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. In this context, WHO recommends: i) deployment of ITNs that are prequalified by WHO, and ii) IRS with a product prequalified by WHO. The exception to this is dichlorodiphenyltrichloroethane (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 [29].

Insecticide-treated nets (ITNs)
WHO recommends ITNs – which in many settings continue to be long-lasting insecticidal nets (LLINs) – 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. An ITN repels, disables or kills mosquitoes that come into contact with the insecticide on the netting material thereby protecting the individual user. ITNs can produce a "community effect" whereby even members of the community who do not sleep under a net gain some protection due to the effect of the treated nets on mosquito longevity (and therefore vectorial capacity). Large-scale field trials [30][31] and transmission models [32][33] suggest that absolute coverage of ≥50% of effectively treated nets is expected to result in community-wide protection of non-users

in most settings and that, within these, further gains are realized as coverage increases. A community effect of ITNs has, however, not been observed in all settings [34][35]. WHO GMP has initiated a systematic review of the evidence base on the "community effect" of ITNs to further investigate observed presence/absence of this effect depending on contextual factors and study designs, as well as the relationship between coverage and community-level impact in different transmission settings where this effect has been observed.

Three main ITN classes are recognized a WHO:
- ITNs designed to kill host-seeking insecticide-susceptible mosquito populations that have demonstrated publich 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 including both conventionally treated nets that rely on periodic re-treatment by dipping nets into an insecticide formulation, and factory-treated LLINs made of netting material with insecticide incorporated within or bound around the fibres. LLINs are defined as retaining their effective biological activity for at least 20 WHO standard washes under laboratory conditions and 3 years of recommended use under field conditions.
- ITNs designed to kill host-seeking insecticide-resistant mosquitoes and for which a first-in-class product has demonstrated public health value compared to the

epidemiological impact of pyrethroid-only nets. This class includes nets that are treated with insecticides other than pyrethroid-based formulations and those with a pyrethroid insecticide and a synergist such as piperonyl butoxide (PBO).

- ITNs designed to sterilize and/or reduce the fecundity of host-seeking insecticide-resistant mosquitoes for which a first-in-class product has demonstrated public health value compared to the epidemiological impact of pyrethroid-only nets. This class is provisionally thought to include pyrethroid + pyriproxyfen nets and will be created once the public health value of a first-in-class ITN product containing an insect growth regulator has been demonstrated.

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 (though hanging nets in direct sunlight should be avoided, as sunlight can affect insecticidal activity).

Indoor residual spraying (IRS)

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.

Insecticide-treated nets (2019)

> ### Pyrethroid-only nets
>
> Pyrethroid-only long-lasting insecticidal nets (LLINs) prequalified by WHO are recommended for deployment in all malaria-endemic settings.
>
> <div style="background:green">*Strong recommendation, high-certainty evidence*</div>
>
> *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).*

Evidence To Decision

> #### Benefits and harms
>
> - ITNs significantly reduce all-cause child mortality, malaria mortality, *P. falciparum* incidence and prevalence, and incidence of severe 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
>
> 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.

Resources and 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 [36] followed the original 2003 analysis which included insecticide-treated curtains and ITNs together and includes 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 if the effects were different and the results from studies evaluating insecticide-treated curtains were consistent with the results of those evaluating ITNs. The Guidelines Development Group drew on the analysis to make recommendations related to ITNs only.

The systematic review [36] produced high certainty evidence that, compared to no nets, ITNs are effective in 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.

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') [1]. 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 VCAG. In 2017, a separate recommendation applicable to pyrethroid nets treated with a synergist ('pyrethroid-PBO nets') was formulated based on the latest available evidence [37].

Research priorities:
- Determine the effectiveness of next-generation nets and insecticides in areas where resistance to pyrethroids is high
- Generate evidence for assessing the impact of insecticide resistance on key outcomes (malaria mortality, clinical disease and prevalence of infection).
- Determine the comparative effectiveness of different net types
- Determine the effectiveness of nets in situations of residual/outdoor transmission
- Determine the role of ITN deployment in transmission 'hotspots' and elimination settings.

Pyrethroid-PBO nets (2019)

Pyrethroid-PBO nets prequalified by WHO are conditionally recommended for deployment instead of pyrethroid-only ITNs 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.

Conditional recommendation, moderate certainty evidence

WHO recommends pyrethroid-PBO nets that have been prequalified by WHO for areas where resistance in the principal malaria vector(s) 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.

Pyrethroid-PBO nets combine pyrethroids and a synergist, which acts by inhibiting certain metabolic enzymes within the mosquito before they can have a toxic effect . 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.

Evidence To Decision

Benefits and harms

- Prevalence of malaria may be decreased with pyrethroid-PBO nets compared to standard 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

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.

Resources and 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

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 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.

Epidemiological data from one cluster RCT indicated that a pyrethroid-PBO net product had additional public health value compared to a pyrethroid-only LLIN product in an area

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where the principal malaria vector(s) had confirmed pyrethroid resistance of moderate intensity conferred (at least in part) by monooxygenase-based resistance mechanism, as determined by standard procedures. On the basis of the current evidence, WHO has concluded and recommended the following:

- Based on the epidemiological findings and the need to deploy products that are effective against pyrethroid-resistant mosquitoes, pyrethroid-PBO nets are being 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 intermediate level (as defined above), 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 LLINs or IRS) will not be

reduced; the primary goal must remain the achievement and maintenance of optimal coverage for all people at risk of malaria.
- Further evidence on pyrethroid-PBO nets is required to support the refinement of WHO guidance regarding the conditions for the deployment of products in this class.
- 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.

Further details are available in the full document online [35]. The conditional recommendation will be updated based on a systematic review published in late 2018[38], once data from an ongoing second study with epidemiological outcomes have been assessed by the VCAG.

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

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 such as through antenatal care clinics (ANC) and the expanded programme on immunization (EPI).

Recipients of ITNs should be advised (through appropriate communication strategies) to continue using their nets beyond the 3-year expected lifespan of the net, irrespective of the condition and age of the net, until a replacement net is available.

Good practice statement

Justification

Achieving and maintaining universal coverage with ITNs for malaria prevention and control
In December 2017, WHO published updated recommendations on achieving and maintaining universal coverage with LLINs [39]. These recommendations were developed and revised based on expert opinion through broad consultation, including multiple rounds of reviews by the MPAG. Below, these recommendations have been summarized and slightly revised to clarify that these recommendations are not specific to LLINs, but apply to ITNs in general.

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 antenatal care (ANC)

clinics and the Expanded Programme on Immunization (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 1 ITN for every 2 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 1 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

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where the most recent population census is more than 5 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 3 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 also be justified during humanitarian emergencies, as the resulting increase in population movement may leave populations uncovered by vector control and potentially increase 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. School-based distribution should be discontinued in campaign years to avoid over-supply of ITNs. In areas where school-based distributions are operating at scale and achieve optimal coverage, these distributions may even be sufficient to replace mass distribution campaigns.

'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, and based on 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 also 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 of specific population groups at risk of malaria may also be warranted if standard nets are unlikely to suit the lifestyle of these groups, 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 behaviour change communication 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, there will be a need to

accurately track ITN coverage at the district level. Subnational responses should be triggered if coverage falls below programmatic targets. Tracking must differentiate 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).

Management of old ITNs (2019)

Old ITNs should only be collected where there is assurance that: i) communities are not left uncovered, 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.

Recipients of ITNs should 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).

Good practice statement

Justification

Currently, LLINs and the vast majority of their packaging (bags and baling materials) are made of non-biodegradable plastics [40].The large-scale deployment of LLINs 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 currently do not have the resources to manage LLIN collection and waste disposal programmes.

A pilot study was conducted to examine patterns of LLIN 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 VCTEG and MPAG on best practices with respect to managing LLIN waste.

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

- LLINs 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 but 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 LLINs 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 LLINs and other nets may be used for a variety of alternative purposes, usually due to perceived ineffectiveness of the net, loss of net physical integrity or presence of another net.
- LLINs that no longer serve a purpose are generally disposed of at the community level along with other household waste by either discarding them in the environment, burning them in the open, or placing them into pits.
- LLIN collection was not implemented on a large scale or sustained in any of the pilot study countries. It may be feasible to recycle LLINs, 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 LLINs from bags at the point of distribution and burning discarded bags and old LLINs, which can produce highly toxic fumes including dioxins, and ii) discarding old LLINs 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 LLINs 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 LLINs. Environmental regulations; leadership and guidance from national environmental authorities; and oversight from international agencies, such as the United Nations Environment Programme, are all necessary.

It is important to determine whether the environmental benefits outweigh the costs when identifying the best disposal option for old LLINs and their packaging. For malaria programmes in most endemic countries, there are limited options for dealing with the 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 LLINs, 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 LLINs 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 not yet been fully studied, the expected negative health and environmental impacts of leaving it in the community are considered less than amassing the waste 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 LLINs 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 LLINs and packing materials in the environment in collaboration with other relevant partners.

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Indoor residual spraying (2019)

IRS deploying a product prequalified by WHO is recommended in most malaria-endemic settings. DDT has not been prequalified; it 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.

> *Strong recommendation, low-certainty evidence*

WHO recommends IRS with a product that has been prequalified by WHO for 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 considered an appropriate intervention where:
- *the majority of the vector population feeds and rests inside houses;*
- *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.*

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 team to enter 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

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.

Resources and other considerations

- 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 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

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vector density and longevity and, therefore, to reduce malaria transmission. However, few RCTs have been conducted on IRS and so the availability of data suitable for use in a Cochrane-style meta-analysis is limited. The Guidelines Development Group 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. A systematic review of evidence from non-randomized studies will be undertaken to further underpin this recommendation or modify it as appropriate.

Insecticide formulations for IRS [20] fall into five major insecticide classes with three modes of action, based on their primary target site in the vector:

Sodium channel modulators
- Pyrethroids: alphacypermethrin, deltamethrin, lambda-cyhalothrin, etofenprox, bifenthrin, cyfluthrin
- Organochlorines: DDT

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 pre-qualified by WHO; as of February 2019, there were no DDT IRS formulations prequalified. The products listed have been prequalified based on 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 [42]. 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 inside houses;
- 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
Indoor residual spraying (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 [43] aims to assist malaria programme managers, entomologists and public health officers in designing, implementing and sustaining high-quality IRS programmes.

Research priorities:
- Impact of IRS in urbanized areas with changing housing designs
- Impact of IRS on insecticide-resistant populations
- Generate high-quality evidence on the impact of insecticide rotations as an insecticide resistance management tool
- Impact of IRS in different mosquito behaviour/settings (outdoor transmission)

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.

Good practice statement

Evidence To Decision

Benefits and harms

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- IRS may decrease the incidence of malaria compared to ITNs. There may be little or no difference in parasite prevalence between IRS and ITNs.
- No undesirable effects were identified in the systematic review. However, as stated under the evidence to decision table for ITNs, insecticide treated 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. Similarly, IRS may play an as yet undetermined role in insecticide resistance development in *Anopheles* vectors; it requires householders to grant permission for spray team to enter house; householders are required 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

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 Guidelines Development Group 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 insecticide-treated nets are considered to be an equally effective alternative intervention.

Resources

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, there 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 definite conclusion on their comparative effectiveness. WHO therefore currently views these two interventions as of equal effectiveness and there is no general recommendation to guide selection of one over the other. Preferences of national malaria programmes, beneficiaries or donors are usually based on operational factors, such perceived or actual implementation challenges (see Section 4.1.6.2) and the requirement for insecticide resistance prevention, mitigation and management (see Section 4 text). 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 into a prioritization process that considers the cost and effectiveness 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

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

Priority should 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.

Conditional recommendation against combining the core interventions to reduce morbidity and mortality, moderate-certainty evidence

In settings where there is optimal ITN coverage as specified in the strategic plan has been achieved and where these 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.

Evidence To Decision

Benefits and harms

- No benefit of adding IRS to areas where 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

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.

Resources and other considerations

- The degree of pyrethroid resistance and its impact on the effectiveness of 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 conducted in 2014 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 *[44]*. However, the combination of these interventions may be considered for resistance prevention, mitigation or management should sufficient resources be available (see the following text and

Section 4.1.6.2). 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.

Research priorities:
- The evidence base for combining no-pyrethroid IRS with ITNs in the context of insecticide resistance management needs to be expanded.
- The acceptability of combined interventions by householders and communities needs to be determined.
- The evidence for an impact of IRS + ITNs vs IRS only needs to be explored and synthesized.
- Correlating entomological outcomes (from experimental hut trials and cone bioassays) with epidemiological outcomes is required.
- New tools for monitoring the quality of IRS and ITN interventions are needed.

Considering combination once optimal coverage has been achieved (2019)

Once optimal coverage with either ITNs or IRS has been achieved, programmes may consider deploying the other intervention as an approach to prevent, manage and mitigate insecticide resistance. The ITN and IRS products selected for co-deployment must not contain the same insecticide class(es). For instance, IRS with a pyrethroid should not be deployed in the same households or areas as ITNs. The decision to deploy a second vector control intervention should only be taken after conducting a prioritization analysis across malaria interventions, not just vector control, to ensure maximum impact of any additional resources.

