Malaria Policy Advisory Committee Meeting

11–13 April 2018, Geneva, Switzerland
Background document for Session 2

World Health Organization

Draft vector control guidelines

March 2018, Geneva, Switzerland

Guidelines for
malaria prevention through vector control

DRAFT

March 2018

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1. Glossary

Anthropophilic	Description of mosquitoes that show a preference for feeding on humans, even when non-human hosts are available Note: A relative term requiring quantification to indicate the extent of the mosquitoes' preference for anthropophily versus zoophily, usually expressed as the human blood index (proportion of mosquitoes that have fed on humans out of total that have fed)
Artemisinin-based combination therapy	The combination of an artemisinin derivative with a longer acting antimalarial drug that has a different mode of action
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 the treatment. Note: When bioassays are used for the periodic monitoring of the continued efficacy of residual insecticide deposits on sprayed surfaces in houses (as in indoor residual spraying), attention should be paid to the environmental conditions and possible adverse factors (e.g. washing, re-plastering, soot) that affect the deposits on treated surfaces; these factors may reduce the effectiveness of treatment in a way that differs from the intrinsic rate of decay of the insecticide.
Biting rate	Average number of mosquito bites received by a host in a unit of time, specified according to host and mosquito species (usually measured by human landing collection) Note: Human malariology mainly requires the "human biting rate" of vectors.
Endemic area	An area in which there is an ongoing, measurable incidence of malaria infection and mosquito-borne transmission over a succession of years
Endemicity, level of	Degree of malaria transmission in an area Note: Various terms have been used to designate levels of endemicity, but none is fully satisfactory. Parasite rate or spleen rate has been used to define levels of endemicity in children aged 2–9 years, i.e. hypoendemic: 0–10%, mesoendemic: 10–50%, hyperendemic: constantly > 50% and holoendemic: constantly ≥ 75% with a low adult spleen rate. Parasite density decreases rapidly between 2 and 5 years of age.
Endophagy	Tendency of mosquitoes to blood-feed indoors Note: Contrasts with exophagy
Endophily	Tendency of mosquitoes to rest indoors Note: Contrasts with exophily; usually quantified as the proportion resting indoors; used in assessing the effect of indoor residual spraying
Entomological inoculation rate	Number of infective bites received per person in a given unit of time in a human population Note: This rate is the product of the "human biting rate" (the number of bites per person per day by vector mosquitoes) and the sporozoite rate (proportion of vector mosquitoes that are infective). At low levels of transmission, the estimated entomological inoculation rate may not be reliable, and alternative methods should be considered for evaluating transmission risk.
Exophagy	Tendency of mosquitoes to feed outdoors Note: Contrasts with endophagy; usually quantified as the proportion biting hosts outdoors versus indoors, conveniently assessed by comparative human landing catches outdoors and indoors or by observation of biting rates on non-human hosts outdoors
Exophily	Tendency of mosquitoes to rest outdoors Note: Contrasts with endophily; usually quantified as the proportion of mosquitoes resting outdoors versus indoors; used in estimating outdoor transmission risks
Indoor residual spraying	Operational procedure and strategy for malaria vector control that involves spraying interior surfaces of dwellings with a residual insecticide to kill or repel endophilic mosquitoes
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	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.

	Note: Insecticides used for malaria vector control are approved by the WHO Pesticide Evaluation Scheme (WHOPES, http://www.who.int/whopes/).
Insecticide resistance	Property of mosquitoes to survive exposure to a standard dose of insecticide; may be the result of physiological or behavioural adaptation Note: The emergence of insecticide resistance in a vector population is an evolutionary phenomenon due to either behavioural avoidance (e.g. exophily instead of endophily) or physiological factors whereby the insecticide is metabolized, not potentiated, or absorbed less than by susceptible mosquitoes.
Integrated vector management	Rational decision-making for optimal use of resources for vector control Note: The aim is to improve the efficacy, cost-effectiveness, ecological soundness and sustainability of vector control activities against vector-borne diseases.
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 Note: The four types of larval source management are: habitat modification, which is a permanent alteration of the environment, e.g. land reclamation; habitat manipulation, which is a recurrent activity, e.g. flushing of streams; larviciding, which is the regular application of biological or chemical insecticides to water bodies; and biological control, which consists of the introduction of natural predators into water bodies.
Larvicide	Substance used to kill mosquito larvae Note: Larvicides are applied in the form of oils (to asphyxiate larvae and pupae), emulsions, or small pellets or granules of inert carrier impregnated with insecticide, which is released gradually when they are placed in water.
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 control	Reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts. Continued interventions are required to sustain control.
Malaria elimination	Interruption of local transmission (reduction to zero incidence of indigenous cases) of a specified malaria parasite in a defined geographical area as a result of deliberate activities. Continued measures to prevent re-establishment of transmission are required. Note: The certification of malaria elimination in a country requires local transmission to be interrupted for all human malaria parasites.
Malaria eradication	Permanent reduction to zero of the worldwide incidence of infection caused by human malaria parasites as a result of deliberate activities. Interventions are no longer required once eradication has been achieved.
Malaria prevalence	Proportion of a specified population with malaria infection at one time
Malarious area	Area in which transmission of malaria is occurring or has occurred during the preceding 3 years
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 recommended use under field conditions. Note: Untreated mosquito nets can also provide substantial protection against mosquito bites, but they have less effect against vectorial capacity and transmission rates. See also Long-lasting insecticidal net.
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.
Prequalification	Process to ensure that health products are safe, appropriate and meet stringent

	quality standards for international procurement Note: Health products are prequalified through an assessment of product dossiers, inspection of manufacturing and testing sites, quality control testing in the case of vaccines and medicines, validation of the performance of diagnostic tests and verification that the products are suitable for use in the destination countries.
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)
Sporozoite	Motile stage of the malaria parasite that is inoculated by a feeding female anopheline mosquito and may cause infection
Spraying, residual	Spraying the interior walls and ceilings of dwellings with a residual insecticide to kill or repel endophilic mosquito vectors of malaria
Surveillance	Continuous, systematic collection, analysis and interpretation of disease-specific data for use in planning, implementing and evaluating public health practice Note: Surveillance can be done at different levels of the health care system (e.g. health facilities, the community), with different detection systems (e.g. case-based: active or passive) and sampling strategies (e.g. sentinel sites, surveys).
Transmission intensity	The frequency with which people living in an area are bitten by anopheline mosquitoes carrying human malaria sporozoites Note: Transmission intensity is often expressed as the annual entomological inoculation rate, which is the average number of inoculations with malaria parasites estimated to be received by one person in a given period. Because of the difficulty of measuring entomological inoculation rate, parasite prevalence in young children is often used as a proxy for transmission intensity.
Transmission, residual	Persistence of transmission after good coverage has been achieved with high-quality vector control interventions to which local vectors are fully susceptible Note: Both human and vector behaviours are responsible for such residual transmission, such as people staying outdoors at night or local mosquito vector species displaying behaviour that allows them to avoid core interventions.
Transmission, seasonal	Transmission that occurs only during some months of the year and is markedly reduced during other months
Transmission, stable	Epidemiological type of malaria transmission characterized by a steady prevalence pattern, with little variation from one year to the next, except as the result of rapid scaling up of malaria interventions or exceptional environmental changes that affect transmission Note: In areas with stable transmission, the affected population often has high levels of immunity, and malaria vectors usually have high longevity and human biting rates
Transmission, unstable	Epidemiological type of malaria transmission characterized by large variation in incidence patterns from one year to the next Note: In areas with unstable transmission, epidemics are common and the population usually has little immunity.
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 Note: Malaria vector species are usually implicated (incriminated) after field collection and dissection indicates that the salivary glands are infected with sporozoites; specific assays can be used to detect and identify circumsporozoite protein, especially where infection rates are low.
Vector control	Measures of any kind against malaria-transmitting mosquitoes, intended to limit their ability to transmit the disease Note: Ideally, malaria vector control results in the reduction of malaria transmission rates by reducing the vectorial capacity to a point at which transmission is interrupted.
Vector susceptibility	The degree to which a mosquito population is susceptible (i.e. not resistant) to insecticides
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
	Source: *WHO malaria terminology* [1]

2. Abbreviations

ANC	Antenatal care
CIDG	Cochrane Infectious Diseases Group
DALY	Disability-adjusted life-year
EIR	Entomological inoculation rate
EPI	Expanded Programme on Immunization
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IRS	Indoor residual spraying
ISO	International Organization for Standardization
ITN	Insecticide-treated net
IVM	Integrated vector management
LLIN	Long-lasting insecticidal net
LSM	Larval source management
PBO	Piperonyl butoxide
PICO	Population, participants or patients; intervention or indicator; comparator or control; outcome
PQ	Pre-Qualification (WHO)
RCT	Randomized controlled trial
VCAG	Vector Control Advisory Group
VCTEG	Technical Expert Group on Malaria Vector Control
WHO	World Health Organization
WHOPES	WHO Pesticide Evaluation Scheme

3. Executive summary

Vector control is a vital component of malaria prevention, control and elimination strategies. This first edition of the World Health Organization's (WHO) *Guidelines for malaria prevention through vector control* contains recommendations based on recent systematic reviews of available evidence and expert opinion on the effectiveness of several vector control interventions and tools. Previous recommendations and guidance published by WHO have also been included in an attempt to provide a consolidated resource for national malaria programmes and their implementing partners.

The *Guidelines* provide specific evidence-based recommendations on:
Core interventions for malaria vector control, namely:

- Insecticide-treated nets (ITNs); and
- Indoor residual spraying (IRS);

Supplementary interventions for use in specific settings and circumstances, including:

- Larval source management (LSM), including habitat modification, habitat manipulation, larviciding and biological control;

Personal protection measures:

- Repellents (topical repellents, insecticide-treated clothing and spatial/airborne repellents)[i];
- Space-spraying.

This first edition of the *Guidelines* was prepared in accordance with the latest WHO standard methods for guideline development.

Recommendations on ITNs
Universal coverage[ii] with long-lasting insecticidal nets (LLINs) treated with a WHO-approved pyrethroid insecticide is recommended as a malaria prevention and control intervention in all malaria-endemic settings. *Strong recommendation for the intervention, high-quality evidence*
A combination of mass free distribution of LLINs through campaigns and continuous distribution through multiple channels, in particular antenatal care (ANC) clinics and the Expanded Programme on Immunization (EPI), is the recommended approach to achieve and maintain universal LLIN coverage. *Good practice statement*
Deployment of pyrethroid-PBO nets is conditionally recommended where the main malaria vector(s) exhibits 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-quality evidence*
Old LLINs should not be disposed of in any water body, as the residual insecticide on the

[i] For personal protection with topical repellents, WHO currently recommends three active ingredients: DEET (diethyltoluamide), IR3535 (3-[N-butyl-N-acetyl]aminopropionic acid ethyl ester) and KBR3023 (also called icaridin or picaridin).

[ii] Universal coverage for malaria vector control is defined as universal access to and use of appropriate interventions by populations at risk of malaria [1].

net can be toxic to aquatic organisms and especially to fish. *Strong recommendation, high-quality evidence*
Recipients of LLINs should be advised (through appropriate communication strategies) to continue using their nets beyond the 3-year minimum recommended lifespan of the net, irrespective of the condition of the net, until a replacement net is available. *Good practice statement*
Recipients of LLINs should be advised (through appropriate communication strategies) to continue using their net even if it is damaged or contains holes, irrespective of the age of the net, until a replacement net is available. *Good practice statement*
Old LLINs should only be collected where there is assurance that: (a) communities are not left uncovered, i.e. new LLINs are distributed to replace old ones; and (b) there is a suitable and sustainable plan in place for safe disposal of the collected material. If LLINs 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, the recommended method of disposal is burial. Burial should be away from water sources and preferably in non-permeable soil. *Good practice statements*

Recommendations on IRS
Universal coverage[iii] with IRS, using WHO-approved insecticides, is recommended as a malaria prevention and control intervention in all malaria-endemic settings. *Strong recommendation for the intervention, moderate-quality evidence*
The use of non-pyrethroid IRS in combination with LLINs is recommended where pyrethroid resistance is compromising the effectiveness of ITNs. Combining IRS with ITNs is not recommended in areas where there is no pyrethroid resistance. *Conditional recommendation, moderate-quality evidence*
Malaria prevention and control and elimination programmes should prioritize the delivery of either ITNs or IRS at high 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. *Good practice statement*

[iii] Universal coverage for malaria vector control is defined as universal access to and use of appropriate interventions by populations at risk of malaria [1].

Recommendations on larval source management
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 aquatic habitats are few, fixed and findable, and its application is both feasible and cost-effective. *Conditional recommendation, low-quality evidence*

Recommendations on space spraying
There is insufficient evidence to determine the effectiveness of space spraying. In addition, it is costly and may not be cost-effective. As a result, space spraying is not recommended and IRS or ITNs should be prioritized instead. *Conditional recommendation <u>against</u> the intervention, very low-quality evidence on the effectiveness of the intervention*

Recommendations on topical repellents, insecticide-treated clothing and spatial/airborne repellents
Topical repellents
Use of topical repellents for malaria prevention is not currently recommended as a public health intervention; however, topical repellents may be beneficial as a tool to provide personal protection against malaria in specific population groups. *Conditional recommendation against the intervention, low-quality evidence*
Insecticide-treated clothing
Use of insecticide-treated clothing for malaria prevention is not currently recommended as a public health intervention; however, insecticide-treated clothing may be beneficial as a tool to provide personal protection against malaria in specific population groups (e.g. refugees, military). *Conditional recommendation against the intervention, low-quality evidence*

Recommendations on housing improvements
Closing open eaves; screening doors and windows with fly screens or mosquito netting; and filling holes and cracks in walls and roofs reduce the entry points mosquitoes use to enter houses. Together with metal roofs, ceilings, and finished interior walls, these modifications may reduce transmission of malaria and other vector-borne diseases. *Good practice statement*

4. Introduction

4.1. Background

Malaria remains an important cause of illness and death in children and adults in countries in which it is endemic. Malaria control requires an integrated approach, including prevention (primarily vector control) and prompt treatment with effective antimalarial agents. WHO's *Guidelines for the treatment of malaria* were first developed in 2006 and have been revised periodically, with the most recent edition published in 2015. To date there has been no equivalent comprehensive guideline document on malaria vector control.

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 recommendations presented in the main body of this document are brief in order to facilitate quick reference. More detail on the evidence base underlying the recommendations is provided in a series of annexes.

4.2. Objectives

The objectives of the *Guidelines* are:

1. To provide evidence-based recommendations for the effective implementation of each of the vector control options currently available for malaria prevention and control;
2. To inform and guide technical decisions on the appropriate choice(s) of vector control options for malaria prevention and control in endemic countries;
3. To support the development of evidence-based national malaria vector control policies and strategies by WHO Member States.

4.3. Scope

The *Guidelines* provide evidence-based recommendations pertaining to vector control tools, technologies and approaches that are currently available for malaria prevention and control. 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.

The *Guidelines* provide specific evidence-based recommendations on:
WHO-recommended core interventions for malaria vector control that are applicable for populations at risk of malaria in most epidemiological and ecological scenarios, namely:

- ITNs, which in most settings are LLINs;
- IRS with a WHO-recommended insecticide;

Supplementary interventions that can be used in addition to the core interventions in specific settings and circumstances, including:

- LSM, including habitat modification, habitat manipulation, larviciding and biological control;

Personal protection measures:

- Repellents (topical repellents, insecticide-treated clothing and spatial/airborne

repellents)[iv];
- Space-spraying.

The vector control recommendations presented in the *Guidelines* are based on a consideration of the combined evidence gained from randomized controlled trials (RCTs) and other types of trials and studies, as well as the experience and expert opinion of the Guideline Development Group and other key stakeholders. Inevitably, gaps in our knowledge remain, especially with respect to new technologies. The *Guidelines* will therefore be subject to regular review, with updates anticipated approximately every two years, or more frequently, as new evidence becomes available.

4.4. Target audience

The *Guidelines* have been developed primarily for programme managers, health professionals, environmental health services professionals, procurement agencies and others responsible for implementing and financing malaria vector control activities in malaria-endemic countries. The *Guidelines* are also intended to be used by international development partners, donors and funding agencies in order to support decision-making on the selection of interventions and procurement of appropriate vector control products.

4.5. Funding

Preparation and printing of the *Guidelines* were funded by the WHO Global Malaria Programme under its umbrella grant agreement with the Bill & Melinda Gates Foundation. No other external source of funding either from bilateral technical partners or from industry was solicited or used.

4.6. Management of conflicts of interest

All members of the Guideline Development Group and the external expert reviewers made declarations of interest, which were managed in accordance with standard WHO procedures and cleared by the Legal Department. The WHO Guideline Steering Group and the co-chairs of the Guideline Development Group were satisfied that there had been a transparent declaration of interests. No case necessitated the exclusion of any Guideline Development Group members or external peer reviewers. No potential conflicts of interest that could have compromised any individual member's stance on equity and human rights were identified. The members of the Guideline Development Group and a summary of the declarations of interest are listed in Annex 1.

4.7. Methods used to formulate recommendations

The first edition of the *Guidelines for malaria prevention through vector control* was prepared in accordance with the latest WHO standard methods for guideline development [2]. The WHO guideline development process involves planning; conducting a ‘scoping’ and needs assessment; establishing an internal WHO Guideline Steering Group and an external Guideline Development Group; formulating key questions in PICO[v] format; commissioning evidence reviews; applying Grading of Recommendations Assessment, Development and Evaluation (GRADE) to the quality of the evidence; and making recommendations. This methodology (see Annex 2) ensures that the link between the evidence base and the recommendations is transparent.

[iv] For personal protection with topical repellents, WHO currently recommends three active ingredients: DEET (diethyltoluamide), IR3535 (3-[N-butyl-N-acetyl]aminopropionic acid ethyl ester) and KBR3023 (also called icaridin or picaridin).

[v] PICO: Population, participants or patients; intervention or indicator; comparator or control; outcome

The WHO Guideline Steering Group is responsible for drafting the scope of the guideline and preparing the planning proposal, formulating questions in PICO format, identifying potential members for the Guideline Development Group, obtaining declarations of interest from Guideline Development Group members and managing any conflicts of interest, and submitting the finalized planning proposal to the Guidelines Review Committee for review.

The Guideline Development Group is an external body whose central task was to develop the evidence-based recommendations contained in the *Guidelines*. The specific tasks of the Guideline Development Group included:

- Providing inputs as to the scope of the *Guidelines*;
- Assisting the Guideline Steering Group in developing 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 quality of the evidence used to inform the recommendations, and providing input where necessary;
- 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 guideline document prior to submission to the Guideline Review Committee.

The Guideline Development Group established for these guidelines consisted of 13 members representing relevant technical experts; intended end-users (programme managers and health professionals responsible for adopting, adapting and implementing the guidelines); representatives of groups affected by the guideline recommendations; and experts in assessing evidence and developing evidence-based guidelines. The Chair of the Guideline Development Group and several of its members are experienced and have expertise in ensuring that equity, human rights, gender and social determinants are taken into consideration in efforts to improve public health outcomes.

The Guideline Development Group used GRADEPro software (https://gradepro.org/), specifically the interactive Evidence-to-Decision Framework, to assist in the process of evidence review and recommendation-setting. The Evidence-to-Decision Framework considers 12 categories to arrive at a recommendation for or against an intervention; these are listed in Table 1 with accompanying descriptions.

Table 1. Criteria used in the Evidence-to-Decision Framework

Criterion	Explanation
Is the problem a priority?	Are the consequences of the problem serious (i.e. severe or important in terms of the potential benefits or savings)? Is the problem urgent? Is it a recognized priority (e.g. based on a national health plan)? Are a large number of people affected by the problem?
How substantial are the desirable anticipated effects?	How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option (taking into account the severity or importance of the desirable consequences and the number of people affected)?
How substantial are the undesirable anticipated effects?	How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option (taking into account the severity or importance of the adverse effects and the number of people affected)?
What is the overall certainty of the evidence of effects?	The less certain the evidence for critical outcomes, the less likely it is that an option should be recommended.
Is there important uncertainty about or variability in how much people value the main outcomes?	How much do those affected by the proposed intervention value the outcomes in relation to the other outcomes? Is there evidence of variability in those values that is large enough to lead to different decisions?
Does the balance between desirable and undesirable effects favour the intervention or the comparison?	The larger the differences between the desirable and undesirable consequences, the more likely it is that a strong recommendation is warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely it is that a weak recommendation is warranted.
How large are the resource requirements (costs)?	The higher the costs of an intervention (the more resources consumed), the less likely it is that a strong recommendation is warranted.
What is the certainty of the evidence of resource requirements (costs)?	The higher the certainty of the evidence of resource requirements, the more confidence there is in making a recommendation for or against the intervention.
Does the cost-effectiveness of the intervention favour the intervention or the comparison?	The more cost-effective an intervention, the more likely it is that it will be recommended over the comparison.
What would be the impact on health equity?	Would the option reduce or increase health inequities? Policies or programmes that reduce inequities are more likely to be a priority than ones that do not (or ones that increase inequities).
Is the intervention acceptable to key stakeholders?	Are key stakeholders likely to find the option acceptable (given the relative importance they attach to the desirable and undesirable consequences of the option; the timing of the benefits, harms and costs; and their moral values)? The less acceptable an option is to key stakeholders, the less likely it is that it will be recommended.
Is the intervention feasible to implement?	The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it will be recommended (i.e. the more barriers there are that would be difficult to overcome).

Evidence-to-Decision Framework summaries for each of the recommendations contained in the *Guidelines* are presented alongside the GRADE tables in Annex 3.

Selected external reviewers consisting of persons interested in the subject of the guideline, as well as individuals who will be affected by the recommendations, conducted a peer review of the draft *Guidelines* document prior to its submission to the Guideline Review Committee for approval.

4.7.1. Sources of evidence

Following the Guidelines scoping meeting, the Cochrane Infectious Diseases Group (CIDG) at the Liverpool School of Tropical Medicine in Liverpool, United Kingdom, was commissioned to undertake systematic reviews and to assess the quality of the evidence for each priority question. This included new systematic reviews on the combined use of

IRS with ITNs; and space spraying. Existing systematic reviews covering larviciding, the use of larvivorous fish, and ITNs were updated. GRADE tables for IRS were produced based on the existing 2010 review (as no new studies have been published since 2010), and an ongoing systematic review on topical insect repellents was completed.

The inclusion criteria for the reviews were RCTs and quasi-experimental designs, including controlled before-and-after studies, interrupted time series (controlled and uncontrolled), and stepped wedge designs. All reviews and updates involved searches of the CIDG Specialized Register; the Cochrane Central Register of Controlled Trials, the Cochrane Library; MEDLINE (PubMed); Embase (OVID); CABS Abstracts (Web of Science); and LILACS (BIREME). The WHO International Clinical Trials Registry Platform, ClinicalTrials.gov and the ISRCTN registry were also searched to identify trials in progress. A combination of controlled vocabulary terms and free-text terms was used, including: malaria, mosquito, *Anopheles*, insecticides, bednets, ITN, IRS, and additional terms for the interventions specific to each review. Detailed search terms are reported in the Appendix of each review protocol, as published in the Cochrane Database of Systematic Reviews. Searches were not limited by time or publication language. Reference lists of all included studies were reviewed and the “similar articles” function in MEDLINE was used to see if additional studies could be identified.

In formulating its recommendations, the Guideline Development Group also considered additional evidence that was deemed not suitable for inclusion and analysis under the Cochrane systematic review process. IRS, for example, is a core intervention for malaria prevention and control that has been used successfully in malaria-endemic countries for decades, but few RCTs have been conducted. Therefore, the availability of data suitable for use in a Cochrane-style meta-analysis is limited. The large body of evidence from the original implementation trials of IRS and from national control programmes will be the subject of a separate systematic review by the Global Malaria Programme as a contribution to the *Guidelines*.

Pre-existing WHO recommendations and guidance relevant to malaria, and specifically to vector control, were reviewed by the Guideline Development Group. A list of all pre-existing guidance and recommendations is provided in Annex 4.

4.7.2. Quality of evidence

The quality of the evidence from the systematic reviews was assessed for each outcome and rated on a four-point scale (Table 2), after considering the risk of bias (including publication bias) and the consistency, directness and precision of the effect estimates. The terms used in the quality assessments refer to the Guideline Development Group’s level of confidence in the estimate of effect (and not to the scientific quality of the investigations reviewed):

Table 2. The four classes of quality of evidence used in GRADE

Quality of Evidence	Interpretation
High	The Group is very confident in the estimate of effect and considers that further research is very unlikely to change this confidence.
Moderate	The Group has moderate confidence in the estimate of effect and considers that further research is likely to have an important impact on that confidence and may change the estimate.

Low	The Group has low confidence in the estimate of effect and considers that further research is very likely to have an important impact on that confidence and is likely to change the estimate.
Very Low	The Group is very uncertain about the estimate of effect.

4.7.3. Presentation of evidence and link to recommendations

For ease of reference, the recommendations are presented in a simplified descriptive form in the main document. The recommendations are summarized in boxes at the start of each section (green); an evidence box (blue) is also presented for each recommendation. The complete GRADE tables and additional references are provided in Annex 3.

4.7.4. Formulation of recommendations

The systematic reviews, the GRADE tables and other relevant materials were provided to all members of the Guideline Development Group. Recommendations were formulated after considering the quality of the evidence, the balance of benefits and harms, and the feasibility of the intervention. Although cost is a critical factor in setting national vector control policies and was broadly considered in the recommendation formulation process, no formal, explicit analyses of the costs and cost-effectiveness of the various interventions were conducted.