> *Good practice statement*

Justification

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 maximised. 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 4.1.6.2). Therefore, WHO guidance developed based on the 2014 review differentiated between the effect of combined interventions on malaria morbidity and mortality versus the utility of this approach in a resistance management strategy [15].

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 these remain effective, IRS may have limited utility in reducing malaria morbidity and mortality. However, IRS may be implemented as part of an insecticide resistance management (IRM) strategy in areas where there are ITNs [19].
- If ITNs and IRS are to be deployed together in the same geographical location, IRS should be conducted with a non-pyrethroid insecticide.
- 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.
- 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 monitoring and evaluation (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.

These findings and conclusions were substantiated by a systematic review of the evidence (currently under peer review) that was conducted in preparing the Guidelines [45]. However, subsequently released results from a study in one setting in Sudan showed that pyrethroid-only ITNs plus IRS

with a non-pyrethroid reduced malaria incidence to a greater extent than ITNs alone in an area with pyrethroid resistance *[17]*. An update to the systematic review will be required as additional evidence is currently being generated.

Moreover, 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.

Considering supplementary interventions once optimal coverage of ITNs or IRS has been achieved (2019)

Once optimal coverage with either ITNs or IRS has been achieved, recommended supplementary interventions with proven public health value may be deployed in specific settings and circumstances.

Good practice statement

The decision to deploy a supplementary vector control intervention should only be taken after conducting a prioritization analysis across malaria interventions, not just vector control, to ensure maximum impact of any additional resources.

Justification

Supplementary interventions such as larval source management (LSM) can 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. The VCAG on new tools, technologies and approaches is currently evaluating a number of new interventions that have the potential to address residual transmission. Implementation of supplementary interventions should be in accordance with the principles outlined in the *Global vector control response 2017–2030 [12][13]*.

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

In areas with ongoing local malaria transmission (irrespective of both the preintervention and current level of transmission), 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.

Good practice statement

Justification

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 *[26]*. 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 EIRs and case importation rates, and lower coverage of active case detection and case management

[27].

Scale-back in areas where transmission has been interrupted (2019)

Countries and partners should invest in health systems, particularly in the strengthening of disease and entomological surveillance, to be able to identify potential areas for geographical scale-back as well as having the capacity for timely detection and appropriate response to a potential resurgence of malaria.

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

Good practice statement

Justification

During the pre-elimination and elimination phases, ensuring optimal 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 [28].

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 'effective 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 ITN/LLIN.

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

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 that is a pre-condition for determining whether vector control can be scaled back (or focalized).

4.1.3 - Supplementary interventions

Larval source management (LSM)
LSM is the management of aquatic habitats (water bodies) that are potential larval habitats for mosquitoes in order to prevent the completion of development of the immature stages (eggs, larvae and pupae) and hence the production of adult mosquitoes. There are four types of LSM:

- Habitat modification: a permanent alteration to the environment, e.g. land reclamation;
- Habitat manipulation: a recurrent activity, e.g. flushing of streams;
- Larviciding: the regular application of biological or chemical insecticides to water bodies;

- Biological control: the introduction of natural predators into water bodies.

In general, environmental management (habitat modification and manipulation) should, where feasible, be the primary strategy to reduce the availability of larval habitats. However, no systematic reviews have so far been conducted to inform the development of WHO guidance in this area, and the Guidelines Development Group therefore did not consider habitat modification and manipulation in developing the 1st edition of the Guidelines. Independent systematic reviews of the available evidence on these interventions will be conducted to inform the inclusion of guidance as part of revision to the Guidelines.

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 malaria prevention 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. They 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 protective 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 the repellents seem to be major obstacles to achieving such potential impact. [47] 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. It is most often deployed in response to epidemics or outbreaks of mosquito-borne disease, such as dengue.

Housing improvements

Available evidence indicates that poor-quality housing and neglected peridomestic environments are risk factors for the transmission of malaria, arboviral diseases (e.g. dengue, yellow fever, chikungunya, Zika virus disease), Chagas disease and leishmaniasis. [48] Closing open eaves, screening doors and windows with fly screens or mosquito netting, and filling holes and cracks in walls and roofs reduce the mosquitoes' entry points into houses. Together with metal roofs, ceilings, and finished interior walls, these modifications may 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. [50] However, specific evidence-based recommendations on housing and vector-borne diseases are still needed. To this end, the WHO Department of Public Health, Environmental and Social Determinants of Health is currently developing housing and health guidelines. To support the development of these guidelines, WHO has commissioned a systematic review of housing and vector-borne diseases by the CIDG. Once available, the outcomes of this review will be presented to the Guidelines Development Group with a view to formulating evidence-based recommendations for inclusion in both the housing and the malaria vector control guidelines.

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Larviciding (2019)

The regular application of biological or chemical insecticides to water bodies (larviciding) is recommended for malaria prevention and control 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.

Conditional recommendation, low-certainty evidence

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 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.

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

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.

Resources and other considerations

Determination of whether or not specific habitats 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 conducted in 2019 on larviciding [51] 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. Larviciding is most likely to be cost-effective in urban areas where the appropriate conditions are more likely to be present. Larviciding is not

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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.

The WHO 2013 Operational manual on Larval Source Management [49] concludes that LLINs 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.

Larvivorous fish (2019)

No recommendation can be made because evidence on the effectiveness (or harms) of larvivorous fish was not 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 Guidelines Development Group 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

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

There systematic review conducted in 2017 on use of larvivorous fish [52] did not identify any studies demonstrating impact on malaria and so there is insufficient evidence to support a recommendation. The Guidelines Development Group recognizes that there are specific setting in which the intervention is currently implemented, and in these specific settings programme staff consider it to be effective. In some of the setting 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 Guidelines Development Group acknowledges that there may be data at country/programme level that it is not aware of.

Research priorities:

- Well-designed epidemiological studies (not larval density sampling) should be conducted in areas where

programmes include larvivorous fish in order to   generate an evidence base.

Topical repellents (2019)

Deployment of topical repellents for malaria prevention at the community level is not recommended; however, topical repellents may be beneficial as an intervention to provide personal protection against mosquito bites.

Conditional recommendation against deployment, low-certainty evidence

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 there is no significant impact on malaria 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

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.

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 *[53]* 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 priorities:

- Investigations of the potential public health value of topical repellents in specific settings and target populations.

Insecticide-treated clothing (2019)

Deployment of insecticide-treated clothing for malaria prevention at the community level is not recommended; however, insecticide-treated clothing may be beneficial as an intervention to provide protection against malaria in specific population groups.

> *Conditional recommendation against deployment, low-certainty evidence*

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 LLINs
- 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

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.

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 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 [53]. There was no evidence available on epidemiological effects in the general at-risk population.

Research priorities:

- Investigations of potential epidemiological impact on malaria in the general population.
- Identification of approaches to increase compliance
- Development of formulations that improve the durability of insecticidal efficacy.

Spatial/Airborne repellents (2019)

No recommendation on the deployment of spatial/airborne repellents in the prevention and control of malaria can be made until ongoing studies assessing malaria epidemiological outcomes have been completed.

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.

Justification

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.

Research priorities:
- Investigations of the potential for a 'push-pull' effect of

spatial/airborne repellents, whereby vector mosquitoes may simply move from a treated area to a neighbouring untreated area.
- Good quality, well-designed trials generating epidemiological evidence on the effects of spatial/airborne repellents as a malaria prevention and control tool.
- Development of better insecticide formulations that provide a longer lasting effect.

Space spraying (2019)

Space spraying should not be undertaken for malaria control, and IRS or ITNs should be prioritized instead.

> *Conditional recommendation against deployment, very low-certainty evidence*

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

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

Resources and other considerations

- The costs are anticipated to be high and cost-effectiveness to be limited of this intervention

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- 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 [54]. 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 Guidelines Development Group therefore felt it necessary to develop a clear recommendation against space spraying for malaria control.

Research priorities:

- Demonstrate evidence of impact, particularly in emergency situations, through design of high-quality trials.

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 [55]. 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 [56].

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 [57]:

- 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 [58].

Larviciding for malaria vector control is currently not deployed at the scale of LLINs 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 [59] 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 [60]. 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 [61] 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 13th 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

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determinants into WHO's support at country level [62].

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 1st edition of the Guidelines, resource implications and the cost-effectiveness of vector control interventions could largely only be addressed through expert opinion. Although it is recognized that such considerations should ideally be based on evidence, sufficient clarity on how to collate and present data for this area of the Guidelines was not available at the time of writing. Expanded evidence-based recommendations on resource implications will be developed and incorporated as part of revision to the Guidelines.

At present, 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 [63]. 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

covered in the Guidelines.

Cost-effectiveness analysis – the comparison of the costs and outcomes of alternative interventions – can be a helpful tool for measuring the magnitude of additional health gained per additional unit of resources spent. WHO offers a series of tools to facilitate country-level cost-effectiveness analysis, notably through the CHOICE project [64]. Using the cost-effectiveness ratio in combination with cost-effectiveness thresholds, as applied in the above-mentioned review, provides some indication of the value for money of an intervention. Value for money, however, should not be used as a standalone criterion for decision-making, but rather used alongside other considerations, including affordability and budget impact analysis, among others [65]. The development of further guidance to inform resource use will be a focus in preparing explicit recommendations on resource use as part of the GRADE tables, using work by other WHO departments as a guide [66]. Given that resource considerations are highly context-specific and hence unlikely to be detailed enough to inform the prioritization of resources for vector control at country level, further work to guide country-level decision-making is also foreseen, but will be outside the scope of this global guidance document.

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 [67].

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 [28]. 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 [68] 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 with a WHO PQ listing 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 LLIN 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

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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

During the development of the Guidelines, a number of areas were identified that require additional work to enhance the guidance provided here. Key areas to be addressed as part of revision to the Guidelines:

- To conduct a systematic review of data on IRS interventions from studies other than cluster RCTs. Despite its long tradition and the large body of associated operational experience, few RCTs have been conducted on IRS. The Guidelines Development Group agreed that the strength of the current recommendations on IRS, and their specifics, could be enhanced through a systematic review of additional data from non-randomized studies.
- To conduct additional systematic reviews on housing and on two LSM interventions, namely habitat modification and manipulation.
- To review current evidence on resource use and draft expanded GRADE tables that include this information as an initial step guiding the prioritization of interventions. This process should follow examples provided in other WHO guidance, such as the interim policy guidance on the use of delamanid in the treatment of multidrug-resistant tuberculosis [66].
- To develop a chapter to guide the collection of cost data alongside research studies for inclusion in the trial design manual recently issued by WHO on behalf of the VCAG [69]. Collection of cost data early on in the process of evaluating new interventions will make a useful contribution to building an evidence base on resource use, which can be drawn on for subsequent editions of the Guidelines.
- To conduct a systematic review of cost and cost-effectiveness data on all vector control interventions in order to complement the evidence base upon which recommendations are developed and identify knowledge gaps in these areas.
- To identify basic resources associated with the recommendations, including health system resources (training, supervision, etc.) to support countries in developing their own resource need and budget impact assessments.
- To develop further guidance on the deployment of improved or interventions in special situations, for example, with the aim of controlling residual transmission and 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 *[70]*. 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 *[71]*.

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 *[72]*.

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 *[73]*.

Please refer to the WHO Mass drug administration for falciparum malaria: a practical field manual *[74]*.

4.2.1 - Intermittent preventive treatment of malaria in pregnancy (IPTp)

Intermittent preventive treatment in pregnancy (2015)

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.

Strong recommendation, high-certainty evidence

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 *[75]*, 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) [76]*.

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

Overall certainty of evidence for all critical outcomes: high.

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 [75]. 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.

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4.2.2 - Intermittent preventive treatment of malaria in infants (IPTi)

Intermittent preventive treatment in infants (2015)

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.

Strong recommendation*

*unGRADEd recommendation, anticipated to be updated in 2021

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 *[78]*.

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* $\geq$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 [78]*.

Justification

Evidence supporting the recommendation
The recommendation is based on a pooled analysis of 6 randomised pacebo controlled studies on SP-IPTi conducted in areas of moderate to high transmission of malaria *[77]*:

- 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 randomised pacebo 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%)], anemia [21.3% (95% CI: 8.3%–32.5%)], hospital admissions associated with malaria parasitemia [38.1% (95% CI 12.5%–56.2%)], and all-cause hospital

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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)

Seasonal malaria chemoprevention (2015)

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.

Strong recommendation, high-certainty evidence

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 unitl 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 [80]*.

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

Overall certainty of evidence for all critical outcomes: high.

Justification

GRADE

In a systematic review [79], 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.

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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* [81].

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 [82] 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 [83].

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 [84]. 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 [85] and control of laboratory services.

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 [86].

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*) [87] [88][89]. 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 [90].

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 [91]:
- 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 [92];
- 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 [93], 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 [94].

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 [95]. 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 [83].

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 [96].

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 [97]; 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.

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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 [98].

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.

Good practice statement

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

Treating uncomplicated *P. falciparum* malaria (2015)

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).

> *Strong recommendation, high-certainty evidence*

- artesunate + pyronaridine (currently unGRADEd)

- -

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 [99] 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 [103]. 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 artesunatepyronaridine 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. [102] 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 Saftey 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 [103]. 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

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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* [104].

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).

Undesireable 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.

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) [100][101].

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 Guideline Development Group 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.