The Guideline Development Group discussed the proposed wording of each recommendation and rated the strength of each recommendation in accordance with the four-point scale presented in Table 2. Any disagreements among the members were resolved through extensive discussions at the meetings, and through subsequent e-mail correspondence and teleconferencing. The final draft was circulated to the Guideline Development Group and external peer reviewers. Comments from external reviewers were incorporated into the revised guidelines as appropriate. Consensus was reached on all the recommendations, strength of evidence and the wording of the guidelines. Voting was required in only one instance, specifically in relation to larviciding. The majority view was that a conditional recommendation FOR either the intervention (larviciding) or the comparison (no larviciding) be issued. The minority view was that a conditional recommendation FOR the intervention (larviciding) be issued.

4.7.5. Strength of recommendations

Each recommendation was classified as strong or conditional using the criteria in Table 3:

Table 3. Classification of recommendations

Strength of Recommendation	Interpretation		
	For policy-makers	For programme managers / technicians	For end-users
Strong	This recommendation can be adopted as policy in most situations.	Most individuals should receive the recommended intervention.	Most people in your situation would want the recommended intervention.
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.

4.7.6. Dissemination

The *Guidelines* are published in printed form and electronically on the WHO website in three languages (English, French and Spanish). A library of all supporting documentation is available on the WHO website (www.who.int). WHO headquarters will work closely with its regional and country offices to ensure the wide dissemination of the guidelines to all malaria-endemic countries. The guidelines will also be disseminated through regional, subregional and country meetings, as appropriate. Member States will be supported to adapt and implement these guidelines, in particular to ensure that they are readily accessible to all stakeholders.

4.7.7. Updating

It is anticipated that the evidence will be reviewed regularly and updated every two years, or more frequently if new evidence becomes available. A mechanism will be established for the periodic monitoring and evaluation of the use of the *Guidelines* in countries.

4.7.8. User feedback

User feedback on the first edition of the *Guidelines* will be collected as part of all dissemination activities both informally and by directing users to the generic WHO Global Malaria Programme email address: infogmp@who.int. In addition, an online survey will be conducted to capture user experiences prior to development of the second edition of the *Guidelines.*

5. Malaria and related entomological and vector control concepts

5.1. 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*) 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 the forested regions of South-East Asia and particularly the island of Borneo.

5.2. Classification of endemicity

The intensity of transmission depends on factors related to the parasite, the vector, the human host and the environment. Transmission is more intense in places where the mosquito lifespan is longer and where the females prefer to bite humans rather than other animals (see Box 1). 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 long lifespan and strong human biting habit of the African vector species is one of the reasons that 90% of the world's malaria cases occur in Africa.

In many places, transmission is seasonal, with the peak occurring during and just after the rainy season. Malaria epidemics can occur when the climate and other conditions suddenly favour transmission in areas where people have little or no immunity to malaria. Epidemics can also occur when people with low immunity move into areas with intense malaria transmission, for instance to find work or as refugees. The intensity of malaria transmission in a given geographical area has important consequences for the pattern and distribution of clinical disease in the human population and influences the choice of vector control measures.

Box 1: Malaria transmission dynamics, vectorial capacity and the entomological inoculation rate [3]

An important concept in the epidemiology of disease is the basic reproduction rate (R_0), which is the average number of secondary cases of a disease arising from each primary infection in a defined population of susceptible individual hosts. Vectorial capacity is the entomological component of the basic reproduction rate of malaria and describes the average number of inoculations from a single case of malaria in a unit of time (usually a day) that the vector population transmits to humans, where all vectors biting an infected person become infective. The usual formula for vectorial capacity (C), in terms of a daily rate, as derived by Garrett-Jones [4], is:

$$C = \frac{ma^2 P^n}{-\log_e P}$$

where *ma* = the number of bites/person/day, *a* = the proportion of females feeding on humans divided by the duration of the gonotrophic cycle in days, P^n = the probability of a mosquito surviving to become infective, and $1/-\log_e P$ = the expected duration of life in days. Reducing vectorial capacity reduces R_0.

Entomological inoculation rate (EIR)

Vectorial capacity is an indirect method of estimating a vector's transmission rate. A more direct way is to use the EIR, which is defined as the number of infective bites received per person per night. The EIR is calculated as:

EIR = [Human biting rate (*ma*)] x [sporozoite rate (*s*)]

Annual EIRs must be reduced to less than 1 in order to substantially reduce the prevalence of malaria infection [5]. In areas of low transmission where the EIR is < 1 to 2, a reduction in the inoculation rate will result in an almost proportionate reduction in the prevalence (and incidence rate) of malaria. When the EIR exceeds 10, there is great redundancy in the infectious reservoir, and thus larger reductions in transmission are required to make a significant impact on malaria prevalence.

The EIR is a major driver of the epidemiology of malaria and the pattern of clinical disease in a given area. EIRs range from more than 100 in some parts of tropical Africa [6] to ≤ 0.01 in the Caucasus and Central Asia, where malaria transmission is only barely sustained. In much of Asia and Latin America, EIRs are < 10 (often around 1–2), and malaria in these regions is unstable and seasonal. In much of West Africa, the EIR ranges from 10–100 and malaria is stable. EIR and transmission intensity can also vary significantly over smaller spatial scales (between villages), as well as seasonally and across years.

Under conditions of 'stable malaria transmission', i.e. where populations are continuously and constantly exposed to a high frequency of malarial inoculation (the EIR exceeds 10 infective bites per person per year), partial immunity to clinical disease is acquired in early childhood, resulting in a reduced risk of developing severe malaria. In situations where transmission is stable, clinical disease is confined mainly to young children before they have acquired partial immunity. These children may develop high parasite densities that can progress very rapidly to severe malaria. By contrast, adolescents and adults are partially immune and consequently seldom suffer clinical disease, although they often have

low densities of parasites in their blood. This is the situation in many parts of sub-Saharan Africa. Immunity is modified during pregnancy, such that pregnant women, especially those undergoing their first pregnancy, are at increased risk of severe malaria. Immunity is gradually lost, at least partially, when individuals move out of an endemic area for long periods of time (usually many years).

In areas of 'unstable malaria transmission', which prevail in much of Asia, Latin America and the remaining parts of the world where malaria is endemic, the intensity of malaria transmission fluctuates widely by season and year and over relatively small distances. *P. vivax* is an important cause of malaria in these regions. The EIR is usually < 5 per year and often < 1 per year, although there are usually small foci of higher transmission. Asymptomatic parasitaemia is also common in these areas. The generally low level of transmission retards the acquisition of immunity, so that people of all ages – adults and children alike – suffer from acute clinical malaria, with a significant risk that the disease will progress to severe malaria if left untreated. Epidemics may occur in areas of unstable malaria transmission when the inoculation rate increases rapidly following a sudden increase in vector population density or longevity. Epidemics manifest as a very high incidence of malaria in all age groups. During epidemics, severe malaria is common if prompt, effective treatment is not widely available. Non-immune travellers to a malaria-endemic area are at particularly high risk for severe malaria if their infection is not detected promptly and treated effectively.

In areas where population-wide coverage with effective vector control and wide-scale deployment of artemisinin-based combination therapies (ACTs) have been achieved, the number of inoculations from infective mosquitoes is usually greatly reduced. This reduction will in turn be followed by a corresponding change in the clinical epidemiology of malaria in the area and an increasing risk of an epidemic if control measures are not sustained.

5.3. Main vectors, behaviour, distribution

Malaria is transmitted primarily 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. Annex 5 presents a list of the major vector species by WHO region, along with a brief description of the key ecological and behavioural characteristics relevant to control.

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, female mosquitoes rest for a period until their wings have fully expanded and hardened. After taking an initial meal of plant nectar, female mosquitoes seek a blood meal 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 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 methods.

After blood-feeding, female mosquitoes rest in order to digest the blood meal and mature their eggs. Female mosquitoes may rest indoors or outdoors, 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 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 use 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 in general exhibits an outdoor biting and resting habit, but it may exhibit indoor biting and resting tendencies, depending on the availability of alternative hosts.

5.4. Background and rationale for vector control

Together, the major vector-borne diseases account for around 17% of the estimated global burden of communicable diseases, claiming more than 700 000 lives every year [7]. Vector control interventions have one of the highest returns on investment in public health. Vector control is an essential component of malaria prevention, control and elimination [8]. Effective vector control programmes that reduce disease can advance human and economic development. Aside from direct health benefits, reductions in vector-borne diseases will enable greater productivity and growth, reduce household poverty, increase equity and women's empowerment, and strengthen health systems [9]. Vector control is highly effective in reducing disease transmission through its impact on the daily survival rate of vector mosquitoes, which is the key factor in determining the transmission intensity of malaria parasites (see Box 1). For example, a recently published review [10] found that *P. falciparum* infection prevalence in endemic Africa halved and the incidence of clinical disease fell by 40% between 2000 and 2015. Malaria control interventions have averted an estimated 663 (542–753 credible interval) million clinical cases since 2000, 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.

Vector control has a proven track record in the prevention and control of vector-borne disease and has been in use since the role of arthropods in the transmission of diseases to humans was first elucidated in the late 19th and early 20th centuries. Prior to the 1940s, the focus of malaria control efforts was on eliminating the aquatic sites in which mosquito larvae develop, primarily through environmental modification including land drainage. Following the discovery of the insecticidal properties of DDT in the 1940s and subsequent

discovery of other insecticides, the focus of malaria vector control shifted to the use of insecticide compounds to target both the larval and adult stages of mosquito vectors.

5.4.1. Global Technical Strategy for Malaria 2016–2030

The past decade has seen renewed global emphasis on malaria vector control. This has been the result of the rapid expansion of malaria prevention and control efforts around the 2008 'universal access' goals promoted by the United Nations and partners, and the accompanying increase in available financial resources. The *Global Technical Strategy for malaria 2016–2030* provides a comprehensive framework to guide countries in their efforts to accelerate progress towards malaria elimination, including the implementation of vector control. The Strategy emphasizes the need for universal coverage of core malaria interventions for all populations at risk and highlights the importance of using high-quality surveillance data (including on entomology) for decision-making. WHO promotes universal coverage[vi] of effective vector control for all at-risk populations (see section 6.1).

WHO recommends specific vector control interventions primarily based on evidence of their protective efficacy against infection and/or disease in humans (i.e. their epidemiological efficacy). The core malaria vector control tools recommended by WHO are LLINs [11,12] and IRS [13], which are considered to be similarly effective. WHO recommends LSM as a supplementary method in locations where malaria vector aquatic habitats are “few, fixed and findable” [14].

5.4.2. Global Vector Control Response 2017–2030

In 2017, the World Health Assembly welcomed the *Global vector control response 2017–2030* [7] and adopted a resolution to use an integrated approach to the control of vector-borne diseases. The approach builds on the concept of integrated vector management (IVM)[vii], but with renewed focus on improved human capacity at national and subnational levels, and an emphasis on strengthening infrastructure and systems, particularly in areas vulnerable to vector-borne diseases.

The vision of WHO and the broader infectious diseases community is a world free of human suffering from vector-borne diseases. The ultimate aim of the Global Vector Control Response is to reduce the burden and threat of vector-borne diseases through effective, locally adapted, sustainable vector control. As part of this vision, the Response sets ambitious yet feasible global targets that are aligned with disease-specific strategic goals and Sustainable Development Goal 3.3, with interim milestones to track progress. 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 are presented in Table 4.

Effective and locally adaptive vector control systems depend on two foundational elements: (i) enhanced human, infrastructural and health system capacity within all locally relevant sectors for vector surveillance and vector control delivery, monitoring and evaluation; and (ii) increased basic and applied research to underpin optimized vector control, and innovation for the development of new tools, technologies and approaches.

[vi] Universal coverage for malaria vector control is defined as universal access to and use of appropriate interventions by populations at risk of malaria

[vii] WHO defines IVM as a rational decision-making process to optimize the use of resources for vector control.

Both elements are required to ensure the maximum impact of sustainable vector control by using an evidence-based approach to planning and implementation.

Table 4. Priority national and regional activities and associated targets for 2017–2022 for implementation of the Global Vector Control Response

		Priority activities	2018		2020		2022	
			Countries	WHO regions	Countries	WHO regions	Countries	WHO regions
		National and regional vector control strategic plans developed/adapted to align with global vector control response	≥ 25%	≥ 2	≥ 50%	≥ 4	100%	All 6
FOUNDATION	A	National vector control needs assessment conducted or updated and resource mobilization plan developed (including for outbreak response)	≥ 25%		≥ 50%		≥75%	
	A	National entomology and cross-sectoral workforce appraised and enhanced to meet identified requirements for vector control	≥ 10%		≥ 25%		≥ 60%	
	A	Relevant staff from Ministries of Health and/or their supporting institutions trained in public health entomology	≥ 10%		≥ 25%		≥ 60%	
	A	National and regional institutional networks to support training/education in public health entomology and technical support established and functioning	≥ 25%	≥ 2	≥ 50%	≥ 4	≥75%	All 6
	B	National agenda for basic and applied research on entomology and vector control established and/or progress reviewed	≥ 25%		≥ 50%		≥75%	
PILLARS	1	National inter-ministerial task force for multi-sectoral engagement in vector control established and functioning	≥ 50%		≥ 75%		≥ 90%	
	2	National plan for effective community engagement and mobilization in vector control developed	≥ 25%		≥ 50%		≥75%	
	3	National vector surveillance systems strengthened and integrated with health information systems to guide vector control	≥ 25%		≥ 50%		≥75%	
	4	National targets for protection of at-risk population with appropriate vector control aligned across vector-borne diseases	≥ 25%		≥ 50%		≥75%	22

Effective and sustainable vector control is achievable only with sufficient human resources, an enabling infrastructure and a functional health system. WHO recommends the use of a vector control needs assessment 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.

Action is required in four key areas (pillars) to attain effective, locally adapted and sustainable vector control. These four areas are aligned with IVM and include: (1) strengthening inter- and intra-sectoral action and collaboration; (2) engaging and mobilizing communities; (3) enhancing vector surveillance and monitoring and evaluation of interventions; and (4) scaling up and integrating tools and approaches.

Pillar 1. Strengthen inter- and intra-sectoral action and collaboration

Effective coordination of vector control activities is required between health and non-health sectors (e.g. other ministries and authorities, development partners, and the private sector), as well as within the health sector (e.g. national malaria and other vector-borne disease programmes, water, hygiene and sanitation initiatives, health management information systems section). This will maximize efficiencies, have greater impact than isolated, uncoordinated activities and harness the diverse capital available in various areas.

Following a situation analysis, key stakeholders should be convened into an inter-ministerial task force, the mandate of which is the oversight, coordination and strengthening of vector control. Membership in the task force should extend to local authorities and communities, as well as to development partners and the private sector.

Pillar 2. Engage and mobilize communities
Vector control is critically dependent on harnessing local knowledge and skills within communities. Community engagement and mobilization requires working with local residents to improve vector control and build resilience against future disease outbreaks. Where appropriate participatory community-based approaches are in place, communities are supported to take responsibility for and implement vector control. Participatory community-based approaches aim to ensure that healthy behaviours become part of the social fabric and that communities take ownership of vector control at both the intra- and peri-domiciliary levels.

Communication strategies are needed in order to tailor approaches to local and disease-specific needs. These should use multiple channels, including mass, local and social media, and involve various actors in order to promote information and provoke dialogue.

Pillar 3. Enhance vector surveillance and monitoring and evaluation of interventions
The capacity of vectors to transmit pathogens and their susceptibility to vector control measures vary by species, location and time, and are dependent upon local environmental factors. Vector control implementation must therefore be based on up-to-date data on the local vectors. Vector surveillance involves the regular and systematic collection, analysis and interpretation of entomological or snail distribution data for health risk assessment and for the planning, implementation, monitoring and evaluation of vector control. Evidence-based decision-making at national level requires entomological, epidemiological and intervention data. These data should be linked in order to stratify transmission risk for planning preventive control measures, guiding routine vector and epidemiological surveillance, and facilitating assessments of the impact of interventions.

Pillar 4. Scale up and integrate tools and approaches
A key action to maximize the public health impact of vector control is the deployment and expansion of interventions appropriate to the epidemiological and entomological context. Proven and cost-effective vector control interventions include LLINs, IRS, space spraying, larviciding, use of molluscicides, and environmental management for specific target vectors.

One intervention can have multiple effects against several vectors and diseases, for example, ITNs against malaria and lymphatic filariasis (in settings where *Anopheles* mosquitoes are the principal vector), IRS against malaria and leishmaniasis in India, and larval control for malaria and dengue vectors in cities with particular vector habitats. Approaches effective against *Aedes* spp. mosquitoes can have an impact on dengue, chikungunya, Zika virus disease and yellow fever where their distributions overlap.

The decision to use a vector control intervention in a particular setting or situation should be based on clear evidence of its efficacy. Implementation must be to a high standard and at optimal coverage. Achieving sufficient coverage for at-risk populations with evidence-based and cost-effective tools offers the greatest immediate opportunity to reduce infections and disease.

In some settings, multiple vector control interventions can have greater impact in reducing transmission or disease burden than one alone; however, programmes should avoid an approach that overlays multiple interventions to compensate for deficiencies in implementation of any one tool; this may divert resources and attention away from reaching the full impact of existing interventions and lead to resource wastage.

5.4.3. The role of vector control in malaria burden reduction and elimination

WHO defines malaria elimination 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. Continued measures to prevent re-establishment of transmission are required [15].

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. Interventions are no longer required once eradication has been achieved.

Vector control strategies in conjunction with case management (prompt access to diagnosis and effective treatment) are critical for reducing malaria morbidity and mortality and reducing malaria transmission. The Global Technical Strategy for malaria states that it is essential for malaria programmes to “ensure universal access to malaria prevention, diagnosis and treatment” for at-risk populations (Pillar 1). This goal includes effective vector control as a major component, with a significant budgetary allocation.

Access to effective vector control interventions will need to be maintained in the majority of countries, even as malaria transmission is substantially reduced. 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 [16].

Once elimination has been achieved, vector control may be “focalized” rather than scaled back, i.e. the intervention should be made available for defined at-risk populations to prevent reintroduction or resumption of local transmission.

WHO recommends that malaria programmes stratify their national malaria situation 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; differentiate strata by transmission intensity, particularly if different intensities are being addressed by different sets of interventions; and determine geographical variations and population characteristics that are associated with vulnerability. Optimal coverage of ITNs/LLINs or IRS should be ensured and maintained in strata that are receptive and vulnerable to malaria transmission.

Once stratification has been completed, specific packages of interventions may be designed for implementation in the various strata identified. These intervention packages 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.

WHO recommends that all programmes working towards malaria elimination establish and maintain their capacity to conduct IRS for rapid clearance of transmission foci and as an adjunct or targeted control measure, even where ITNs/LLINs are the core vector control strategy and especially in areas where the vectors are resistant to pyrethroid insecticides.

It is acknowledged that even full implementation of core interventions cannot halt malaria parasite transmission in all settings. Residual malaria parasite transmission occurs even with good access to and use of the core vector control interventions, as such residual transmission is the result of both human and vector behaviours, for example, 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 the IRS or ITN/LLIN intervention tools.

Supplementary vector control interventions, including LSM, and the deployment of new vector control technologies to specifically address the problem of residual transmission should be implemented in accordance with the principles of IVM and comply with current WHO recommendations.

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.

In these foci, the vector species should be identified and their susceptibility to currently used insecticides evaluated. Supplementary vector control may be justified in some settings, such as for vectors that are not vulnerable to ITNs/LLINs or IRS due to physiological or behavioural resistance.

Once elimination has been achieved, vector control coverage should be maintained in receptive areas where there is a substantial risk for reintroduction (vulnerable areas). WHO therefore recommends the following:

- In areas with recent local malaria transmission (residual non-active foci), a reduction in vector control is not recommended. Optimal coverage with effective malaria vector control (including the use of new tools when they become available) of all people in such areas should be pursued and maintained.
- In areas where transmission has been interrupted for more than 3 years (cleared foci), any reduction in vector control should be based on a detailed analysis, including assessment of the receptivity and vulnerability of the area and the capacity for active disease surveillance and response.
- Countries and partners should continue to invest in health systems, including continuous support for malaria surveillance; when receptivity is reduced, a reduction in vector control may be considered in some geographical areas.

6. Recommendations by type of intervention:

6.1. Insecticide-treated nets (ITNs)

ITNs, usually LLINs, are recommended by WHO as a core intervention 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. The two categories of ITN 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.
- LLIN: 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 recommended use under field conditions.

Untreated mosquito nets can also provide substantial protection against mosquito bites, but they have less effect against vectorial capacity and transmission rates. ITNs / LLINs produce a 'community effect', whereby even members of the community that do not sleep under a net gain some protection as a result of the effect of treated nets on mosquito longevity (and therefore vectorial capacity). Large-scale field trials [17], [18] and transmission models [19],[20] suggest that absolute coverage of ≥50% use of effectively-treated nets is expected to achieve useful community-wide protection of non-users in all scenarios, and increasing gains are realised as coverage is increased further. ITNs / LLINs are most effective where the main malaria vector mosquitoes bite predominantly at night after people have retired under their nets. ITNs / LLINs can be used both indoors and outdoors, wherever they can be suitably hung (hanging nets in direct sunlight should be avoided, as sunlight can affect bioefficacy of the insecticide). All LLIN products currently recommended / pre-qualified by WHO (see http://www.who.int/pq-vector-control/en/) contain a pyrethroid, with some also containing a synergist such as piperonyl butoxide (PBO) or the pyrrole insecticide chlorfenapyr.

Recommendations on ITNs
Universal coverage[viii] with LLINs treated with a WHO-approved pyrethroid insecticide is recommended as a malaria prevention and control intervention in all malaria-endemic settings. *Strong recommendation for the intervention, high-quality evidence*
A combination of mass free distribution of LLINs through campaigns and continuous distribution through multiple channels, in particular ANC clinics and the EPI, is the recommended approach to achieve and maintain universal LLIN coverage. *Good practice statement*
Deployment of pyrethroid-PBO nets is conditionally recommended where the main malaria vector(s) exhibits pyrethroid resistance that is: a) confirmed, b) of intermediate

[viii] Universal coverage for malaria vector control is defined as universal access to and use of appropriate interventions by populations at risk of malaria [1].

level, and c) conferred (at least in part) by a monooxygenase-based resistance mechanism, as determined by standard procedures. *Conditional recommendation*
Old LLINs should not be disposed of in any water body, as the residual insecticide on the net can be toxic to aquatic organisms and especially to fish. *Strong recommendation, high-quality evidence*
Recipients of LLINs should be advised (through appropriate communication strategies) to continue using their nets beyond the 3-year minimum recommended lifespan of the net, irrespective of the condition of the net, until a replacement net is available. *Good practice statement*
Recipients of LLINs should be advised (through appropriate communication strategies) to continue using their net even if it is damaged or contains holes, irrespective of the age of the net, until a replacement net is available. *Good practice statement*
Old LLINs should only be collected where there is assurance that: (a) communities are not left uncovered, i.e. new LLINs are distributed to replace old ones; and (b) there is a suitable and sustainable plan in place for safe disposal of the collected material. If LLINs 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, the recommended method of disposal is burial. Burial should be away from water sources and preferably in non-permeable soil. *Good practice statements*

Summary of evidence from Cochrane 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 individually RCTs; 12 studies compared ITNs with untreated nets, and 11 studies compared ITNs with no nets; 12 studies were conducted in sub-Saharan Africa, six studies were conducted in the Americas, four studies in south-east Asia, and one study in the Indian subcontinent

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* 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* 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)

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)

The Cochrane systematic review produced high-certainty evidence that 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*, compared to no nets. 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. Any undesirable effects are considered to be trivial.

The current WHO policy recommendation for ITNs/LLINs applies only to those mosquito nets that have a current WHO Pre-Qualification (PQ) or a prior WHOPES recommendation and that contain only an insecticide of the pyrethroid class[ix] (categorized as 'pyrethroid-only LLINs') [12]. For LLINs that currently do not have a policy recommendation, including nets treated with another class of insecticide either alone or in addition to a pyrethroid insecticide, WHO will determine the data requirements for assessing their public health value based on technical advice from the Vector Control Advisory Group (VCAG). In 2017, a separate recommendation applicable to pyrethroid nets treated with a synergist ('pyrethroid-PBO nets') was formulated based on the latest available evidence. This recommendation is included in section 6.1.1 of the *Guidelines* [21].

[ix] As per the Insecticide Resistance Action Committee Mode of Action Classification Scheme, available on the IRAC website: www.irac-online.org

6.1.1. Pyrethroid-PBO nets

Mosquito nets that include both a pyrethroid insecticide and the synergist piperonyl butoxide (PBO) have become available. PBO is a synergist that 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).