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)

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

Strong recommendation, high-certainty evidence

Evidence To Decision

Benefits and harms

Desirable effects
- Fewer patients taking ACTs containing 3 days of an artemisinin derivative experience treatment failure within the

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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

For all critical outcomes: High.

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 effect 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.

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Treating uncomplicated *P. falciparum* malaria (2015)

> **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.
>
> *Strong recommendation**
>
> *unGRADEd recommendation, anticipated to be updated in 2021

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) [105][106] 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 is 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

Treating uncomplicated *P. falciparum* malaria (2015)

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.

Strong recommendation, low-certainty evidence

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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 *[109]*. 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)
10ᵃ 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 [110]*.

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

Overall certainty of evidence for all critical outcomes: low.

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 *[107]*:

- 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

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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 pre-elimination or 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 [108].

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-optimalexposure to antimalarialdrugs.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.

First trimester of pregnancy (2015)

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

> **Strong recommendation***

*unGRADEd recommendation, anticipated to be updated in 2021

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 anymedicine to potentiallypregnant 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).

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 [111][112].

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

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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 5kg 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)

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.

<div style="background:green;color:white;">*Strong recommendation**</div>

*unGRADEd recommendation, anticipated to be updated in 2021

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.

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 despites 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.

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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.
>
> *Good practice statement*

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)

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

Strong recommendation, high-certainty evidence

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)

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.

Good practice statement

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][113][114]*. Irrelevant 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 *[114]*. 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 *[114]*. 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 *[115]*. 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 [116]* 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 *[117]*. 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 *[118]*. The major complication is anaemia in young children. In Papua province, Indonesia *[118]*, and in Papua New Guinea *[119]*, 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 *[120][121]*. During pregnancy, infection with *P. vivax*, as with *P. falciparum*, increases the risk for abortion and reduces birth weight *[122][111]*. 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 *[122]*.

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) *[123][124]*. 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 *[125]*.

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.

Blood stage infection (2015)

> If the malaria species is not known with certainty, treat as for uncomplicated.
>
> *Good practice statement*

Blood stage infection (2015)

> 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, high-certainty evidence*

Practical Info

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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

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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
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.

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

Overall certainty of evidence for all critical outcomes: high.

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Justification

GRADE

In a systematic review of ACTs for the treatment of *P. vivax* malaria *[126]*, 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 parasitemia 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.

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Blood stage infection (2015)

Treat pregnant women in their first trimester who have chloroquine-resistant *P. vivax* malaria with quinine.

Strong recommendation, very low-quality evidence

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).

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

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

Good practice statement

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) [127]* and *Guide to G6PD deficiency rapid diagnostic testing to support P. vivax radical cure [128]*.

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

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.

Strong recommendation, high-certainty evidence

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

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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

Overall certainty of evidence for all critical outcomes: high.

Justification

GRADE

In a systematic review of primaquine for radical cure of *P. vivax* malaria [129], 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

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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.

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

> 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.
>
> *Conditional recommendation, very low-certainty evidence*

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

Overall certainty of evidence for all critical outcomes: very low.

Justification

GRADE

In a systematic review of primaquine for radical cure of *P. vivax* malaria *[129]*, 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 manifestationsso, 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.

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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.

Good practice statement

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.

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

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.

Conditional recommendation, moderate-certainty evidence

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

Overall certainty of evidence for all critical outcomes: moderate.

Justification

GRADE
In a systematic review of malaria chemoprophylaxis in pregnant women *[130]*, chloroquine prophylaxis against *P. vivax* during pregnancy was directly evaluated in one trial conducted in Thailand in 2001. In comparison with no chemoprophylaxis:

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- 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

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

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.

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 oedema[b]	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* [131].

5.5.1 - Artesunate

Treating severe malaria (2015)

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, high-certainty evidence

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* [133].

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

Overall certainty of evidence for all critical outcomes: high.

Justification

GRADE

In a systematic review of artesunate for severe malaria *[132]*, 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.

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Revised dose recommendation for parenteral artesunate in young children (2015)

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.

Strong recommendation based on pharmacokinetic modelling*

*unGRADEd recommendation, anticipated to be updated in 2021

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) [134][135]. 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.

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5.5.2 - Parenteral alternatives when artesunate is not available

Parenteral alternatives where artesunate is not available (2015)

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

Conditional recommendation, low-certainty evidence

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

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.

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 *[136]*. 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

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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. --

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.

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Treating cases of suspected severe malaria pending transfer to a higher- level facility (pre-referral treatment) (2015)

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.

Strong recommendation, moderate-certainty evidence

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* [138].

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

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Overall certainty of evidence for all critical outcomes: moderate.

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 [137].

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 - Chemoprevention in special risk groups

Please refer to Section 4.2 Preventive chemotherapies.

5.7 - Other considerations in treating malaria

5.7.1 - 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 there by 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 pre-elimination or 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 facliparum 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.

5.7.2 - 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 *[139]*.

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.

Good practice statement

5.7.3 - 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

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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 [140].

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.

Monitoring the efficacy of antimalarial drugs (2015)

> All malaria programmes should regularly monitor the therapeutic efficacy of antimalarial drugs using the standard WHO protocols.
>
> *Good practice statement*

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 [140] and Methods for surveillance of antimalarial drug efficacy [141] 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 [142]
- Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010-2019) [143]

5.8 - 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 *[91][94]*.

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 artemisin-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

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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 *[144]*. 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 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.

National adaptation and implementation (2015)

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

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 [145]* 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.

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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.

Good practice statement

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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 *[146]*, 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 *[147]*.

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 *[148]*.

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" [149].

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 [26].

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)) [150]. 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.

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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, 2018). 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 across the topics covered in this guideline [151][152].

Organization and process
The WHO guideline development process involves planning; conducting a "scoping" and needs assessment; establishing an internal WHO Guidelines Steering Group and an external Guidelines Development Group; formulating key questions in PICO (Population, Intervention, Comparison, Outcome) format; commissioning evidence reviews; applying Grading of Recommendations Assessment, Development and Evaluation (GRADE) to the certainty of evidence; and making recommendations. This methodology ensures that the link between the evidence base and the recommendations is transparent. The guidelines were consolidated and will be continuously updated as new evidence becomes available in the online MAGIC publication platform (www.magicapp.org) and published in user-friendly formats available on all devices.

WHO Guidelines Steering Groups were responsible for drafting the scope of the Guidelines and preparing the planning proposal, formulating key questions, identifying potential members for the Guidelines Development Group (GDG), obtaining declarations of interest from GDG members, managing any conflicts of interest, and submitting a finalized planning proposal to the Guidelines Review Committee (GRC) for review and approval. The Steering group may also be responsible for managing the process of updating the guideline recommendations.

Guidelines Development Groups (GDG) were external bodies of experts and end-users whose central task was to develop the evidence-based recommendations contained in the Guidelines. The specific tasks of the Guidelines Development Group included:

- Providing inputs as to the scope of the Guidelines;
- Building on the work of the Guidelines Steering Group to finalize the key questions in PICO format;
- Choosing and ranking priority outcomes to guide the evidence reviews and focus the recommendations;
- Examining the GRADE evidence profiles or other assessments of the certainty of evidence used to inform the recommendations;
- Interpreting the evidence, with explicit consideration of 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 issues and evidence gaps, and providing guidance on how to address these; and
- Reviewing and approving the final recommendations prior to submission to the Guidelines Review Committee.

Multiple GDGs were established to develop the WHO Guidelines for Malaria (see Section 10. Contributors and interests). They were composed of members balanced according to geographical representation and gender, and deemed free of important conflicts of interest (see section below) across the following categories:

- relevant technical experts (e.g physicians with clinical expertise; 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.

The Chairs of the GDGs and/or members had expertise in ensuring that equity, human rights, gender and social determinants were taken into consideration in efforts to improve public health outcomes.

Guideline methodologists
Experts in guideline development processes complemented the technical expertise of the GDG members. Methodologists had expertise in systematic reviews, GRADEing of evidence, and the translation of evidence into recommendations. They supported in the planning, scoping and the development of key questions and supported the GDG to formulate evidence-informed recommendations in a transparent and explicit manner.

Sources of evidence
Following the initial GDG meeting, systematic reviews already published were identified or were commissioned to systematically assess the quality of the evidence for each priority question across the guideline topics.

The reviews involved extensive searches for published and unpublished trials and 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 assessed were in accordance with those recommended by the GDG for consideration in the evidence reviews and included: rate of all-cause child mortality; incidence rate of malaria; incidence rate of severe malaria episodes; rate of clinical malaria; rate of uncomplicated episodes of *P. falciparum* illness; malaria incidence; 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; and number of larval sites positive for immature vector stages. Epidemiological outcomes, namely

demonstration that an intervention had proven protective efficacy to reduce or prevent infection and/or disease in humans, were prioritized over entomological ones, given that the correlation between epidemiological and entomological outcomes has not been well established. The specific search methods, inclusion criteria, data collection and analysis plans for each evidence review are detailed in the published review protocols.

When little evidence was available from randomized trials, the group considered published reviews of non-randomized studies including: quasi-experimental designs, including controlled before-and-after studies, interrupted time series (controlled and uncontrolled), and stepped wedge designs. In formulating its recommendations, the Guidelines Development Group also considered additional evidence that was deemed unsuitable for inclusion and analysis under the Cochrane systematic review process, particularly in developing the Evidence-to-Decision Frameworks. The GDGs used GRADEPro software or the MagicApp platform, and the interactive Evidence-to-Decision Framework to assist in the process of evidence review and recommendation-setting.

The Evidence-to-Decision Framework considers 12 criteria to arrive at a recommendation for or against an intervention; these are [153]:

1. Is the problem a priority?
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. What is the certainty of the evidence of resource requirements (costs)?
7. Does the cost-effectiveness of the intervention favor the intervention or the comparison?
8. What would be the impact on health equity?
9. Is the intervention acceptable to key stakeholders?
10. Is the intervention feasible to implement?

The Evidence-to-Decision 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 research evidence tab.

Certainty of evidence

The certainty of evidence from the systematic reviews was assessed for each outcome and rated on a four-point scale (Table 1), after considering the risk of bias (including publication bias) and the consistency, directness and precision of the effect estimates. The terms used in the certainty assessments refer to the GDG's level of confidence in the estimate of effect and not to the scientific quality of the investigations reviewed.

Table 1: The four classes of certainty of evidence used in GRADE

Certainty of evidence	Interpretation
High	The Group is very confident in the estimate of effect and considers that further research is very unlikely to change this confidence.
Moderate	The Group has moderate confidence in the estimate of effect and considers that further research is likely to have an important impact on that confidence and may change the estimate.
Low	The Group has low confidence in the estimate of effect and considers 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. Recommendations were formulated after considering the certainty of evidence, the balance of benefits and harms, values and preferences, and the feasibility of the intervention (Table 2). Values and preferences were taken into account through discussions on the relative value beneficiaries place on the outcomes of the intervention, and on the relative acceptability of the intervention to the beneficiaries. Although cost is a critical factor in setting national policies and was broadly considered in the recommendation formulation process, explicit analyses of the costs and cost-effectiveness of the various interventions did not form part of the reviews. Expanded evidence-based recommendations on resource implications will be developed where possible and incorporated into the Guidelines. Pre-existing WHO recommendations and guidance relevant to malaria, were also reviewed and in some cases revised by the Guidelines Development Group.

The GDG discussed the proposed wording of each recommendation at in-person meetings, through e-mail correspondence and/or teleconferencing, and rated the strength of each recommendation in accordance with the four-point scale presented in Table 1. The guideline development process aimed to generate group consensus through open and transparent discussion; voting on specific points was available as an option to finalize recommendations on which no consensus could be reached.

Table 2: Factors other than certainty of evidence considered in the formulation of recommendations

Factors considered	Rationale
Balance of benefits and harm	The more the expected benefits outweigh the expected risks, the more likely it is that a strong recommendation will be made. When the balance of benefits and harm is likely to vary by setting or is a fine balance, a conditional recommendation is more likely.
Values and preferences	If the recommendation is likely to be widely accepted or highly valued, a strong recommendation is more likely.
Feasibility	If an intervention is achievable in the settings in which the greatest impact is expected, a strong recommendation is more likely.

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
Conditional	Substantial debate is required at national level, with the involvement of various stakeholders.	Some individuals should receive the recommended intervention, if certain criteria are met.	Some people in your situation would want the recommended intervention if certain criteria are met.

Types of guidance

Two types of guidance are presented in the Malaria Guidelines.

- Intervention 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 adherence to the statement are large and unequivocal, and that the implications of the statement are common sense. These statements are often not supported by a systematic review of evidence and have usually been 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 using criteria in Table 3.

Table 3: Classification of recommendations

Strength of recommendation	Interpretation		
	For policy-makers	For programme managers/ technicians	For end-users

Presentation of evidence and recommendations

For clarity, the recommendations are presented in individual boxes on the MAGICapp platform with color-coded strength of recommendations and labeled by strength based on the evidence reviewed. More information is available through expanding the tabs directly below the recommendation: the research evidence; the Evidence to Decision table; 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. Summary of Findings tables show sources for estimates of effect).

External review and WHO approval

The external review groups (see Section 10) were composed of persons interested in the subject of the Guidelines and includes 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 external review group reviewed the draft guideline prior to its submission to the Guidelines Review Committee for approval. The role of the group was to identify any errors or missing data and to provide comment on clarity, setting-specific issues, and implications for implementation. The group was not expected to change the recommendations formulated by the GDG. If major concerns 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 draft was circulated to the Guidelines Development Group and the External Review Group.

Management of conflicts of interest

All members of the guideline development groups made declarations of interests, which were managed in accordance with WHO procedures and summarized at the beginning of each meeting. The WHO Guideline Steering Group and the chairs of the

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Guidelines Development Group had to be satisfied that there had been a transparent declaration of interests and appropriate management of any interests identified. 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 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 UN and other procurement agencies in 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.

9 - GLOSSARY

Please also refer to the *WHO malaria terminology [154]* 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 lifethreatening
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.	case, locally acquired	A case acquired locally by mosquito-borne transmission
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)	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
capture site	Site selected for periodic sampling of the mosquito population of a locality for various purposes	case, presumed	Case suspected of being malaria that is not confirmed by a diagnostic test
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, recrudescent	Malaria case attributed to the recurrence of asexual parasitemia after antimalarial treatment, due to incomplete clearance of asexual parasitemia of the same genotype(s) that caused the original illness. A recrudescent case must be distinguished from reinfection and relapse, in case of *P. vivax* and *P. ovale*
case, fever	The occurrence of fever (current or recent) in a person	case, relapsing	Malaria case attributed to activation of hypnozoites of *P. vivax* or *P. ovale* acquired previously
case, imported	Malaria case or infection in which the infection was acquired outside the area in which it is diagnosed	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, 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 detection	One of the activities of surveillance operations, involving a search for malaria cases in a community
case, indigenous	A case contracted locally with no evidence of importation and no direct link to transmission from an imported case	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, 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 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, introduced	A case contracted locally, with strong epidemiological evidence linking it directly to a known imported case (first-generation local transmission)	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			disease
case management	Diagnosis, treatment, clinical care, counselling and follow-up of symptomatic malaria infections		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
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		combination therapy	A combination of two or more classes of antimalarial medicine with unrelated mechanisms of action
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		coverage	A general term referring to the fraction of the population of a specific area that receives a particular intervention
cerebral malaria	Severe *P. falciparum* malaria with impaired consciousness (Glasgow coma scale < 11, Blantyre coma scale < 3) persisting for > 1 hour after a seizure		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 section 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.
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 3 consecutive years and a national surveillance system and a programme for the prevention of reintroduction are in place		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.
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.		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
chemoprophylaxis	Administration of a medicine, at predefined intervals, to prevent either the development of an infection or progression of an infection to manifest		cure rate	Percentage of treated individuals whose infection is cured
			cyto-adherence	Propensity of malaria-infected erythrocytes to adhere to the

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	endothelium of the microvasculature of the internal organs of the host	schizontocidal	liver or the blood
diagnosis	The process of establishing the cause of an illness (for example, a febrile episode), including both clinical assessment and diagnostic testing	endemic area	An area in which there is an ongoing, measurable incidence of malaria infection and mosquito-borne transmission over a succession of years
diagnosis, molecular	Use of nucleic acid amplification-based tests to detect the presence of malaria parasites	endemicity, level of	Degree of malaria transmission in an area
diagnosis, parasitological	Diagnosis of malaria by detection of malaria parasites or Plasmodium-specific antigens or genes in the blood of an infected individual	endophagy	Tendency of mosquitoes to blood-feed indoors
		endophily	Tendency of mosquitoes to rest indoors.
diapause	Condition of suspended animation or temporary arrest in the development of immature and adult mosquitoes	entomological inoculation rate	Number of infective bites received per person in a given unit of time, in a human population
dosage regimen (or treatment regimen)	Prescribed formulation, route of administration, dose, dosing interval and duration of treatment with a medicine	epidemic	Occurrence of a number of malaria cases highly in excess of that expected in a given place and time
dose	Quantity of a medicine to be taken at one time or within a given period	epidemiological investigation	Study of the environmental, human and entomological factors that determine the incidence or prevalence of infection or disease
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	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*.
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	exophagy	Tendency of mosquitoes to feed outdoors
		exophily	Tendency of mosquitoes to rest outdoors
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	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
drug safety	(see Medicine safety)		
drug, gametocidal	A drug that kills male and/or female gametocytes, thus preventing them from infecting a mosquito	fixed-dose combination	A combination in which two antimalarial medicines are formulated together in the same tablet, capsule, powder, suspension or granule
drug,	A drug that kills schizonts, either in the		

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	hyperparasitaemia	A high density of parasites in the blood, which increases the risk that a patient's condition will deteriorate and become severe malaria
gametocyte	Sexual stage of malaria parasites that can potentially infect anopheline mosquitoes when ingested during a blood meal	hypnozoite	Persistent liver stage of P. vivax and P. ovale malaria that remains dormant in host hepatocytes for variable periods, from 3 weeks to 1 year (exceptionally even longer), before activation and development into a pre-erythrocytic schizont, which then causes a blood-stage infection (relapse)
gametocyte rate	Percentage of individuals in a defined population in whom sexual forms of malaria parasites have been detected	importation rate	Rate of influx of parasites via infected individuals or infected *Anopheles* spp. mosquitoes
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	importation risk	Probability of influx of infected individuals and/or infective anopheline mosquitoes
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.	incidence, malaria	Number of newly diagnosed malaria cases during a defined period in a specified population
gonotrophic discordance (dissociation)	Female mosquitoes that take more than one blood meal per gonotrophic cycle	incubation period	Period between inoculation of malaria parasites and onset of clinical symptoms
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	index, host preference	Proportion of blood-fed female *Anopheles* mosquitoes that fed on the host species and/or individual of interest
house	Any structure other than a tent or mobile shelter in which humans sleep	index, human blood	Proportion of mosquito blood meals from humans
household	The ecosystem, including people and animals occupying the same house and the accompanying vectors	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
house-spraying	Application of liquid insecticide formulation to specified (mostly interior) surfaces of buildings	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
human landing catch	A method for collecting vectors as they land on individuals	indoors	Inside any shelter likely to be used by humans or animals, where mosquitoes may feed or rest

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infection, chronic	Long-term presence of parasitaemia that is not causing acute or obvious illness but could potentially be transmitted	insecticide, dose	Amount of active ingredient of insecticide applied per unit area of treatment (mg/m2) for indoor residual spraying and treated mosquito nets, or per unit of space (mg/m3) for space spraying and per unit area of application (g/ha or mg/m2) or per volume of water (mg/L) for larvicides
infection, mixed	Malaria infection with more than one species of *Plasmodium*		
infection, reservoir of	Any person or animal in which plasmodia live and multiply, such that they can be transmitted to a susceptible host	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
infection, submicroscopic	Low-density blood-stage malaria infections that are not detected by conventional microscopy	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
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)	insecticide resistance	Property of mosquitoes to survive exposure to a standard dose of insecticide; may be the result of physiological or behavioural adaptation
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 rotation	Strategy involving sequential applications of insecticides with different modes of action to delay or mitigate resistance
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 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, 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, fumigant	Insecticide that acts by releasing vapour from a volatile substance
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, 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	Rational decision-making for optimal use of resources for vector control

intermittent preventive treatment in infants	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		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.
intermittent preventive treatment in pregnancy	A full therapeutic course of antimalarial medicine given to pregnant women at routine prenatal visits, regardless of whether the woman is infected with malaria		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.
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.		malaria infection	Presence of Plasmodium parasites in blood or tissues, confirmed by diagnostic testing
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		malaria mortality rate	Number of deaths from malaria per unit of population during a defined period
larvicide	Substance used to kill mosquito larvae		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.
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.		malaria prevalence	Proportion of a specified population with malaria infection at one time
long-lasting insecticidal net	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 3 years of recommended use under field conditions.		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 case	(See Case, malaria)		malaria reintroduction	Malaria reintroduction is 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, 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 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		infections is detected
malaria, cross-border	Malaria transmission associated with the movement of individuals or mosquitoes across borders	mass testing and treatment	Testing an entire population and treating individuals with a positive test result
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	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
malariogenic potential	Potential level of transmission in a given area arising from the combination of malaria receptivity, importation rate of malaria parasites and infectivity.	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.
malariometric survey	Survey conducted in a representative sample of selected age groups to estimate the prevalence of malaria and coverage of interventions	monotherapy	Antimalarial treatment with a single active compound or a synergistic combination of two compounds with related mechanisms of action
malarious area	Area in which transmission of malaria is occurring or has occurred during the preceding 3 years	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
mass drug administration	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	national malaria case register	Centralized database with individual records of all malaria cases registered in a country
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	net, insecticide-treated	Mosquito net that repels, disables or kills mosquitoes that come into contact with the insecticide on the netting material. The two 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 3 years of
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		

	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.	population at risk	Population living in a geographical area where locally acquired malaria cases have occurred in the past 3 years
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.	population, target	An implementation unit targeted for activities or services (e.g. prevention, treatment)
oocyst rate	Percentage of female *Anopheles* mosquitoes with oocysts on the midgut	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
ookinete	Motile stage of malaria parasite after fertilization of macrogamete and preceding oocyst formation	pre-patent period	Period between inoculation of parasites and the first appearance of parasitaemia
parasitaemia	Presence of parasites in the blood	prequalification	Process to ensure that health products are safe, appropriate and meet stringent quality standards for international procurement
parasitaemia, asymptomatic	The presence of asexual parasites in the blood without symptoms of illness	preventive chemotherapy	Use of medicines either alone or in combination to prevent malaria infections and their consequences
parasite clearance time	Time between first drug administration and the first examination in which no parasites are present in the blood by microscopy	prophylaxis	Any method of protection from or prevention of disease; when applied to chemotherapy, it is commonly termed "chemoprophylaxis".
parasite density	Number of asexual parasites per unit volume of blood or per number of red blood cells	prophylaxis, causal	Complete prevention of erythrocytic infection by destroying the pre-erythrocytic forms of the parasite
parasite density, low	Presence of *Plasmodium* parasites in the blood at parasite density below 100 parasites/μl	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.
patent period	Period during which malaria parasitaemia is detectable	rapid diagnostic test	Immunochromatographic lateral flow device for rapid detection of malaria parasite antigens
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.	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

screening, testing, treating or drug administration	administering drugs to a subset of a population in a given area in response to the detection of an infected person		than one nucleus
receptivity	Receptivity of an ecosystem to transmission of malaria	screening	Identification of groups at risk that may require further intervention, such as diagnostic testing, treatment or preventive services
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.	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
recurrence	Reappearance of asexual parasitaemia after treatment, due to recrudescence, relapse (in P. vivax and P. ovale infections only) or a new infection	sensitivity (of a test)	Measured as the proportion of people with malaria infection (true positives) who have a positive result
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	serological assay	Procedure used to measure antimalarial antibodies in serum
		severe anaemia	Haemoglobin concentration of < 5 g/100 mL (haematocrit < 15%)
reintroduction risk	The risk that endemic malaria will be re-established in a specific area, after its elimination	severe falciparum malaria	Acute falciparum malaria with signs of severe illness and/or evidence of vital organ dysfunction
relapse	Recurrence of asexual parasitaemia in P. vivax or P. ovale infections arising from hypnozoites	single-dose regimen	Administration of a medicine as a single dose to achieve a therapeutic objective
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)	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
resistance	(See Drug resistance, Insecticide resistance)	sporozoite	Motile stage of the malaria parasite that is inoculated by a feeding female anopheline mosquito and may cause infection
ring form (ring stage, ring-stage trophozoite)	Young, usually ring-shaped malaria trophozoites, before pigment is evident by microscopy	sporozoite rate	Percentage of female *Anopheles* mosquitoes with sporozoites in the salivary glands
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	spray round	Spraying of all sprayable structures in an area designated for coverage in an indoor residual spraying programme during a discrete period

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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	transmission intensity	The frequency with which people living in an area are bitten by anopheline mosquitoes carrying human malaria sporozoites
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	transmission season	Period of the year during which most mosquito-borne transmission of malaria infection occurs
spraying frequency	Number of regular applications of insecticide per house per year, usually by indoor residual spraying	transmission, re-establishment of	Renewed presence of a measurable incidence of locally acquired malaria infection due to repeated cycles of mosquito-borne
spraying interval	Time between successive applications of insecticide	transmission, interruption of	Cessation of mosquito-borne transmission of malaria in a geographical area as a result of the application of antimalarial measures
spraying, focal	Spray coverage by indoor residual spraying and/or space spraying of houses or habitats in a limited geographical area	tranmission, perennial	Transmission that occurs throughout the year with no great variation in intensity
spraying, residual	Spraying the interior walls and ceilings of dwellings with a residual insecticide to kill or repel endophilic mosquito vectors of malaria	transmission, residual	Persistence of malaria transmission following the implementation in time and space of a widely effective malaria programme
surveillance	Continuous, systematic collection, analysis and interpretation of disease-specific data and use in planning, implementing and evaluating public health practice	transmission, seasonal	Transmission that occurs only during some months of the year and is markedly reduced during other months
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.	transmission, stable	Epidemiological type of malaria transmission characterized by a steady prevalence pattern, with little variation from one year to an- other except as the result of rapid scaling up of malaria interventions or exceptional environmental changes that affect transmission
testing, malaria	Use of a malaria diagnostic test to determine whether an individual has malaria infection	transmission, unstable	Epidemiological type of malaria transmission characterized by large variation in incidence patterns from one year to another
tolerance	A response in a human or mosquito host to a given quantum of infection, toxicant or drug that is less than expected	trap, mosquito	Device designed for capturing mosquitoes with or without attractant components (light, CO2, 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	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
treatment, anti-relapse	Antimalarial treatment designed to kill hypnozoites and thereby prevent relapses or late primary infections with *P. vivax* or *P. ovale*	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
treatment, directly observed	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	vector control	Measures of any kind against malaria-transmitting mosquitoes, intended to limit their ability to transmit the disease
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	vector susceptibility	The degree to which a mosquito population is susceptible (i.e. not resistant) to insecticides
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	vector, principal	The species of *Anopheles* mainly responsible for transmitting malaria in any particular circumstance
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.	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
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.	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
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.	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.
uncomplicated malaria	Symptomatic malaria parasitaemia without signs of severity or evidence of vital organ dysfunction		

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10 - CONTRIBUTORS AND INTERESTS

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10.1 - Guidelines for malaria vector control

The following outlines the constitution of the Guidelines Development Group, Guidelines Steering Group, and External Review Group. 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

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
- 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

- 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
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- 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

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

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- 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
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- 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
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- 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

- 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
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Declaration of interests
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

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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 since 2007, some of which will continue 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 neighboring household communities in Cambodia, which in November 2017 was awaiting ethical approval.