On the basis of the current evidence, WHO concludes and recommends the following:

1. Epidemiological data from one cluster randomized controlled trial indicated that a pyrethroid-PBO net product had additional public health value compared to a pyrethroid-only LLIN product in an area where the main malaria vector had confirmed pyrethroid resistance of moderate intensity conferred (at least in part) by monooxygenase-based resistance mechanism as determined by standard procedures. This conclusion is based on a comparison of malaria infection rates in children in village clusters allocated pyrethroid-PBO nets (Olyset®Plus) and rates in village clusters allocated pyrethroid-only LLINs (Olyset® Net) over a period of 2 years in Muleba, United Republic of Tanzania. Entomological data from experimental hut studies on several similar pyrethroid-PBO products conducted in areas of pyrethroid resistance support the finding that pyrethroid-PBO nets are more effective at killing resistant mosquitoes. Mathematical modelling work drawing on relevant entomological data indicates that the added benefit of pyrethroid-PBO nets compared to pyrethroid-only LLINs is expected to be the greatest where pyrethroid resistance is at “intermediate levels”, meaning where mosquito mortality after exposure to a pyrethroid insecticide in WHO test kits or CDC bottle assays ranges from 10% to 80%. The benefit of pyrethroid-PBO nets is expected to diminish where bioassay mortality is outside of this range. Pyrethroid-PBO nets are not expected to have any added benefit in areas where the main malaria vectors are susceptible to pyrethroids and/or do not harbour resistance mechanism(s) that are affected by PBO, i.e., monooxygenase-based resistance mechanism.
2. Based on the epidemiological findings and the need to deploy products that are effective against pyrethroid-resistant mosquitoes, pyrethroid-PBO nets are being given an interim endorsement as a new WHO class of vector control products. As an exception, this establishment of an interim class is based on a single epidemiological study instead of two studies, as required by VCAG for the assessment of a new product class. The endorsement is based on epidemiological evidence of the greater effectiveness of pyrethroid-PBO nets in areas of intermediate level resistance. Full confirmation of the class will require VCAG’s assessment of data from a second epidemiological trial. Meanwhile, all pyrethroid-PBO nets that have a WHOPES recommendation or WHO prequalification listing will be considered to be at least as effective as pyrethroid-only LLINs at preventing malaria infections – and possibly more effective in areas with intermediate levels of pyrethroid resistance conferred by a monooxygenase-based resistance mechanism.
3. National malaria control programmes and their partners should consider the deployment of pyrethroid-PBO nets in areas where the main 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 indoor residual spraying [IRS]) will not be reduced; the primary goal must remain the achievement and maintenance of universal coverage for all people at risk of malaria.

4. 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:
    a) VCAG will review data from the third intervention year of the ongoing randomized control trial in Tanzania once they become available. This will determine whether the higher effectiveness of the pyrethroid-PBO net (compared to a pyrethroid-only LLIN) has continued to be observed over the full period for which an LLIN is expected to retain its biological activity (i.e., a minimum of 3 years). These data will contribute to our understanding of whether the pyrethroid-PBO product under evaluation meets the former WHOPES requirements of an LLIN.
    b) VCAG will review further epidemiological trial data as soon as they become available, such as from a randomized controlled trial planned in Uganda using two pyrethroid-PBO nets (the same product as is being tested in Tanzania, treated with PBO on all panels, and another pyrethroid-PBO net with only the net roof treated with PBO). These data will provide additional evidence on how pyrethroid-PBO nets perform in another geographical setting and whether there are notable differences in effectiveness between products in this class. If VCAG is able to confirm additional public health value, it will allow the interim endorsement of pyrethroid-PBO nets to be converted into the full establishment of the class.
    c) The effectiveness of other pyrethroid-PBO nets in comparison to the product for which data were generated in Tanzania needs to be determined. Evaluation procedures to determine whether other products in a class perform at least as well as the product(s) for which epidemiological data were generated, and for which a product class has been established, are under development. Comparing the effectiveness of different pyrethroid-PBO nets will be aided by:
    c.i. Identifying appropriate entomological indicators to assess the effectiveness of subsequent products entering an existing product class, given that these products will not be required to generate epidemiological data;
    c.ii. Conducting comparative experimental hut trials on different pyrethroid-PBO nets to determine the relative effectiveness of different compositions of net (e.g., PBO applied to the roof panel of the net only versus all panels of the net), as well as different formulations including initial PBO treatment dosages and release properties;
    c.iii. Conducting bioassays using characterized reference strains of insecticide-resistant Anopheles mosquito(es) on pyrethroid-PBO nets following a minimum of 2 to 3 years of routine use to determine the bioavailability and chemical retention of PBO over time. Current information suggests that PBO retention rates and wash resistance indices are much lower than for the pyrethroid component of the formulations. Studies should be conducted on the PBO-LLIN product assessed in Tanzania, with comparative studies performed on other products of the same class.
    d) Further investigations (laboratory and field studies) are required to determine if there is an antagonistic effect between PBO and the organophosphate pirimiphos-methyl, which is an insecticide recommended for IRS. To date, limited evidence from laboratory studies and the randomized controlled trial

in Tanzania suggests that this is not an operational concern; however, further studies are needed to determine the generalizability of current findings.

e) Further research will be required to investigate the relationship between entomological indices and epidemiological outcomes for vector control products in order to determine whether entomological surrogates may be sufficient for assessing the public health value of vector control products not currently covered by a WHO policy recommendation.
f) Synergist testing methods need to be validated, including identification of appropriate sub-lethal concentrations for pre-exposure with PBO in CDC bottle assays.

5. Pyrethroid-PBO nets should not be considered a tool that can effectively manage insecticide resistance in malaria vectors. It is an urgent task to develop and evaluate LLINs treated with non-pyrethroid insecticides and other innovative vector control tools for use across all settings in order to provide alternatives for use in a comprehensive insecticide-resistance management strategy.

6.1.2. Management of old LLINs

WHO notes that currently available LLINs and the vast majority of their packaging (bags and baling materials) are made of non-biodegradable plastics [22]. LLINs entering domestic use in Africa each year contribute approximately 100 000 tonnes of plastic, equivalent to 200 grams per capita per year. 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. Most endemic countries currently do not have the resources to manage LLIN collection and waste disposal programmes. Recycling is not currently a practical option in most malaria-endemic countries (with some exceptions for countries with a well-developed plastics industry). The preferred option for disposing of old LLINs is high-temperature incineration, but this is likely to be logistically difficult and expensive in most settings. Following review of the findings of a pilot study on patterns of LLIN usage and disposal in three African countries (Kenya, Madagascar and Tanzania), the Technical Expert Group on Malaria Vector Control (VCTEG) concluded that the pilot study and other background information were sufficient to form global recommendations on best practices with respect to managing LLIN waste.

6.1.3. Achieving and maintaining universal coverage with LLINs for malaria prevention and control

In December 2017, WHO published updated recommendations on achieving and maintaining universal coverage with ITNs, as follows [23]:

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

Mass campaigns should: a) Distribute 1 LLIN for every 2 persons at risk of malaria. However, for procurement purposes, the calculation to determine the number of LLINs required needs to be adjusted at the population level, since many households have an odd number of members. Therefore, in general, an overall ratio of 1 LLIN for every 1.8 persons

in the target population should be used. In places 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 LLIN campaigns to justify an alternative buffer amount. b) 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 LLINs. In areas where school-based distributions are operating at scale and achieve high coverage, these distributions may even be sufficient to replace mass distribution campaigns.

'Top-up' campaigns (i.e. LLIN 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 LLIN 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 universal coverage and minimize gaps. This unified plan should include a comprehensive net quantification and gap analysis for all public-sector LLIN distribution channels. As much as possible, the plan should also include major LLIN 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 LLIN 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 LLIN 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 LLIN distribution through public-sector channels. Access to LLINs can also be expanded by facilitating the exchange of vouchers or coupons provided through public-sector channels for a free or subsidized LLIN at participating retail outlets. LLIN 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 LLINs 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 LLINs 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 LLINs 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 LLIN distributions should conduct LLIN durability monitoring in line with available guidance. Where there is evidence that LLINs 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 LLINs. 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 LLIN 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 LLIN coverage.

Countries should generate data on defined standard indicators of coverage and access rates in order to ascertain whether universal 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, as developed by the Roll Back Malaria Monitoring and Evaluation Reference Group and adapted by WHO for the World Malaria Report, are: a) the proportion of households with at least one ITN/LLIN; b) the proportion of the population with access to an ITN/LLIN within their household; and c) the proportion of the population reporting having slept under an ITN/LLIN the previous night (by age [<5 years; 5–14 years; 15+ years], gender and access to ITN).

6.2. 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 WHO-recommended (WHOPES) or listed (PQ) insecticide is a core intervention for use in malaria-endemic locations.

Recommendations on IRS
Universal coverage[x] with IRS, using WHO-approved insecticides, is recommended as a malaria prevention and control intervention in all malaria-endemic settings.

[x] Universal coverage for malaria vector control is defined as universal access to and use of appropriate interventions by populations at risk of malaria [1].

Strong recommendation for the intervention, moderate-quality evidence
The use of non-pyrethroid IRS in combination with LLINs is recommended where pyrethroid resistance is compromising the effectiveness of ITNs. Combining IRS with ITNs is not recommended in areas where there is no pyrethroid resistance. *Conditional recommendation, moderate-quality evidence*
Malaria prevention and control and elimination programmes should prioritize the delivery of either ITNs or IRS at high 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. *Good practice statement*

Summary of evidence from Cochrane systematic review
A total of six trials were included in the systematic review – four RCTs and two non-randomized trials. Trials were conducted in India, Mozambique, Nigeria, Pakistan, South Africa and United Republic of Tanzania.

IRS versus no IRS in areas with intense transmission:
- IRS may reduce malaria incidence compared to no IRS
  (Rate Ratio: 0.86; 95% CI [0.77–0.95]; one study; low certainty evidence)
- IRS may make little or no difference in parasite prevalence compared to no IRS
  (Risk Ratio: 0.94; 95% CI [0.82–1.08]; one study; low certainty evidence)

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)

IRS versus ITNs in areas with intense transmission:
- IRS may reduce malaria incidence compared to ITNs
  (Rate Ratio: 0.88; 95% CI [0.78–0.98]; one study; low certainty evidence)
- There may be little or no difference between IRS and ITNs in terms of parasite prevalence
  (Risk Ratio: 1.06; 95% CI [0.91–1.22]; one study; very low certainty evidence)

IRS versus ITNs in areas with unstable transmission:
- IRS may increase malaria incidence compared to ITNs
  (Rate Ratio: 1.48; 95% CI [1.37–1.60]; one study; low certainty evidence)
- IRS may increase parasite prevalence compared to ITNs
  (Risk Ratio: 1.70; 95% CI [1.18–2.44]; one study; low certainty evidence)

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 malaria 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 deceases 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)

As noted in section 6.2, few RCTs have been conducted on IRS and therefore the availability of data suitable for use in a Cochrane-style meta-analysis is limited. The Guideline Development Group considers that the large body of evidence generated from IRS implementation trials and programmatic data from national control programmes, although of lower quality than that obtained from RCTs, is nevertheless sufficient to warrant recommending IRS as a core intervention for malaria prevention and control.

When carried out correctly, IRS is a powerful intervention to rapidly reduce adult mosquito vector density and longevity and, therefore, to reduce malaria transmission.

Insecticides recommended by WHO for IRS fall into five major classes [13] with three modes of action, based on their primary target site in the vector:

- carbamates: bendiocarb, propoxur
- organochlorines: dichlorodiphenyltrichloroethane (DDT)
- organophosphates: malathion, fenitrothion, pirimiphos-methyl
- pyrethroids: alphacypermethrin, deltamethrin, lambda-cyhalothrin, etofenprox, bifenthrin, cyfluthrin
- neonicotinoids: clothianidin

These insecticides are chosen based on their safety for humans and their residual efficacy when applied to a range of interior surfaces of dwellings found in malaria-endemic areas. The minimum residual period of activity of the currently available residual insecticides ranges between 2 and 6 months. They 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 in use;
- 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.

6.2.1. Combination of IRS with LLINs

The evidence provided by the systematic review supports the 2014 WHO guidance for countries [24] on combining IRS and LLINs and the guidance remains valid. A summary of the 2014 guidance is provided. Further background information and details of the evidence on which this guidance was based are available in the original document, which is available online.

1. In settings where there is high coverage with LLINs and LLINs 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 strategy in areas where there are LLINs [25].

2. If LLINs and IRS are to be deployed together in the same geographical location, the IRS should use non-pyrethroid insecticides.

3. Malaria prevention and control and elimination programmes should prioritize the delivery of either LLINs or IRS at high 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.

4. Evidence is needed to determine the effectiveness of combining IRS and LLINs in malaria transmission foci, including in low transmission settings. Evidence is also needed from different eco-epidemiological settings outside of Africa.

5. All programmes in any transmission setting that invest in the combined use of LLINs and IRS 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 LLINs or IRS alone.

6.3. 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.

Recommendations on LSM
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 aquatic habitats are few, fixed and findable, and its application is both feasible and cost-effective. *Conditional recommendation, low-quality evidence*

Summary of evidence from Cochrane systematic review

Larviciding versus no larviciding:
A total of four trials were included in the systematic review, of which only one was an RCT; the remaining three studies were non-randomized.
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 decreases malaria incidence compared to no larviciding
  (Rate Ratio: 0.20; 95% CI [0.16–0.25]; one study; moderate certainty evidence)
- Larviciding may decrease parasite prevalence compared to no larviciding
  (Odds Ratio: 0.72; 95% CI [0.58–0.89]; two studies; low certainty evidence)

Larvivorous fish versus no larvivorous fish:
Fifteen studies were included in the systematic review. Studies were undertaken in the Indian subcontinent (five studies), Africa (five studies), Indonesia (one study), Republic of Korea (two studies) and Tajikistan (two studies).