10.2 - Guidelines for the treatment of malaria

Since the first and second editions of the guidelines were issued in 2006 and 2010, respectively, WHO 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 guidelines development group, formulation of key questions (PICO questions: population, participants or patients; intervention or indicator; comparator or control; outcome), commissioning 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 Technical Guidelines Development Group, 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 *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, England, 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 will be 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 guideline development group met in two technical meetings, in November 2013 and June 2014, to develop and finalize recommendations based on the GRADE tables constructed on the basis of answers to the PICO questions. The Guidelines were written by a subcommittee of the group. At various times during preparation of the guidelines, sections of the document or recommendations were reviewed by external experts and users who were not members of the group; these external peer reviewers are listed below. Treatment recommendations were agreed by consensus, supported by systematic reviews and review of information on pharmacokinetics and pharmacodynamics. Areas of disagreement were discussed extensively to reach consensus; voting was not required.

Members of the guidelines development group
- Professor K.I. Barnes, Division of Clinical Pharmacology, University of Cape Town, South Africa

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

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

Guideline Steering Group
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- Dr K. Carter, Malaria Regional Adviser, WHO Regional Office for the Americas
- Dr N.Dhingra-Kumar,Health Systems Policies and Workforce,WHO,Geneva,Switzerland
- Dr M. Gomes, Special Programme for Research and Training in Tropical Diseases, WHO, Geneva, Switzerland
- Dr P.E. Olumese (*Secretary*), Global Malaria Programme WHO, Geneva, Switzerland
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- Dr A.E.C. Rietveld, Global Malaria Programme WHO, Geneva, Switzerland
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- Dr. M. Warsame, Global Malaria Programme WHO, Geneva, Switzerland Dr W. Were, Child and Adolescent Health, WHO, Geneva, Switzerland

External reviewers
- Dr F. ter-Kuile, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Dr R. McGready, Shoklo Malaria Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
- Professor F. Nosten, Shoklo Malaria Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Guidelines methodologist
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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, was cleared through the Legal Department of WHO.

Dr K. Barnes reported being a grants co-recipient from the Malaria Medicine 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 and Melinda Gates Foundation to conduct Phase IV post licensure studies on "Euratesim"

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

Dr N. Valecha reported serving as an investigator for 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 does not include

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consultancy fees or any form of remuneration.

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Annex: All evidence profiles, sorted by sections

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4.1 - Vector control

4.1.1 - Interventions recommended for large-scale deployment

Clinical Question/ PICO

Population:	People at risk of malaria
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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		No nets	Insecticide-treated nets or curtains		
All-cause mortality	Relative risk 0.83 (CI 95% 0.77 - 0.89) Based on data from 129,714 patients in 5 studies. (Randomized controlled)	**33** per 1000	**27** per 1000 Difference: **6 fewer** per 1000 (CI 95% 8 fewer - 4 fewer)	High	ITNs or curtains reduce the child mortality from all causes.

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		No nets	Insecticide-treated nets or curtains		
P. falciparum uncomplicated episodes	Relative risk 0.54 (CI 95% 0.48 - 0.6) Based on data from 32,699 patients in 5 studies. (Randomized controlled)	**178** per 1000	**96** per 1000 Difference: **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 patients in 2 studies. (Randomized controlled)	**137** per 1000	**60** per 1000 Difference: **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 patients in 5 studies. (Randomized controlled)	**120** per 1000	**83** per 1000 Difference: **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 patients in 2 studies. (Randomized controlled)	**149** per 1000	**91** per 1000 Difference: **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 patients in 2 studies. (Randomized controlled)	**130** per 1000	**130** per 1000 Difference: **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 episodes	Relative risk 0.5 (CI 95% 0.28 - 0.9) Based on data from 5,512 patients in 1 studies. (Randomized controlled)	**256** per 1000	**128** per 1000 Difference: **128 fewer** per 1000 (CI 95% 184 fewer - 26 fewer)	Low Due to very serious indirectness [4]	ITNs or curtains may reduce the incidence of uncomplicated episodes of any Plasmodium species compared to no nets.
Severe malaria episodes	Relative risk 0.56 (CI 95% 0.38 - 0.82) Based on data from	**15**	**8**	High	ITNs or curtains reduce the incidence of severe malaria episodes

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		No nets	Insecticide-treated nets or curtains		
	31,173 patients in 2 studies. (Randomized controlled)	per 1000	per 1000		compared to no nets.
		Difference: **7 fewer** per 1000 (CI 95% 9 fewer - 3 fewer)			

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:	People at risk of malaria
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)

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Untreated nets	Insecticide-treated nets or curtains		
All-cause mortality	Relative risk 0.67 (CI 95% 0.36 - 1.23) Based on data from 32,721 patients in 2 studies. (Randomized controlled)	**19** per 1000	**13** per 1000 Difference: **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 patients in 5 studies. (Randomized controlled)	**180** per 1000	**104** per 1000 Difference: **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 patients in 4 studies. (Randomized controlled)	**85** per 1000	**69** per 1000 Difference: **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 patients in 3 studies. (Randomized controlled)	**143** per 1000	**104** per 1000 Difference: **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 patients in 3 studies. (Randomized controlled)	**168** per 1000	**97** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**85** per 1000	**44** per 1000 Difference: **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 Plasmodium spp. uncomplicated episodes (cumulative	Relative risk 0.47 (CI 95% 0.17 - 1.28) Based on data from 7,082 patients in 2 studies. (Randomized controlled)	**69** per 1000	**32** per 1000 Difference: **37 fewer** per 1000 (CI 95% 57 fewer - 19 more)	Moderate Due to serious imprecision [5]	ITNs or curtains probably reduce the incidence of uncomplicated malaria episodes of any species compared to untreated

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Untreated nets	Insecticide-treated nets or curtains		
incidence)					nets.
Any Plasmodium spp. prevalence	Relative risk 0.17 (CI 95% 0.05 - 0.53) Based on data from 691 patients in 1 studies. (Randomized controlled)	104 per 1000	18 per 1000	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.
		Difference: **86 fewer** per 1000 (CI 95% 99 fewer - 49 fewer)			

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.**

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

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Clinical Question/ PICO

Population:	People at risk of malaria
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).

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		LLIN	PBO		
Prevalence of malaria	Odds Ratio 0.4 (CI 95% 0.2 - 0.8) Based on data from 3,966 patients in 1 studies.	**527** per 1000 Difference: **316 fewer** per 1000 (CI 95% 422 fewer - 105 fewer)	**211** per 1000	**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: People at risk of malaria

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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		no IRS	IRS		
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 patients in 1 studies. (Randomized controlled)	**650** per 1000 Difference: **90 fewer** per 1000 (CI 95% 150 fewer - 40 fewer)	**560** per 1000	**Low** Due to serious indirectness, Due to serious imprecision [1]	

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		no IRS	IRS		
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 patients in 1 studies. (Randomized controlled)	**680** per 1000	**630** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**50** per 1000	**10** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**110** per 1000	**30** per 1000 Difference: **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:	People at risk of malaria
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)

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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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text 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 patients in 1 studies. (Randomized controlled)	**630** per 1000	**550** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**600** per 1000	**640** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**20** per 1000	**30** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**0** per 1000	**0** per 1000 Difference: **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.**

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Clinical Question/ PICO

Population:	People at risk of malaria
Intervention:	IRS
Comparator:	ITNs

Summary

IRS compared to ITNs:
Two RCTs were included in the systematic review. Studies were conducted in an area with intense transmission (United Republic of Tanzania) and an area with unstable transmission (India).
IRS may lead to a greater reduction in malaria incidence than ITNs in areas of intense transmission.
(Rate Ratio: 0.88; 95% CI (0.78–0.98); one study; low certainty evidence)
There may be little or no difference in parasite prevalence between IRS and ITNs in areas of intense transmission.

(Odds Ratio: 1.06; 95% CI (0.91–1.22); one study; low certainty evidence)
IRS may reduce malaria incidence to a lesser extent than ITNs in areas of unstable transmission.
(Rate Ratio: 1.48; 95% CI (1.37–1.60); one study; low certainty evidence)
There may be little or no difference in parasite prevalence between IRS and ITNs in areas of unstable transmission.
(Odds Ratio: 1.70; 95% CI (1.18–2.44); one study; low certainty evidence)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text 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 patients in 1 studies. (Randomized controlled)	630 per 1000	550 per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	600 per 1000	640 per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	20 per 1000	30 per 1000 Difference: **10 more** per 1000 (CI 95% 10 more - 20 more)	Low Due to serious imprecision, Due to serious indirectness [3]	

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
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 patients in 1 studies. (Randomized controlled)	**0** per 1000 Difference: **0 fewer** per 1000 (CI 95% 0 fewer - 0 fewer)	**0** per 1000	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: People at risk of malaria
Intervention: IRS + 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 [44].

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		ITNs	IRS + ITNs		
Malaria incidence	Relative risk 1.17 (CI 95% 0.92 - 1.46) Based on data from 5,249 patients in 2 studies. (Randomized controlled)	**600** per 1000	**700** per 1000	Moderate Due to serious imprecision [1]	IRS in addition to ITNs probably has little or no effect on malaria incidence compared to ITNs alone.
		Difference: **100 more** per 1000 (CI 95% 50 fewer - 280 more)			
Malaria prevalence	Odds Ratio 1.04 (CI 95% 0.73 - 1.48) Based on data from 34,530 patients in 4 studies. (Randomized controlled)	**180** per 1000	**190** per 1000	Low Due to serious inconsistency, Due to serious imprecision [2]	IRS in addition to ITNs may have little or no effect on parasite prevalence compared to ITNs alone
		Difference: **10 more** per 1000 (CI 95% 40 fewer - 70 more)			
Entomological inoculation rate	Relative risk 0.57 (CI 95% 0.26 - 1.25) Based on data from patients in 2 studies. (Randomized controlled)	**1,170** per 1000	**670** per 1000	Very Low Due to serious inconsistency, Due to very serious imprecision [3]	We did not know if there was an effect on the EIR compared to ITNs alone.
		Difference: **500 fewer** per 1000 (CI 95% 870 fewer - 290 fewer)			
Anaemia prevalence (haemoglobin <8g/dl)	Odds Ratio 1.04 (CI 95% 0.83 - 1.3) Based on data from 12,940 patients in 2 studies. (Randomized controlled)	**50** per 1000	**50** per 1000	Moderate Due to serious imprecision [4]	IRS in addition to ITNs probably has little or no effect on anaemia prevalence compared to ITNs alone
		Difference: **0 fewer** per 1000 (CI 95% 10 fewer - 10 more)			

1. **Imprecision: Serious.**
2. **Inconsistency: Serious. Imprecision: Serious.**
3. **Inconsistency: Serious. Imprecision: Very Serious.**
4. **Imprecision: Serious.**

References

46. 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: People at risk of malaria

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| **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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		no larviciding	Larviciding		
Malaria incidence of habitats >1km2	Odds Ratio 1.97 (CI 95% 1.39 - 2.81) Based on data from 1,793 patients in 1 studies. (Observational (non-randomized))	**230** per 1000	**370** per 1000 Difference: **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 patients in 1 studies. (Observational (non-randomized))	**140** per 1000	**190** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**230** per 1000	**50** per 1000 Difference: **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	**90** per 1000 Difference: **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

51. 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: People at risk of malaria
Intervention: Topical repellent
Comparator: placebo or no topical repellent

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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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		placebo or no topical repellent	Topical repellent		
Clinical malaria (P. falciparum)	Relative risk 0.65 (CI 95% 0.4 - 1.07) Based on data from 4,450 patients in 3 studies.	**39** per 1000	**25** per 1000 — Difference: **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 patients in 4 studies.	**15** per 1000	**12** per 1000 — Difference: **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 patients in 2 studies.	**36** per 1000	**48** per 1000 — Difference: **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	**18** per 1000	**19** per 1000	**Low** Due to serious risk of bias, Due	Topical repellents may or may not have a protective effect against