Treated aquatic habitats included wells, domestic water containers, fishponds and pools (seven studies); river bed pools below dams (two studies); rice field plots (four studies); and canals (two studies).

No studies reported on clinical malaria, EIR or adult vector densities; 12 studies reported on density of immature stages; and five studies reported on the number of aquatic habitats positive for immature stages of the vector species.

The studies were not suitable for a pooled analysis.

- It is unknown whether larvivorous fish reduce the density of immature vector stages compared to no larvivorous fish
  (unpooled data; 12 studies; very low certainty evidence)

- Larvivorous fish may reduce the number of larval sites positive for immature vector stages compared to no larvivorous fish
  (unpooled data; five studies; low certainty evidence)

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 generally recommended in rural settings, unless there are particular circumstances limiting the larval habitats, as well as specific evidence confirming that such measures can reduce the malaria incidence rate in the local setting.

The WHO 2013 Operational Manual on LSM [26] concludes that LLINs and IRS remain the backbone of malaria vector control, but LSM represents an additional 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 expert technical opinion and knowledge. The 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 the core interventions of ITNs or IRS:

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

The Guideline Development Group did not consider habitat modification and manipulation in developing the first edition of the *Guidelines*. Recommendations could be included in future editions of the *Guidelines* following a systematic review of the available evidence.

No recommendation can be made at the present time on the use of larvivorous fish as a malaria prevention and control intervention because evidence on the effectiveness or harms of larvivorous fish was not identified during the systematic review.

6.4. 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. It is most often used in epidemics or outbreaks of mosquito-borne disease, such as dengue.

Recommendations on space spraying
There is insufficient evidence to determine the effectiveness of space spraying. In addition, it is costly and may not be cost-effective. As a result, space spraying is not recommended and IRS or ITNs should be prioritized instead. *Conditional recommendation <u>against</u> the intervention, very low-quality evidence on the effectiveness of the intervention*

Summary of evidence from Cochrane systematic review

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)

The reliance on observational studies and the lack of data from RCTs, other trial designs or quasi-experimental studies provides only very low certainty evidence on the effectiveness of space spraying as a malaria prevention and control intervention.

Space spraying is often used during outbreaks of mosquito-borne disease as it has high visibility. The decision to use it is usually based on 'political' considerations, as it can be used to demonstrate that the authorities are 'taking action' in response to the outbreak.

6.5. 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. In these situations, the effectiveness of the core recommended interventions ITNs and IRS may be reduced. Evidence indicates that these interventions may afford high individual protective efficacy against bites from malaria vectors. The use of these personal protective methods in large-scale public health campaigns has been limited.

Recommendations on topical repellents, insecticide-treated clothing and spatial/airborne repellents
Topical repellents
Use of topical repellents for malaria prevention is not currently recommended as a public health intervention; however, topical repellents may be beneficial as a tool to provide personal protection against malaria in specific population groups. *Conditional recommendation against the intervention, LOW certainty evidence*
Insecticide-treated clothing
Use of insecticide-treated clothing for malaria prevention is not currently recommended as a public health intervention; however, insecticide-treated clothing may be beneficial as a tool to provide personal protection against malaria in specific population groups (e.g. refugees, military). *Conditional recommendation against the intervention, LOW certainty evidence*

Summary of evidence from Cochrane systematic review

Topical repellent versus placebo or no topical repellent:
A total of six RCTs were included in the review. Studies were conducted in Bolivia, Cambodia, Pakistan, Thailand and United Republic of Tanzania.

- 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)

Insecticide-treated clothing versus placebo or untreated clothing
Two RCTs were included in the systematic review. Studies were conducted on specific populations in Colombia (military personnel) and Pakistan (Afghan refugees).

- Insecticide-treated clothing may have a protective effect against malaria cases caused by *P. falciparum*
  (RR: 0.49; 95% CI [0.29–0.83]; two studies; low certainty evidence)
- Insecticide-treated clothing may have a protective effect against malaria cases caused by *P. vivax*
  (RR: 0.64; 95% CI [0.40–1.01]; two studies; low certainty evidence)

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
  (RR: 0.24; 95% CI [0.03–1.72]; two studies; very low certainty evidence)

The evidence from the RCTs provides 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.

There is 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).

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 and published.

6.6. Housing improvements

WHO reports that the available evidence shows 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 [27]. The Roll Back Malaria Partnership considers there to be compelling evidence that housing improvements enhance the protection of residents from vector-borne diseases. The protective effect of measures to prevent malaria mosquitoes from entering houses and biting people as they sleep, such as closing eaves and installing ceilings or screening doors and windows, has been established in many settings. Improvements such as metal roofs and sealed walls that reduce resting sites for indoor resting vectors may also reduce overall survivorship and vectorial capacity [28]. The principle of "building the vector out" is at the core of effective housing interventions to prevent vector-borne diseases.

Specific evidence-based recommendations on housing and vector-borne diseases are still needed. To this end, WHO's Department of Public Health, Environmental and Social Determinants of Health is currently developing housing and health guidelines, which will include a chapter that specifically addresses housing and vector-borne diseases and will provide official WHO recommendations based on a systematic review of the available evidence. These forthcoming recommendations, once available, will be included in later editions of the *Guidelines.*

Recommendations on housing improvements
Closing open eaves; screening doors and windows with fly screens or mosquito netting; and filling holes and cracks in walls and roofs reduce the entry points mosquitoes use to enter houses. Together with metal roofs, ceilings, and finished interior walls, these modifications may reduce transmission of malaria and other vector-borne diseases. *Good practice statement*

6.7. Recommended interventions in special situations

6.7.1. Residual transmission

WHO acknowledges that even full implementation of core interventions, including ITNs, will not be sufficient to completely halt malaria parasite transmission across all settings [29]. Some residual malaria parasite transmission occurs even with universal access to and usage of ITNs, as well as in situations where ITN use or IRS is not practical. 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 the core interventions, such as biting outside early in the evening before people have retired indoors and/or resting outdoors.

There is an urgent need for new tools and strategies and greatly improved knowledge of the bionomics of the different sibling species within malaria vector species complexes in order to effectively address residual transmission. While this knowledge is being gained and novel tools and strategies are being developed, national malaria control programmes

must prioritize the effective implementation of current tools to maintain transmission at 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 behaviour, and the effectiveness of existing and novel interventions.

Residual transmission is difficult to measure and thus so too 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.

6.7.2. Epidemics and humanitarian emergencies

The first priorities in the acute phase of a humanitarian emergency are prompt and effective diagnosis and treatment of malaria; however, malaria prevention can also play an important role in reducing transmission [30].

In the acute phase of an emergency, effective diagnosis and treatment are the priorities, but these interventions can be supplemented with distribution of LLINs, first targeting population groups most susceptible to developing severe malaria, but with the ultimate goal of achieving and maintaining universal 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.

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).

Some newer vector control and personal protection tools have been specifically designed for use in acute-phase emergencies. For example, plastic sheeting is increasingly provided in the early stages of humanitarian emergencies to enable affected communities to construct temporary shelters and in these new settlements where shelter is very basic, insecticide-treated plastic sheeting (IPTS) may be an appropriate, acceptable and feasible alternative to LLINs or IRS. Laminated polyethylene tarpaulins that are impregnated with a pyrethroid during manufacture, are suitable for constructing such shelters. Pyrethroid-treated plastic sheeting should not be used in areas where the local malaria vectors are resistant to pyrethroids. Like IRS, ITPS is only useful against indoor resting mosquitoes.

Another novel vector control and personal protection measure with potential for use in emergency situations is the long-lasting impregnated blanket or topsheet, but as with ITPS the evidence base regarding their effectiveness is currently too limited to support a WHO recommendation. 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). The wash resistance of these products

is consistent with that of LLINs. Data from community randomized trials of long-lasting permethrin-treated wash-resistant blankets and topsheets will inform any future recommendations.

The data currently available on the efficacy and safety of insecticide-treated plastic sheeting and other novel vector control tools designed for use in humanitarian emergences are insufficient to support specific formal WHO recommendations. However, operational realities may necessitate the use of interventions for which the evidence base is currently limited when neither IRS nor LLINs are operationally feasible.

In the post-acute phase, universal coverage with ITNs or IRS may be feasible. Use of insecticide-treated plastic sheeting for shelter construction may be appropriate in situations where ITN use or the application of IRS is not possible. However, to date, data to enable the assessment of the potential public health value of this intervention have not been provided to WHO.

6.7.3. Protection of migrant populations and populations engaged in high-risk activities (e.g. gold mining, forest workers, military personnel, etc.)

As noted above, topical repellents and insecticide-treated clothing may be appropriate interventions for providing personal protection to specific populations at high risk of malaria due to occupational exposure, e.g. military personnel, night-shift workers, forestry workers, etc.

6.8. Further guidance on appropriate interventions according to regional eco-epidemiological stratifications

The global strategy for malaria control of 1992 included a global malaria typology that uses environmental characteristics as the primary identifier, but also attempts to relate these to the selection of control interventions. A refined and harmonized version of this global typology is provided in Table 5.

Table 5. Global malaria ecotypes and their occurrence [31]

Malaria ecotype	Where found
Savanna	Sub-Saharan Africa, South-West Pacific
Plains with traditional agriculture outside Africa	South Asia, Central and South America, China
Highland fringe	Africa, South-East Asia, South-West Pacific, South America
Desert fringe and oasis	Sahel, southern Africa, West Asia
Forest and forest fringe	South and South-East Asia, South America
Costal and marshland	Africa, South and South-East Asia, South and Central America
Urban and peri-urban	Africa, South Asia, South America
Agricultural development including irrigation, conflict and sociopolitical disturbances	Superimposed on any of the above ecotypes

The seven global ecotypes described above have been used as a framework to develop

eco-epidemiological stratifications for each of the WHO Regions (AFRO, EMRO, EURO, PAHO, and SEARO and WPRO combined), describing the different ecotypes present in that region and the associated vector species. The applicability of the core recommended vector control interventions (ITNs and IRS) is indicated for each ecotype. These eco-epidemiological stratifications are presented as Annex 6 and are designed to provide additional information to facilitate local decision-making around the prioritization of vector control interventions according to local ecology and epidemiological context.

7. 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 [32]:

- The skills to both manage and implement vector control programmes remain scarce, particularly in the resource-poor countries in most need of effective vector-borne disease control. This has led to control measures that are unsuitable or poorly targeted with insufficient coverage, consequent waste of resources and sometimes avoidable insecticide contamination of the environment.

- The use of insecticides in agriculture and poor management of insecticides in public health programmes have contributed to resistance in disease vectors.

- 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 cooperation between sectors and for adoption of strategies other than those based on insecticides are seldom grasped. In addition, while health sector reform, with its emphasis on decentralization of operational control, poses new challenges, it also affords significant new opportunities for delivering vector control.

7.1. Insecticide resistance

Widespread and increasing insecticide resistance is a threat to effective malaria vector control. Failure to mitigate insecticide resistance is likely to result in an increased burden of disease, with significant cost implications for malaria prevention and control programmes. Given that the core interventions for malaria prevention and control, namely IRS and LLINs, rely on insecticides targeting adult mosquitoes, the spread of insecticide resistance to many malaria-endemic countries and most of the important vectors of malaria in recent years is of critical importance to control programmes.

Monitoring of insecticide resistance in malaria vectors has revealed a picture of increasing prevalence of pyrethroid resistance, especially in West Africa and in *An. funestus*. Currently, 61 countries have reported resistance to at least one insecticide and 50 of those countries have reported resistance to two or more classes of insecticide [33]. WHO maintains a global insecticide resistance database that consolidates information on the status of the insecticide susceptibility of *Anopheles* mosquitoes in malaria-endemic countries [34]. To date, there has been little conclusive evidence of operational failure of vector control programmes as a direct result of insecticide resistance [35]; however, it is likely that this will occur in future if effective resistance management strategies are not designed and implemented. In response to this growing concern, WHO published the

Global plan for insecticide resistance management in malaria vectors (GPIRM) in 2012 [20], which outlines a comprehensive plan for global, regional and national action to address the challenge of insecticide resistance.

In the process of developing the GPIRM, key technical principles for addressing insecticide resistance were defined, as follows:

- Insecticides should be used with care and deliberation in order to reduce unnecessary selection pressure. Countries 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 every year; instead, they should use rotations, mosaics, combinations of interventions, and mixtures (once available).
- Wherever possible, vector control programmes should diversify from pyrethroids in order to preserve their effectiveness. Although pyrethroids will continue to be used for LLINs in the near term, they should not generally be used for IRS where there is high LLIN coverage.
- Insecticide resistance management (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 sustain the effectiveness of vector control interventions.
- The short-term additional costs of IRM should be balanced against the long-term potential public health impact and potential costs of insecticide resistance.

Currently available IRM strategies

Rotation of insecticides: Two, or preferably more, insecticides with different modes of action are rotated every one to two years.