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		placebo or no topical repellent	Topical repellent		
	9,434 patients in 3 studies.	Difference: **1 more** per 1000 (CI 95% 4 fewer - 7 more)		to serious imprecision [4]	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

53. 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:	People at risk of malaria
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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		placebo or untreated clothing	Insecticide-treated clothing		
Clinical malaria (P. falciparum)	Relative risk 0.49 (CI 95% 0.29 - 0.83) Based on data from 997 patients in 2 studies.	**35** per 1000	**17** per 1000	**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
		Difference: **18 fewer** per 1000 (CI 95% 25 fewer - 6 fewer)			

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		placebo or untreated clothing	Insecticide-treated clothing		
Clinical malaria (P. vivax)	Relative risk 0.64 (CI 95% 0.4 - 1.01) Based on data from 997 patients in 2 studies.	**116** per 1000	**74** per 1000 Difference: **42 fewer** per 1000 (CI 95% 69 fewer - 1 more)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	true effect may be substantially different from the estimate of the effect. 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

53. 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:	People at risk of malaria
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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		placebo or no malaria prevention intervention	Spatial/airborne repellents		
Parasitaemia (all species)	Relative risk 0.24 (CI 95% 0.03 - 1.72) Based on data from	**10**	**2**	**Very Low** Due to serious risk of bias, Due	We do not know if spatial repellents protect against malaria.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		placebo or no malaria prevention intervention	Spatial/airborne repellents		
	6,683 patients in 2 studies.	per 1000 Difference: **8 fewer** per 1000 (CI 95% 10 fewer - 8 more)	per 1000	to serious imprecision, Due to serious inconsistency [1]	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

53. 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:	People at risk of malaria
Intervention:	Space spraying
Comparator:	no space spraying

Summary

Space spraying versus no space spraying:
A total of three interrupted time series studies were included in the review. These studies were conducted in Haiti (malathion applied by aerial delivery) and India (malathion applied with handheld sprayers; malathion applied with handheld and vehicle-mounted sprayers). Two controlled before-and-after studies (one cluster per arm) were conducted in El Salvador (pyrethrin and PBO applied with vehicle-mounted sprayers) and Malaysia (alphacypermethrin applied with handheld sprayers).

All of the included studies were observational studies, which are initially categorized as yielding low certainty evidence. The risk of bias in the studies resulted in the certainty of evidence being further downgraded to very low.
It is unknown whether space spraying causes a reduction in incidence of malaria
(Step Rate Ratio: 1.03; 95% CI (0.58–1.82); five studies; very low certainty evidence)
(Slope Rate Ratio: 0.88; 95% CI (0.81–0.94); five studies; very low certainty evidence)

References

54. 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

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Clinical Question/ PICO

Population:	People at risk of malaria
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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		no space spraying	Space spraying		
Malaria cases per month (Instant effect)	Relative risk 1 (CI 95% 0.51 - 1.92) Based on data from patients in 1 studies. (Observational (non-randomized))	**6** per 1000	**6** per 1000 Difference: **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 patients in 1 studies. (Observational (non-randomized))	**6** per 1000	**1** per 1000 Difference: **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.**

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References

54. 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

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	Absolute effect estimates Sulfadoxine–pyrimethamine (2 doses)	Sulfadoxine–pyrimethamine (≥ 3 doses)	Certainty of the Evidence (Quality of evidence)	Plain text summary
Severe anaemia in 3rd trimester	Relative risk 0.73 (CI 95% 0.48 - 1.11) Based on data from 2,196 patients in 6 studies. (Randomized controlled)	**34** per 1000	**25** per 1000 Difference: **9 fewer** per 1000 (CI 95% 18 fewer - 4 more)	Low Due to serious risk of bias and serious imprecision [1]	

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Outcome Timeframe	Study results and measurements	Absolute effect estimates Sulfadoxine–pyrimethamine (2 doses)	Sulfadoxine–pyrimethamine (≥ 3 doses)	Certainty of the Evidence (Quality of evidence)	Plain text summary
Anaemia in 3rd trimester	Relative risk 0.95 (CI 95% 0.9 - 1.01) Based on data from 2,088 patients in 7 studies. (Randomized controlled)	509 per 1000	484 per 1000 Difference: **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 patients in 7 studies. (Randomized controlled)	92 per 1000	63 per 1000 Difference: **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

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Outcome Timeframe	Study results and measurements	Absolute effect estimates Sulfadoxine–pyrimethamine (2 doses)	Sulfadoxine–pyrimethamine (≥ 3 doses)	Certainty of the Evidence (Quality of evidence)	Plain text summary
Miscarriage	Relative risk 1.43 (CI 95% 0.88 - 2.33) Based on data from 2,471 patients in 6 studies. (Randomized controlled)	**0** per 1000	**0** per 1000	**Very Low** Due to serious risk of bias and very serious imprecision [1]	
		Difference: **0 fewer** per 1000 (CI 95% 0 fewer - 0 fewer)			
Stillbirth	Relative risk 1.14 (CI 95% 0.85 - 1.55) Based on data from 2,676 patients in 7 studies. (Randomized controlled)	**30** per 1000	**34** per 1000	**Very Low** Due to serious risk of bias and very serious imprecision [2]	
		Difference: **4 more** per 1000 (CI 95% 4 fewer - 17 more)			
Neonatal mortality	Relative risk 0.88 (CI 95% 0.57 - 1.35) Based on data from 2,405 patients in 6 studies. (Randomized controlled)	**21** per 1000	**18** per 1000	**Very Low** Due to serious risk of bias and very serious imprecision [3]	
		Difference: **3 fewer** per 1000 (CI 95% 9 fewer - 7 more)			
Preterm birth	Relative risk 1.28 (CI 95% 0.9 - 1.82) Based on data from 2,579 patients in 7 studies. (Randomized controlled)	**122** per 1000	**116** per 1000	**Low** Due to serious risk of bias and serious imprecision [4]	
		Difference: **6 fewer** per 1000 CI 95%			
Low birth weight	Relative risk 0.8 (CI 95% 0.69 - 0.94) Based on data from 2,190 patients in 7 studies. (Randomized controlled)	**167** per 1000	**134** per 1000	**High** [5]	
		Difference: **33 fewer** per 1000 (CI 95% 52 fewer - 10 fewer)			
Placental parasitaemia	Relative risk 0.51 (CI 95% 0.38 -	**63**	**32**	**High** [6]	

Outcome Timeframe	Study results and measurements	Absolute effect estimates Sulfadoxine–pyrimethamine (2 doses) Sulfadoxine–pyrimethamine (≥ 3 doses)		Certainty of the Evidence (Quality of evidence)	Plain text summary
Cord blood haemoglobin	0.68) Based on data from 1,436 patients in 6 studies. (Randomized controlled)	per 1000 per 1000 Difference: **31 fewer** per 1000 (CI 95% 39 fewer - 20 fewer)			
	Relative risk	CI 95%			
Mean birth weight	Based on data from: 2,190 patients 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

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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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Placebo	SMC		
Death from any cause (per 1000 per year)	Relative risk 0.66 (CI 95% 0.31 - 1.39) Based on data from 9,533 patients in 6 studies. (Randomized controlled)	3 per 1000	2 per 1000 Difference: **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 patients in 5 studies. (Randomized controlled)	67 per 1000	48 per 1000 Difference: **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 patients in 6 studies. (Randomized controlled)	CI 95%		Moderate Due to serious imprecision [3]	

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Placebo	SMC		
Non-serious adverse events	Relative risk Based on data from 9,533 patients in 6 studies. (Randomized controlled)	CI 95%		**Moderate** Due to serious risk of bias [4]	
Clinical malaria	Based on data from: 9,321 patients 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 patients 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 0.76).		**High** [6]	

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 bednets 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 +

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artesunate was given monthly. Two studies, in which insecticide-treated nets were also distributed, showed that the benefits remained even when use of bednets 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.

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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artemether + lumefantrine	Dihydroartemisinin + piperaquine		
Treatment failure - PCR unadjusted [1] 28 days	Relative risk 0.34 (CI 95% 0.3 - 0.39) Based on data from 6,200 patients in 9 studies. (Randomized controlled)	**230** per 1000	**78** per 1000 Difference: **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 patients in 9 studies. (Randomized controlled)	**30** per 1000	**13** per 1000 Difference: **17 fewer** per 1000 (CI 95% 21 fewer - 11 fewer)	High [4]	
Treatment failure - PCR unadjusted [5]	Relative risk 0.71 (CI 95% 0.65 - 0.78) Based on data from	**450** per 1000	**320** per 1000	High [6]	

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artemether + lumefantrine	Dihydroartemisinin + piperaquine		
63 days	3,200 patients in 2 studies. (Randomized controlled)	Difference: **130 fewer** per 1000 (CI 95% 157 fewer - 99 fewer)			
Treatment failure - PCR adjusted [7] 63 days	Relative risk 0.72 (CI 95% 0.5 - 1.04) Based on data from 2,097 patients in 2 studies. (Randomized controlled)	**60** per 1000	**43** per 1000	**High** [8]	
		Difference: **17 fewer** per 1000 (CI 95% 30 fewer - 2 more)			

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.**

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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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artesunate + mefloquine	Dihydroartemisinin + piperaquine		
Treatment failure - PCR unadjusted [1] 28 days	Relative risk 1.02 (CI 95% 0.28 - 3.72) Based on data from 3,487 patients in 8 studies. (Randomized controlled)	**20** per 1000	**20** per 1000 Difference: **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 patients in 8 studies. (Randomized controlled)	**10** per 1000	**4** per 1000 Difference: **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 patients in 5 studies. (Randomized controlled)	**120** per 1000	**101** per 1000 Difference: **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 patients in 5 studies. (Randomized controlled)	**30** per 1000	**15** per 1000 Difference: **15 fewer** per 1000 (CI 95% 21 fewer - 5 fewer)	High Due to serious inconsistency [8]	

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.

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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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artemether + lumefantrine	Dihydroartemisinin + piperaquine		
Serious adverse events (including deaths)	Based on data from 7,022 patients in 8 studies. (Randomized controlled)	**6** per 1000	**10** per 1000 Difference: **4 more** per 1000 CI 95%	Moderate Due to serious imprecision [1]	
Early vomiting	Relative risk Based on data from 2,695 patients in 3 studies. (Randomized controlled)	**20** per 1000	**30** per 1000 Difference: **10 more** per 1000 CI 95% 0 fewer -	Moderate Due to serious risk of bias [2]	

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artemether + lumefantrine	Dihydroartemisinin + piperaquine		
Vomiting	Relative risk Based on data from 6,761 patients in 9 studies. (Randomized controlled)	90 per 1000	90 per 1000 Difference: **0 fewer** per 1000 CI 95%	Moderate Due to serious risk of bias [3]	
Nausea	Relative risk Based on data from 547 patients in 2 studies. (Randomized controlled)	20 per 1000	20 per 1000 Difference: **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 patients in 7 studies. (Randomized controlled)	120 per 1000	120 per 1000 Difference: **0 fewer** per 1000 CI 95%	Moderate Due to serious risk of bias [5]	
Abdominal pain	Relative risk Based on data from 911 patients in 5 studies. (Randomized controlled)	190 per 1000	160 per 1000 Difference: **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 patients in 5 studies. (Randomized controlled)	150 per 1000	140 per 1000 Difference: **10 fewer** per 1000 CI 95% 0 fewer -	Moderate Due to serious risk of bias [7]	
Headache	Relative risk Based on data from 309 patients in 2 studies. (Randomized controlled)	270 per 1000	330 per 1000 Difference: **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 patients in 2 studies. (Randomized controlled)	10 per 1000	30 per 1000 Difference: **20 more** per 1000 CI 95% 0 fewer -	Low Due to serious risk of bias and serious imprecision [9]	

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artemether + lumefantrine	Dihydroartemisinin + piperaquine		
Dizziness	Relative risk Based on data from 547 patients in 2 studies. (Randomized controlled)	30 per 1000	40 per 1000 Difference: 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 patients in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000 Difference: 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 patients in 5 studies. (Randomized controlled)	170 per 1000	180 per 1000 Difference: 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 patients in 5 studies. (Randomized controlled)	420 per 1000	420 per 1000 Difference: 0 fewer per 1000 CI 95% 0 fewer -	Moderate Due to serious risk of bias [13]	
Coryza	Relative risk Based on data from 832 patients in 2 studies. (Randomized controlled)	680 per 1000	660 per 1000 Difference: 20 fewer per 1000 CI 95% 0 fewer -	Low Due to serious imprecision [14]	
Prolonged QT interval (adverse event)	Relative risk Based on data from 1,548 patients in 1 studies. (Randomized controlled)	30 per 1000	20 per 1000 Difference: 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 patients in 1 studies. (Randomized controlled)	70 per 1000	90 per 1000 Difference: 20 more per 1000 CI 95% 0 fewer -	Low Due to serious imprecision and serious risk of bias [16]	

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artemether + lumefantrine	Dihydroartemisinin + piperaquine		
Prolonged QT interval (Fridericia correction)	Relative risk Based on data from 1,548 patients in 1 studies. (Randomized controlled)	**0** per 1000	**0** per 1000 Difference: **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 patients in 5 studies. (Randomized controlled)	**20** per 1000	**40** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**0** per 1000	**0** per 1000 Difference: **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**

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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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artesunate + mefloquine	Dihydroartemisinin + piperaquine		
Serious adverse events (including deaths)	Based on data from 3,522 patients in 8 studies. (Randomized controlled)	**8** per 1000	**9** per 1000 Difference: **1 more** per 1000 CI 95%	Moderate Due to serious imprecision [1]	
Nausea	Relative risk Based on data from 4,531 patients in 9 studies. (Randomized controlled)	**20** per 1000	**14** per 1000 Difference: **6 fewer** per 1000 CI 95%	Moderate Due to serious risk of bias [2]	
Early vomiting	Relative risk Based on data from 4,114 patients in 9 studies. (Randomized controlled)	**7** per 1000	**6** per 1000 Difference: **1 fewer** per 1000 CI 95%	Moderate Due to serious risk of bias [3]	
Vomiting	Relative risk Based on data from 2,744 patients in 5 studies. (Randomized controlled)	**13** per 1000	**8** per 1000 Difference: **5 fewer** per 1000 CI 95%	Moderate Due to serious risk of bias [4]	
Anorexia	Relative risk	**15**	**13**	Low Due to serious	

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artesunate + mefloquine	Dihydroartemisinin + piperaquine		
	Based on data from 3,497 patients in 6 studies. (Randomized controlled)	per 1000	per 1000	risk of bias and serious imprecision [5]	
		Difference: **2 fewer** per 1000 CI 95%			
Diarrhoea	Relative risk Based on data from 2,217 patients in 5 studies. (Randomized controlled)	**6** per 1000	**8** per 1000	Moderate Due to serious risk of bias [6]	
		Difference: **2 more** per 1000 CI 95%			
Abdominal pain	Relative risk Based on data from 3,887 patients in 7 studies. (Randomized controlled)	**11** per 1000	**11** per 1000	Moderate Due to serious risk of bias [7]	
		Difference: **0 fewer** per 1000 CI 95%			
Headache	Relative risk Based on data from 2,039 patients in 4 studies. (Randomized controlled)	**12** per 1000	**10** per 1000	Low Due to serious risk of bias and serious inconsistency [8]	
		Difference: **2 fewer** per 1000 CI 95%			
Dizziness	Relative risk Based on data from 4,531 patients in 9 studies. (Randomized controlled)	**36** per 1000	**26** per 1000	Moderate Due to serious risk of bias [9]	
		Difference: **10 fewer** per 1000 CI 95%			
Sleeplessness	Relative risk Based on data from 2,551 patients in 6 studies. (Randomized controlled)	**21** per 1000	**10** per 1000	Moderate Due to serious risk of bias [10]	
		Difference: **11 fewer** per 1000 CI 95%			
Fatigue	Relative risk Based on data from 872 patients in 2 studies. (Randomized controlled)	**8** per 1000	**3** per 1000	Low Due to serious risk of bias and serious indirectness [11]	
		Difference: **5 fewer** per 1000 CI 95%			
Nightmares	Relative risk Based on data from 220	**10** per 1000	**1** per 1000	Low Due to serious risk of bias and	

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Outcome Timeframe	Study results and measurements	Absolute effect estimates Artesunate + mefloquine	Dihydroartemisinin + piperaquine	Certainty of the Evidence (Quality of evidence)	Plain text summary
	patients in 1 studies. (Randomized controlled)	Difference: **9 fewer** per 1000 CI 95%		serious indirectness [12]	
Anxiety	Relative risk Based on data from 522 patients in 1 studies. (Randomized controlled)	**11** per 1000	**1** per 1000	Low Due to serious risk of bias and serious indirectness [13]	
		Difference: **10 fewer** per 1000 CI 95%			
Blurred vision	Relative risk Based on data from 464 patients in 1 studies. (Randomized controlled)	**9** per 1000	**4** per 1000	Low Due to serious risk of bias and serious indirectness [14]	
		Difference: **5 fewer** per 1000 CI 95%			
Tinnitus	Relative risk Based on data from 220 patients in 1 studies. (Randomized controlled)	**9** per 1000	**4** per 1000	Low Due to serious risk of bias and serious indirectness [15]	
		Difference: **5 fewer** per 1000 CI 95%			
Palpitations	Relative risk Based on data from 1,175 patients in 3 studies. (Randomized controlled)	**18** per 1000	**11** per 1000	Moderate Due to serious risk of bias [16]	
		Difference: **7 fewer** per 1000 CI 95%			
Cough	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized controlled)	**10** per 1000	**8** per 1000	Low Due to serious risk of bias and serious imprecision [17]	
		Difference: **2 fewer** per 1000 CI 95%			
Dyspnoea	Relative risk Based on data from 220 patients in 1 studies. (Randomized controlled)	**9** per 1000	**3** per 1000	Low Due to serious risk of bias and serious imprecision [18]	
		Difference: **6 fewer** per 1000 CI 95%			
Prolonged QT interval (adverse event)	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized	**4** per 1000	**5** per 1000	Low Due to serious risk of bias and serious imprecision [19]	
		Difference: **1 more** per 1000			

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artesunate + mefloquine	Dihydroartemisinin + piperaquine		
	controlled)	CI 95%			
Prolonged QT interval (Bazett correction)	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized controlled)	**4** per 1000	**9** per 1000	**Low** Due to serious risk of bias and serious imprecision [20]	
		Difference: **5 more** per 1000 CI 95%			
Prolonged QT interval (Fridericia correction)	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized controlled)	**5** per 1000	**4** per 1000	**Low** Due to serious risk of bias and serious imprecision [21]	
		Difference: **1 fewer** per 1000 CI 95%			
Arthralgia	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized controlled)	**6** per 1000	**5** per 1000	**Moderate** Due to serious risk of bias [22]	
		Difference: **1 fewer** per 1000 CI 95%			
Myalgia	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized controlled)	**6** per 1000	**6** per 1000	**Moderate** Due to serious risk of bias [23]	
		Difference: **0 fewer** per 1000 CI 95%			
Urticaria	Relative risk Based on data from 719 patients in 2 studies. (Randomized controlled)	**2** per 1000	**1** per 1000	**Low** Due to serious risk of bias and serious imprecision [24]	
		Difference: **1 fewer** per 1000 CI 95%			
Pruritus	Relative risk Based on data from 872 patients in 2 studies. (Randomized controlled)	**3** per 1000	**2** per 1000	**Low** Due to serious risk of bias and serious imprecision [25]	
		Difference: **1 fewer** per 1000 CI 95%			
Rash	Relative risk Based on data from 220	**1** per 1000	**0** per 1000	**Low** Due to serious risk of bias and	

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artesunate + mefloquine	Dihydroartemisinin + piperaquine		
	patients in 1 studies. (Randomized controlled)	Difference: **1 fewer** per 1000 CI 95%		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

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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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artemether + lumefantrine	Artesunate + pyronaridine		
Treatment failure on day 28 (PCR-unadjusted)	Relative risk 0.6 (CI 95% 0.4 - 0.9) Based on data from 1,720 patients in 2 studies. (Randomized controlled)	70 per 1000	42 per 1000 Difference: **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 patients in 2 studies. (Randomized controlled)	10 per 1000	17 per 1000 Difference: **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 patients in 2 studies. (Randomized controlled)	170 per 1000	145 per 1000 Difference: **25 fewer** per 1000 (CI 95% 80 fewer - 61 more)	Moderate Due to serious indirectness [3]	

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artemether + lumefantrine	Artesunate + pyronaridine		
Treatment failure on day 42 (PCR-adjusted)	Relative risk 1.53 (CI 95% 0.73 - 3.19) Based on data from 1,472 patients in 2 studies. (Randomized controlled)	**20** per 1000	**31** per 1000 Difference: **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

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artesunate + mefloquine	Artesunate + pyronaridine		
Treatment failure on day 28 (PCR-unadjusted)	Relative risk 0.35 (CI 95% 0.17 - 0.73) Based on data from 1,200 patients in 1 studies. (Randomized controlled)	40 per 1000	14 per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	20 per 1000	8 per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	80 per 1000	69 per 1000 Difference: **11 fewer** per 1000 (CI 95% 34 fewer - 25 more)	Moderate Due to serious indirectness [3]	
Treatment failure on day 42 (PCR-adjusted)	Relative risk 1.64 (CI 95% 0.89 - 3) Based on data from 1,116 patients in 1 studies. (Randomized controlled)	40 per 1000	66 per 1000 Difference: **26 more** per 1000 (CI 95% 4 fewer - 80 more)	Low Due to serious 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.

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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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Comparator antimalarial	Pyronaridine alone or with artesunate		
Elevated alanine aminotransaminase activity (Grade 3, 4 toxicity)	Relative risk 4.17 (CI 95% 1.38 - 12.61) Based on data from 3,523 patients in 4 studies. (Randomized controlled)	**2** per 1000	**8** per 1000 Difference: **6 more** per 1000 (CI 95% 1 more - 23 more)	Moderate Due to serious indirectness [1]	
Elevated aspartate aminotransferase activity (Grade 3, 4 toxicity)	Relative risk 4.08 (CI 95% 1.17 - 14.26) Based on data from 3,528 patients in 4 studies. (Randomized controlled)	**2** per 1000	**8** per 1000 Difference: **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 patients in 3 studies. (Randomized controlled)	**2** per 1000	**1** per 1000 Difference: **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 patients in 3 studies. (Randomized controlled)	**3** per 1000	**6** per 1000 Difference: **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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artemether + lumefantrine	Artemisinin + naphthoquine		
Treatment failure on day 28 (PCR-unadjusted)	Relative risk 1.54 (CI 95% 0.27 - 8.96) Based on data from 297 patients in 2 studies. (Randomized controlled)	**10** per 1000	**15** per 1000 Difference: **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 patients in 2 studies. (Randomized controlled)	**0** per 1000	**0** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**20** per 1000	**118** per 1000 Difference: **98 more** per 1000 (CI 95% 5 fewer - 932 more)	Very Low Due to serious indirectness and very serious imprecision [3]	

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artemether + lumefantrine	Artemisinin + naphthoquine		
Parasite clearance: parasitaemia on day 2	Relative risk 0.15 (CI 95% 0.01 - 2.92) Based on data from 297 patients in 2 studies. (Randomized controlled)	**20** per 1000	**3** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**20** per 1000	**39** per 1000 Difference: **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

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Dihydroartemisinin + piperaquine	Artemisinin + naphthoquine		
Treatment failure on day 28 (PCR-unadjusted)	Relative risk Based on data from 143 patients 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 patients 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 patients in 1 studies. (Randomized controlled)	30 per 1000	27 per 1000 Difference: 3 fewer per 1000 (CI 95% 26 fewer - 158 more)	Very Low Due to serious indirectness and very serious imprecision [3]	
Treatment failure on day 42 (PCR-adjusted)	Relative risk 0.19 (CI 95% 0.01 - 3.82) Based on data from 141 patients in 1 studies. (Randomized controlled)	30 per 1000	6 per 1000 Difference: 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 patients 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 patients 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 patients in 1 studies. (Randomized controlled)	80 per 1000	110 per 1000 Difference: 30 more per 1000 (CI 95% 38 fewer - 216 more)	Very Low Due to serious indirectness and very serious imprecision [7]	

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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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artesunate 1 day plus sulfadoxine-pyrimethamine	Artesunate 3 days plus sulfadoxine-pyrimethamine		
Parasitological failure 14 days	Relative risk 0.36 (CI 95% 0.27 - 0.5) Based on data from 1,276 patients in 4 studies. (Randomized controlled)	**19** per 1000 Difference: **12 fewer** per 1000 (CI 95% 14 fewer - 9 fewer)	**7** per 1000	**High** 1	
Parasitological failure - PCR-unadjusted 28 days	Relative risk 0.62 (CI 95% 0.54 - 0.71) Based on data from 1,260 patients in 4 studies. (Randomized controlled)	**47** per 1000 Difference: **18 fewer** per 1000 (CI 95% 22 fewer - 14 fewer)	**29** per 1000	**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 patients in 4 studies. (Randomized controlled)	**33** per 1000 Difference: **18 fewer** per 1000 (CI 95% 21 fewer - 15 fewer)	**15** per 1000	**High** 3	*Corresponding risk calculated is different than what is reported in WHO document*
Gametocytaemia 7 days	Relative risk 0.74 (CI 95% 0.58 - 0.93) Based on data from 1,260 patients in 4 studies. (Randomized controlled)	**20** per 1000 Difference: **5 fewer** per 1000 (CI 95% 8 fewer - 1 fewer)	**15** per 1000	**High** 4	
Gametocytaemia 14 days	Relative risk 0.8 (CI 95% 0.57 - 1.14) Based on data from 1,199 patients in 4 studies. (Randomized controlled)	**11** per 1000 Difference: **2 fewer** per 1000 (CI 95% 5 fewer - 2 more)	**9** per 1000	**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 patients in 4 studies. (Randomized controlled)	**3** per 1000 Difference: **2 fewer** per 1000 (CI 95% 3 fewer - 0 fewer)	**1** per 1000	**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