Combination of interventions: Two or more insecticide-based vector control interventions are used in a house (e.g. pyrethroids on nets and an insecticide of a different class on the walls), so that the same insect is likely, but not guaranteed, to come into contact with the second insecticide if it survives exposure to the first.

Mosaic spraying: One compound is used in one geographic area and a different compound in neighbouring areas – the two being of different insecticide classes; further research is required on the use of mosaic spraying.

Mixtures: Two or more compounds of different insecticide classes are mixed to make a single product or formulation, so that the mosquito is guaranteed to come into contact with the two classes at the same time.
Rotations, combinations and mosaic spraying are all IRM strategies available for IRS. The use of combinations is the only strategy currently applicable to LLINs. Mixtures are not yet available for either LLINs or IRS.

Draft preliminary guidance on the core malaria vector control interventions that are considered most appropriate under different insecticide resistance scenarios is under

development and presented in Table 6.

Table 6. DRAFT guidance for identification of appropriate core malaria vector control interventions on the basis of insecticide resistance monitoring outcomes. Indicated are options that are preferred (+) or not preferred (-). This table considers the current resistance profile[1] of major malaria vectors at representative sites to insecticide(s) used in available interventions.

Intervention		Class	Pyrethroid insecticide(s) resistance						Non-pyrethroid insecticide(s) resistance - CA, NE, OC, OP, PR			
			Resistance status		Resistance intensity		Resistance mechanisms		Resistance status		Resistance mechanisms	
			No confirmed resistance [2]	Confirmed resistance [3]	Moderate or low [4]	High [2]	P450s not detected and/or shown to not be involved	P450s detected and/or shown to be fully or partially involved	No confirmed resistance to class [2]	Confirmed resistance to class [3]	Mechanisms known to confer resistance to class not detected	Mechanisms known to confer resistance to class detected
Resistance Outcomes (see Figure 1)												
ITN	a	Pyrethroid-only nets	+			-	+			+		
	b	Pyrethroid plus synergist nets	-	+ [5]			-	+				
	c	Non-pyrethroid insecticide nets		+		+			+ [6]			
	d	Nets containing pyrethroid plus another insecticide	TBD									
	e	Nets containing IGR or sterilizing agent/s	TBD									
IRS	f	Pyrethroid formulation [8]	+	-	-	-				+		
	g	OP, OC or CA formulation [8]		+		+			+ [7]	-	+	-
	h	Other fast-acting insecticide formulations [8]		+		+			+ [7]	-	+	-
	i	Slow-acting insecticide formulations [8]		+		+			+ [7]	-	+	-
	j	Formulations with an IGR or sterilizing agent/s	TBD									
Combination	k	Pyrethroid-only nets including LLINs + non-pyrethroid IRS formulation [8]	-	+		+			+ [7]		+	

CA=carbamates; NE=neonicotinoids; OC=organochorines; OP=organophosphates; PR=pyrroles; TBD=to be determined

[1] data should be for mosquitoes collected within the previous 24 month period; if available for multiple time points, the most recent data should to be considered

[2] for all major vector species to all insecticides tested of the class

[3] for at least one major vector species to at least one insecticide of the class

[4] including moderate to high intensity where 10x intensity concentration has not been tested

[5] where % mosquito mortality in standard bioassays with the insecticide used on the ITN is 10-80%

[6] where there is no confirmed resistance to the insecticide class(es) used in the ITN

[7] where there is no confirmed resistance to the insecticide class(es) used in the IRS formulation

[8] to be applied in rotation and/or mosaics with insecticide formulations of a different mode of action

Countries should develop and implement national insecticide resistance monitoring and management plans in accordance with the 2017 WHO *Framework for a national plan for monitoring and management of insecticide resistance in malaria vectors* [36].

In WHO's September 2017 guidance (revised in December 2017) on the deployment of

pyrethroid-PBO nets, it notes: *epidemiological data from one cluster randomized controlled trial indicated that a pyrethroid-PBO net product had additional public health value compared to a pyrethroid-only LLIN product in an area where the main malaria vector had confirmed pyrethroid resistance of moderate intensity conferred (at least in part) by monooxygenase-based resistance mechanism as determined by standard procedures.*

Furthermore, WHO recommends: National malaria control programmes and their partners should consider the deployment of pyrethroid-PBO nets in areas where the main 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.

WHO guidance on the use of IRS in combination with LLINs concludes that, in settings where there is high coverage with LLINs and LLINs remain effective, IRS may have limited utility in reducing malaria morbidity and mortality. However, IRS may be implemented in areas where there are LLINs as part of an IRM strategy; in this case, a non-pyrethroid insecticide must be used for the IRS component.

Test procedures for insecticide resistance monitoring in malaria vector mosquitoes were updated in 2016 and are available online [37].

7.2. Acceptability, end-user suitability 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 are 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 [38].

Larviciding is not currently in widespread use as a malaria vector control tool and so is unlikely to be familiar to many communities. 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 are likely to 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.

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, and WHO Member States lack specific guidance in this area. The Seventieth World Health Assembly [39] 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 on 23–24 February 2017 to identify the ethical issues associated with vector-borne diseases. Once this proposed guidance is available, it will be included in future editions of 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 use 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 scheme for new vector control interventions in order to ensure that these are fully and properly assessed prior to any WHO recommendation for their deployment.

7.3. Resource implications and prioritisation

In this first edition of the *Guidelines for malaria prevention through vector control,* considerations of resource implications and cost-effectiveness of vector control interventions could largely only be addressed through expert opinion. It is recognized that such considerations should, ideally, be based on evidence, but guidance on how to collate and present data for this area of the guidelines was not available at the time of writing; a chapter to guide incorporation of information on resource use is currently under development by the WHO Guideline Review Committee and will be used to develop expanded evidence-based recommendations on resource implications in the 2nd edition of these guidelines.

At present, the most recently systematic review of the cost and cost-effectiveness of vector control interventions was published in 2011 drawing on studies published between 1990 and 2010 [40]. The body of evidence collated was on ITN/LLIN and IRS in few sub-Saharan sites. The authors found large variations in intervention delivery costs, reflecting different contexts but also varying types of costing methodologies; these studies were rarely undertaken alongside clinical and epidemiological evaluations. The review, reported that ITN/LLIN and IRS were consistently found to be cost-effective across studies, but evidence to determine their comparative cost-effectiveness was insufficient. WHO GMP is working with partners to update the evidence review on the costs and cost-effectiveness evidence of vector control interventions covered in the *Guidelines*.

Cost-effectiveness analysis – the comparison of 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 [41]. Cost-effectiveness ratio used in combination with cost-effectiveness thresholds, as applied in the above mentioned review, provides some indication of the value for money of an intervention. It should, however, not be used as a standalone criterion for decision making but alongside other considerations, including amongst others, affordability and budget impact analysis [42]. Development of further guidance to inform resource use will be a focus of work in preparation for the 2nd edition of these guidelines, with a view of including explicit recommendations on resource use as part of the GRADE tables, using work by other WHO departments to guide this work [43]. Given that resource considerations are highly context-specific and hence unlikely to be sufficiently detailed to inform prioritization of resources for vector control at country level, further work on guiding country-level decision making is also foreseen but will be outside the scope of this global guidance document.

7.4. Equity, gender and human rights

The aim of all WHO's work 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. Integration of equity, human rights, gender and social determinants is expressed in the WHO 12th General Programme of Work, in the Gender, Equity and Human Rights Mainstreaming Programme Area, Outcome 3.3: "Gender, equity and human rights integrated into the Secretariat's and countries' policies and programmes".

In pursuit of this outcome, WHO is committed to providing guidance on the integration of sustainable approaches that advance health equity, promote and protect human rights, are gender-responsive and address social determinants into WHO programmes and institutional mechanisms; promoting disaggregated data analysis and health inequality monitoring; and providing guidance on the integration of sustainable approaches that advance health equity, promote and protect human rights, are gender-responsive and address social determinants into WHO's support at country level [44].

WHO advocates for universal coverage with recommended vector control tools. As such, all malaria vector control interventions are expected to be implemented without discrimination on the basis of age, sex, ethnicity, religion or other characteristic. 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. Countries applying to the Global Fund for financing for malaria prevention and control are required to include programmes to reduce human rights and gender-related

barriers to services that are appropriate to the specific country context. In addition, countries must ensure that all health service provision meets the five human rights standards, as outlined in the Global Fund's Grant Framework Agreement.

Country programmes are encouraged to use available tools to assist them in addressing human rights and gender-related barriers to equitable access. One such tool is the Malaria Matchbox, which includes the following four modules:

- Module 1: Identifying those most affected by malaria, but without access to services
- Module 2: Understanding how biological, environmental, social and cultural factors impact malaria
- Module 3: Evaluating access to services
- Module 4: Defining and operationalizing activities to address challenges and reach targets

The Guideline Development Group and the Guideline Review Committee were instructed to develop and review the recommendations contained in the *Guidelines,* giving due consideration to human rights, gender and equity.

7.5. Human resources and entomological capacity

The Global Vector Control Response 2017–2030 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 will help to appraise current capacity, define what is necessary to conduct proposed activities, identify opportunities for improved efficiencies in vector control, and guide resource mobilization.

Formulating an inventory of existing human, infrastructural, 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 [45].

7.6. Public–private partnerships in malaria vector control

A 2006 review of the role of public–private sector partnerships in malaria prevention and control concluded that in malaria-endemic developing countries, informal and formal private-sector providers play a critical role in malaria prevention and control, displaying a wide spectrum of relationships between public and private actors and civil society in the provision of public health and health care services [46].

At country level, private-sector entities are often represented on Global Fund Country Coordinating Mechanisms, where they are able to engage with their public-sector counterparts and other stakeholders around identifying national priorities for resource allocation. Private-sector companies also participate in programme implementation in countries, serving as Principal Recipients or sub-recipients of Global Fund grants.

At the global level, public–private partnerships are accelerating investments (knowledge and resources) in research activities geared towards new product development. One such example is the Innovative Vector Control Consortium (www.ivcc.com). The private sector is also contributing to global decision-making, for example by holding seats on the Board of the Global Fund and the Roll Back Malaria Partnership Board. As members of governing bodies, the private sector can effectively represent its constituency and influence policy and funding decisions.

The aims of public–private partnerships are to:

- Increase coverage, especially for essential health care priorities;
- Improve the quality of care delivered by providers; and
- Control excessive health care costs to users, especially the poor.

Potential roles for public–private partnerships in vector control for malaria prevention, control and elimination include:

- Conducting research and development on new vector control products;
- Making products available at cost, below cost or free of charge;
- Implementing employer-funded vector control interventions (e.g. in factories, plantations, etc.);
- Supporting product distribution (e.g. LLIN campaigns);
- Designing and engaging in behaviour change communication, health education and awareness-raising (social media, radio and TV, etc.);
- Providing laboratory services;
- Engaging in programme implementation (e.g. as Global Fund Principal Recipients or sub-recipients);
- Training (e.g. in IRS);
- Participating in global and regional decision-making through Board representation;
- Engaging in Corporate Social Responsibility initiatives.

In 2011, Roll Back Malaria published a review of the economic returns available to businesses investing in malaria prevention and control, based on an economic analysis of malaria prevention and control programmes operated by three companies in Zambia [47]. The report concluded that significant benefits accrued to the companies in the form of reduced absenteeism and reduced expenditures at company clinics. Together, these benefits produced an estimated rate of return on investment of 28%.

Some examples of public–private partnerships include:

- Papua New Guinea Industry Malaria Initiative (http://www.pimi.org.pg)
- Freeport-McMoRan Copper & Gold, Inc. and Freeport Indonesia [48]
- Newmont Mining, Batu Hijau, Indonesia
- Pilipinas Shell Foundation, Inc., Philippines [49]
- Tree plantations in Sabah, Malaysia [50]
- Marathon Oil, Equatorial Guinea
- Zambia Sugar

- Mopani Copper Mines, Zambia
- Konkola Copper Mines, Zambia
- Mozal and the Lubombo Spatial Development Initiative, Mozambique
- AngloGold Ashanti, Ghana

7.7. Community mobilization and participation

The World Bank defines community participation as the process by which communities influence the decisions and resources that directly affect them. Community participation should ideally commence at the inception and planning stage of any new programme or intervention. Community participation is a dynamic process through which communities progressively take greater responsibility for health care, moving away from being mere recipients of services, resources and development interventions towards being active partners or owners of the interventions [51].

8. Monitoring and evaluation of vector control tools

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 tools is covered in the WHO operational manual on malaria surveillance, monitoring and evaluation.

8.1. Quality assurance of vector control interventions

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

Control failures may be due to a variety of factors, including misapplication of the intervention, poor quality of the control tools, failure to achieve full coverage, or insecticide resistance. Quality assurance efforts should be continuous, systematic and independent. Continuous monitoring and supervision are required to ensure that staff are adequately trained and following technical guidelines for pesticide application and personal safety. IVM 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 [52] details the quality assurance steps and processes involved in procuring pharmaceutical products and diagnostics, but the principles are also 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 use 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 guidelines 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 LLINs, this may require testing of 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 that have no country-specific data on certain LLIN or IRS products, or where anecdotal data on poor performance of certain products may be available, can make post-marketing surveillance a priority. Agreement on the need and scope of the proposed activities should be reached by in-country stakeholders, including the national regulatory authority. All studies should follow WHO guidance.