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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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		ACT	ACT + primaquine		
Malaria incidence, prevalence or entomological inoculation rate	Relative risk Based on data from 0 patients in 0 studies.	CI 95%			
People infectious to mosquitoes	Relative risk Based on data from 0 patients in 0 studies.	CI 95%			Limited observational data from mosquito feeding studies suggests that 0.25 mg/kg bw may rapidly reduce the infectivity of gametocytes to mosquitoes.
Participants with gametocytes on microscopy or PCR (day 8) (dose < 0.4 mg/kg bw) [1]	Relative risk 0.67 (CI 95% 0.44 - 1.02) Based on data from 223 patients in 1 studies. (Randomized controlled)	**34** per 1000	**23** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**35** per 1000	**11** per 1000 Difference: **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 patients in 7 studies. (Randomized controlled)	**30** per 1000	**9** per 1000 Difference: **21 fewer** per 1000 (CI 95% 23 fewer - 19 fewer)	**High** [6]	

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		ACT	ACT + primaquine		
Mean percentage change in haemoglobin (Hb) [7]	Based on data from: 101 patients 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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Chloroquine	ACT		
Remaining parasitaemia at 24 h	Relative risk 0.42 (CI 95% 0.36 - 0.5) Based on data from 1,652 patients in 4 studies. (Randomized controlled)	**520** per 1000	**218** per 1000	High [1]	
		Difference: **302 fewer** per 1000 (CI 95% 333 fewer - 260 fewer)			
Still febrile after 24 h	Relative risk 0.55 (CI 95% 0.43 - 0.7) Based on data from 990 patients in 2 studies. (Randomized controlled)	**290** per 1000	**160** per 1000	Moderate Due to serious inconsistency [2]	
		Difference: **130 fewer** per 1000 (CI 95% 165 fewer - 87 fewer)			
Effective treatment of blood-stage infection as	Relative risk 0.58 (CI 95% 0.18 - 1.9) Based on data from 1,622 patients in 5	**30** per 1000	**17** per 1000	High [3]	
		Difference: **13 fewer** per 1000			

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Chloroquine	ACT		
assessed by recurrent parasitaemia before day 28	studies. (Randomized controlled)	(CI 95% 25 fewer - 27 more)			
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 patients in 1 studies. (Randomized controlled)	**60** per 1000	**16** per 1000	Low Due to serious indirectness and serious imprecision [4]	
		Difference: **44 fewer** per 1000 (CI 95% 55 fewer - 4 fewer)			
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 patients in 3 studies. (Randomized controlled)	**400** per 1000	**228** per 1000	Moderate Due to serious indirectness [5]	
		Difference: **172 fewer** per 1000 (CI 95% 240 fewer - 72 fewer)			
Serious adverse events	Relative risk 1 (CI 95% 0.14 - 7.04) Based on data from 1,775 patients in 5 studies. (Randomized controlled)	**0** per 1000	**0** per 1000	High [6]	
		Difference: **0 fewer** per 1000 (CI 95% 0 fewer - 0 fewer)			

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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Alternative ACT	Dihydroartemisinin + piperaquine		
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 patients in 3 studies. (Randomized controlled)	350 per 1000 Difference: **280 fewer** per 1000 (CI 95% 322 fewer - 178 fewer)	70 per 1000	Moderate Due to serious inconsistency [1]	
Post-treatment prophylaxis as assessed by recurrent	Relative risk 0.21 (CI 95% 0.1 - 0.46) Based on data from 179 patients in 2 studies.	340 per 1000	71 per 1000	Low Due to serious risk of bias and serious	

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Outcome Timeframe	Study results and measurements	Absolute effect estimates Alternative ACT Dihydroartemisinin + piperaquine		Certainty of the Evidence (Quality of evidence)	Plain text summary
parasitaemia between days 28 and 42 - with primaquine	(Randomized controlled)	Difference: **269 fewer** per 1000 (CI 95% 306 fewer - 184 fewer)		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 patients in 1 studies. (Randomized controlled)	**330** per 1000	**132** per 1000 Difference: **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)

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		No primaquine	Primaquine 14 days		
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 patients in 10 studies. (Randomized controlled)	80 per 1000	48 per 1000 Difference: **32 fewer** per 1000 (CI 95% 42 fewer - 20 fewer)	High 1	
Serious adverse events	Based on data from: 1,740 patients 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 patients 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)

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Outcome Timeframe	Study results and measurements	Absolute effect estimates 7 days primaquine	14 days primaquine	Certainty of the Evidence (Quality of evidence)	Plain text summary
P. vivax relapse defined as reappearance of P. vivax parasitaemia > 30 days after starting primaquine	Relative risk 0.45 (CI 95% 0.25 - 0.81) Based on data from 126 patients in 1 studies. (Randomized controlled)	**420** per 1000	**189** per 1000 Difference: **231 fewer** per 1000 (CI 95% 315 fewer - 80 fewer)	Low Due to serious indirectness and serious imprecision [1]	
Severe adverse events	Based on data from: 126 patients 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 patients 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	Absolute effect estimates Placebo	Chloroquine prophylaxis	Certainty of the Evidence (Quality of evidence)	Plain text summary
Clinical malaria	Relative risk				

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Placebo	Chloroquine prophylaxis		
P. vivax parasitemia	Relative risk 0.02 (CI 95% 0 - 0.26) Based on data from 951 patients in 1 studies. (Randomized controlled)	CI 95% **70** per 1000	**1** per 1000	Moderate Due to serious imprecision [1]	
		Difference: **69 fewer** per 1000 (CI 95% 70 fewer - 52 fewer)			
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 patients in 1 studies. (Randomized controlled)	**509** per 1000	**484** per 1000	Moderate Due to serious imprecision [2]	
		Difference: **25 fewer** per 1000 (CI 95% 51 fewer - 5 more)			
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	Absolute effect estimates Quinine Artesunate		Certainty of the Evidence (Quality of evidence)	Plain text summary
Death	Relative risk 0.76 (CI 95% 0.65 - 0.9) Based on data from 5,765 patients in 4 studies. (Randomized controlled)	**109** per 1000	**83** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**11** per 1000	**14** per 1000 Difference: **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 patients in 3 studies. (Randomized controlled)	**28** per 1000	**38** per 1000 Difference: **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 patients in 4 studies. (Randomized controlled)	**30** per 1000	**19** per 1000 Difference: **11 fewer** per 1000 (CI 95% 16 fewer - 4 fewer)	High [4]	
Time to hospital discharge (days)	Based on data from: 113 patients 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

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trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: No serious.** There was no statistical heterogeneity between the trials (I² = 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.
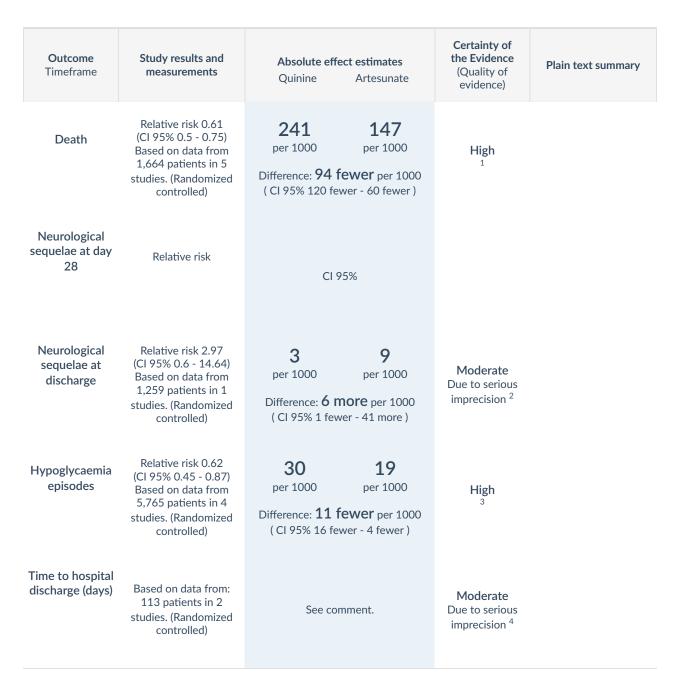
3.   **Risk of bias: No serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: No serious.** There was no statistical heterogeneity between the trials (I² = 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 (I² = 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

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Quinine	Artesunate		
Death	Relative risk 0.61 (CI 95% 0.5 - 0.75) Based on data from 1,664 patients in 5 studies. (Randomized controlled)	**241** per 1000	**147** per 1000 Difference: **94 fewer** per 1000 (CI 95% 120 fewer - 60 fewer)	High [1]	
Neurological sequelae at day 28	Relative risk	CI 95%			
Neurological sequelae at discharge	Relative risk 2.97 (CI 95% 0.6 - 14.64) Based on data from 1,259 patients in 1 studies. (Randomized controlled)	**3** per 1000	**9** per 1000 Difference: **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 patients in 4 studies. (Randomized controlled)	**30** per 1000	**19** per 1000 Difference: **11 fewer** per 1000 (CI 95% 16 fewer - 4 fewer)	High [3]	
Time to hospital discharge (days)	Based on data from: 113 patients 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.
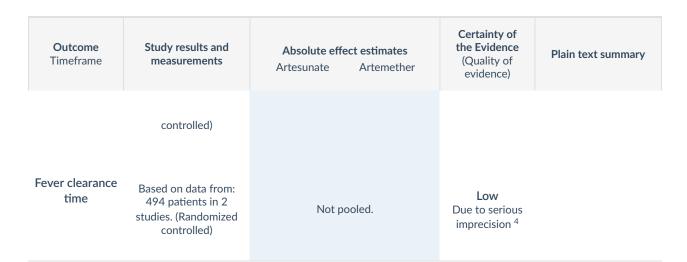
2. **Risk of bias: No serious.** This trial was unblinded, but the nature of the sequelae makes observer or reporting bias unlikely. **Inconsistency: No serious.** Not applicable, as only one trial. **Indirectness: No serious.** This trial was conducted in sites in four countries in Asia with the standard 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.

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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 did not. Neither trial was blinded. **Inconsistency: No serious.** There was no statistical heterogeneity (I² = 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% confidenc..

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 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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artesunate	Artemether		
Death	Relative risk 0.55 (CI 95% 0.34 - 0.92) Based on data from 494 patients in 2 studies. (Randomized controlled)	**148** per 1000	**81** per 1000 Difference: **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 patients in 2 studies. (Randomized controlled)	Not pooled.		Moderate Due to serious imprecision [2]	
Parasite clearance time	Based on data from: 494 patients in 2 studies. (Randomized	Not pooled.		Moderate Due to serious imprecision [3]	

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Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Artesunate	Artemether		
Fever clearance time	controlled) Based on data from: 494 patients 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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Quinine	Artemether		
Death	Relative risk 0.96 (CI 95% 0.76 - 1.2) Based on data from 1,447 patients in 12 studies. (Randomized controlled)	170 per 1000	163 per 1000 Difference: **7 fewer** per 1000 (CI 95% 41 fewer - 34 more)	Moderate Due to serious imprecision [1]	

Outcome Timeframe	Study results and measurements	Absolute effect estimates Quinine	Artemether	Certainty of the Evidence (Quality of evidence)	Plain text summary
Neurological sequelae at discharge	Relative risk 0.84 (CI 95% 0.66 - 1.07) Based on data from 968 patients in 7 studies. (Randomized controlled)	**220** per 1000	**185** per 1000 Difference: **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 patients 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 patients 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 patients 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	Absolute effect estimates Quinine	Artemether	Certainty of the Evidence (Quality of evidence)	Plain text summary
Death	Relative risk 0.59 (CI 95% 0.42 - 0.83) Based on data from 716 patients in 4 studies. (Randomized controlled)	**208** per 1000	**123** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**4** per 1000	**12** per 1000 Difference: **8 more** per 1000 (CI 95% 3 fewer - 107 more)	Moderate Due to serious imprecision [2]	
Coma resolution time	Based on data from: 683 patients in 3 studies. (Randomized controlled)	Not pooled.		Low Due to serious inconsistency and serious imprecision [3]	
Parasite clearance time	Based on data from: 716 patients in 4 studies.	Not pooled.		Moderate Due to serious imprecision [4]	
Fever clearance time	Based on data from: 716 patients 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

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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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Placebo	Rectal artesunate		
All-cause mortality (in Asia) 7-30 days	Relative risk 0.44 (CI 95% 0.23 - 0.82) Based on data from 2,010 patients in 1 studies. (Randomized controlled)	**31** per 1000	**14** per 1000 Difference: **17 fewer** per 1000 (CI 95% 24 fewer - 6 fewer)	**Low** Due to serious inconsistency and serious imprecision [1]	
All-cause mortality (in Africa) 7-30 days	Relative risk 0.81 (CI 95% 0.63 - 1.04) Based on data from 6,040 patients in 1 studies. (Randomized controlled)	**44** per 1000	**36** per 1000 Difference: **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 patients in 1 studies. (Randomized controlled)	**41** per 1000	**30** per 1000 Difference: **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	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Placebo	Rectal artesunate		
All-cause mortality 7-30 days	Relative risk 2.21 (CI 95% 1.18 - 4.15) Based on data from 4,018 patients in 1 studies. (Randomized controlled)	**7** per 1000	**15** per 1000 Difference: **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.

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