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

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

The only currently available tool for assessing the quality of the application of insecticide to walls and other internal surfaces by IRS is the WHO cone bioassay (preferably using fully susceptible anophelines obtained from insectaries). Colorimetric assays are under development; these will 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.

9. Research agenda to inform development of subsequent Guideline editions

During the development of this first edition of the *Guidelines*, a number of areas were identified that require additional work to enhance the guidance provided here. Key areas to be addressed in 2018/19 in preparation of the second edition of the *Guidelines* will be:

- To conduct a systematic review of data on IRS interventions from studies not meeting the inclusion criteria outlined in section 4.7.1. Despite its long tradition of

use and large body of associated operational experience, few RCTs have been conducted on IRS. The Guideline Development Group agreed that the strength of the current recommendations on IRS, as well as their specifics, could be enhanced through a systematic review of additional data from lower quality studies.

- 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, following examples provided in other WHO guidance, such as the interim policy guidance on the use of delamanid in the treatment of multidrug-resistant tuberculosis [53].
- 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 VCAG [54]. Collection of cost data early on during evaluation of new tools will make a useful contribution towards building an evidence-based on resource use, to be drawn on during subsequent editions of the *Guidelines.*
- To conduct a systematic review of costs and cost-effectiveness data of all vector control interventions 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 develop their own resource need and budget impact assessments.
- To develop further guidance on the use of interventions and new tools in special situations, for example, residual transmission and the protection of specific populations with high occupational exposure to risk of contracting malaria.

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1. WHO malaria terminology. Geneva: World Health Organization; 2017 (WHO/HTM/GMP/2016.6; http://www.who.int/malaria/publications/atoz/malaria-terminology/en/).
2. WHO handbook for guideline development. Geneva: World Health Organization; 2012 (http://www.who.int/kms/guidelines_review_committee/en/).
3. Silver JB. Mosquito ecology: field sampling methods, 3rd ed. New York: Springer; 2008.
4. Garrett-Jones C. The human blood index of malaria vectors in relation to epidemiological assessment. Bull World Health Organ. 1964;30:241–61.
5. Shaukat AM, Breman JG, McKenzie FE. Using the entomological inoculation rate to assess the impact of vector control on malaria parasite transmission and elimination. Malar J. 2010;9:122.
6. Hay SI, Rogers DJ, Toomer JF, Snow RW. Annual Plasmodium falciparum entomological inoculation rates (EIR) across Africa: literature survey, Internet access and review. Trans R Soc Trop Med Hyg. 2000;94:113–27.
7. Global vector control response 2017–2030. Geneva: World Health Organization; 2017 (http://www.who.int/vector-control/publications/global-control-response/en/).
8. Global Technical Strategy for malaria 2016–2030. Geneva: World Health Organization; 2016 (http://www.who.int/malaria/areas/global_technical_strategy/en/).
9. Investing to overcome the global impact of neglected tropical diseases. Geneva: World Health Organization; 2015 (http://www.who.int/neglected_diseases/9789241564861/).
10. Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. Nature. 2015;526(7572):207–11.
11. Insecticide-treated mosquito nets: a position statement. Geneva: World Health Organization; 2007 (http://www.bvsde.paho.org/bvsacd/cd66/ITNspospaperfinal.pdf).
12. Achieving universal coverage with long-lasting insecticidal nets in malaria control. Geneva: World Health Organization; 2014 (http://www.who.int/malaria/publications/atoz/who_recommendations_universal_coverage_llins.pdf).
13. Indoor residual spraying: an operational manual for IRS for malaria transmission, control and elimination. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/publications/atoz/9789241508940/en/).

14. Larval source management: a supplementary measure for malaria vector control. An operational manual. Geneva: World Health Organization; 2013 (http://www.who.int/malaria/publications/atoz/9789241505604/en/).
15. A framework for malaria elimination. Geneva: World Health Organization; 2017 (http://www.who.int/malaria/publications/atoz/9789241511988/en/).
16. Risks associated with scale-back of vector control after malaria transmission has been reduced. Information note. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/publications/atoz/scale-back-vector-control.pdf).
17. Hawley W.A., Phillips-Howard P.A., ter Kuile F.O. et al. Community-wide effects of permethrin-treated bednets on child mortality and malaria morbidity in western Kenya. Am. J. Trop. Med. Hyg. 2003;68(Suppl. 4):121–127.
18. Russell TL, Lwetoijera DW, Maliti D et al. Impact of promoting longerlasting insecticide treatment of bednets upon malaria transmission in a rural Tanzanian setting with preexisting high coverage of untreated nets. Malaria J. 2010;9(1):187
19. Govella NJ, Okumu, FO, Killeen GF. Short Report: Insecticide-Treated Nets Can Reduce Malaria Transmission by Mosquitoes Which Feed Outdoors. Am. J. Trop. Med. Hyg. 2010;82(3):415-419.
20. Birget PLG, Koella JC. An Epidemiological Model of the Effects of Insecticide Treated Bed Nets on Malaria Transmission. PLoS ONE. 2015. 10(12):e0144173.doi:10.1371/journal. pone.0144173.
21. Conditions for deployment of mosquito nets treated with a pyrethroid and piperonyl butoxide. Geneva: World Health Organization; 2017 (WHO/HTM/GMP/2017.17; http://www.who.int/malaria/publications/atoz/use-of-pbo-treated-llins/en/).
22. WHO recommendations on the sound management of old long-lasting insecticidal nets. Geneva: World Health Organization; 2014 (WHO/HTM/GMP/MPAC/2014.1; http://www.who.int/malaria/publications/atoz/who-recommendation-managing-old-llins/en/).
23. Achieving and maintaining universal coverage with long-lasting insecticidal nets for malaria control. Geneva: World Health Organization; 2017 (WHO/HTM/GMP/2017.20; http://www.who.int/malaria/publications/atoz/who_recommendation_coverage_llin/en/).
24. Guidance for countries on combining indoor residual spraying and long-lasting insecticidal nets. Geneva: World Health Organization, March 2014.
25. Global plan for insecticide resistance management in malaria vectors. Geneva: World Health Organization; 2012 (http://www.who.int/malaria/publications/atoz/gpirm/en/).
26. Larval source management. A supplementary measure for malaria vector control. An operational manual. Geneva: World Health Organization; 2013.
27. Keeping the vector out: housing improvements for vector control and sustainable development. Geneva: World Health Organization; 2017 (http://www.who.int/phe/news/keeping-the-vector-out/en/).
28. Housing and malaria. Consensus statement. Geneva: Roll Back Malaria Partnership; 2015 (https://malariaworld.org/sites/default/files/RBM%20VCWG%20Housing%20and%20Malaria%20Consensus%20Statement_final.pdf).
29. Guidance note on the control of residual malaria parasite transmission. Geneva: World Health Organization; 2014 (WHO/HTM/GMP/MPAC/2014.5; http://www.who.int/malaria/publications/atoz/guidance-control-residual-transmission/en/).
30. Malaria control in humanitarian emergencies: an inter-agency field handbook. 2nd ed. Geneva: World Health Organization; 2013 (http://www.who.int/malaria/publications/atoz/9789241548656/en/).
31. Schapira A, Boutsika K. Malaria ecotypes and stratification. Adv Parasitol. 2012;78:97–167.
32. Global strategic framework for integrated vector management. Geneva: World Health Organization; 2004 (WHO/CDS/CPE/PVC/2004.10; http://www.who.int/malaria/publications/atoz/who_cds_cpe_pvc_2004_10/en/).
33. Insecticide resistance. Geneva: World Health Organization; 2017 (www.who.int/malaria/areas/vector_control/insecticide_resistance/en/, accessed 18 December 2017).
34. WHO global insecticide resistance database. Geneva: World Health Organization; 2017 (http://www.who.int/malaria/areas/vector_control/insecticide_resistance_database/en/, accessed 18 December 2017).
35. Implications of insecticide resistance for malaria vector control. Geneva: World Health Organization; 2016 (WHO/HTM/GMP/2016.8.rev;

http://www.who.int/malaria/publications/atoz/insecticide-resistance-implications/en/).
36. Framework for a national plan for monitoring and management of insecticide resistance in malaria vectors. Geneva: World Health Organization; 2017 (http://www.who.int/malaria/publications/atoz/9789241512138/en/).
37. Test procedures for insecticide resistance monitoring in malaria vector mosquitoes. Geneva: World Health Organization; 2016 (http://www.who.int/malaria/publications/atoz/9789241511575/en/).
38. Indoor residual spraying. Use of indoor residual spraying for scaling up global malaria control and elimination. Geneva: World Health Organization; 2006 (WHO/HTM/MAL/2006.1112; http://www.who.int/malaria/publications/atoz/htm_mal_2006_1112/en/).
39. Seventieth World Health Assembly. Agenda item 14.2. Global vector control response: an integrated approach for the control of vector-borne diseases. WHA70.16. 31 May 2017.
40. White MT, Conteh L, Cibulskis R, Ghani A. Cost and cost-effectiveness of malaria control interventions – a systematic review. Malaria Journal 2011 : 10 :337.
41. Cost effectiveness and strategic planning (WHO-CHOICE). Geneva: World Health Organization (http://www.who.int/choice/cost-effectiveness/en/, accessed 9 January 2018).
42. Bertram MY, Lauer JA, De Joncheere K, Edejer T, Hutubessy R, Kieny MP, Hill SR. Cost-effectiveness thresholds: pros and cons. Bull World Health Organ. 2016;94(12):925-930.
43. The use of delamanid in the treatment of multidrug-resistant tuberculosis: Interim policy guidance. Geneva: World Health Organization; 2014.
44. Integrating equity, gender, human rights and social determinants into the work of WHO. Roadmap for action 2014–2019. (WHO/FWC/GER/15.2; http://www.who.int/gender-equity-rights/knowledge/roadmap/en/).
45. Core structure for training curricula on integrated vector management. Geneva: World Health Organization; 2012 (http://www.who.int/neglected_diseases/vector_ecology/resources/9789241502788/).
46. Partnerships for malaria control: engaging the formal and informal private sectors. Geneva: World Health Organization; 2006 (TDR/GEN/06.1; http://www.who.int/tdr/publications/tdr-research-publications/partnership-malaria-control/en/).
47. Mouzin E, Sedlmayr R, Miller J, Stetketee R, Banda P, Chiyota G, et al. Business investing in malaria control: economic returns and a healthy workforce. Progress & Impact Series, No. 6, May 2011. Geneva: World Health Organization and Roll Back Malaria; 2011 (http://www.path.org/publications/files/MCP_rbm_pi_rpt_6.pdf).
48. Community health. Jakarta: PT Freeport Indonesia (https://ptfi.co.id/en/csr/safety-and-health/community-health, accessed 10 January 2018).
49. Movement against malaria: winning the fight with the Pilipinas Shell Foundation. In: Sharing Value Asia [website]. Public Affairs Asia; 2014 (http://sharingvalue.asia/movement-against-malaria-winning-the-fight-with-the-pilipinas-shell-foundation/, accessed 12 January 2018).
50. Sanders KC, Rundi C, Jelip J, Rashman Y, Smith Gueye C, Gosling RD. Eliminating malaria in Malaysia: the role of partnerships between the public and commercial sectors in Sabah. Malar J. 2014;13:24.
51. Global Partnership to Roll Back Malaria. Community involvement in rolling back malaria. Geneva: World Health Organization; 2002 (WHO/CDS/RBM/2002.42; http://www.who.int/malaria/publications/atoz/who_cds_rbm_2002_42/en/).
52. A Model Quality Assurance System for Procurement Agencies. Geneva: World Health Organization; 2007 (WHO/PSM/PAR/2007.3; http://www.who.int/medicines/publications/ModelQualityAssurance.pdf).
53. The use of delamanid in the treatment of multidrug-resistant tuberculosis. Interim policy guidance. Geneva: World Health Organization; 2016 (WHO/HTM/TB/2016.14; http://www.who.int/tb/publications/Delamanid_interim_policy/en/).
54. How to design vector control efficacy trials. Guidance on phase III vector control field trial design provided by the Vector Control Advisory Group. Geneva: World Health Organization; 2017 (WHO/HTM/NTD/VEM/2017.03; http://www.who.int/neglected_diseases/vector_ecology/resources/WHO_HTM_NTD_VEM_2017.03/en/).

10. Annexes

- List of members of the Guideline Development Group and summary of members' declarations of interest
- WHO guideline development process
- GRADE tables assessing the quality of evidence
- Previously issued WHO recommendations and guidance
- Principal malaria vectors and information on key ecology and behaviours by WHO region
- Eco-epidemiological stratifications

Annex 1. List of members of the Guideline Development Group and summary of members' declarations of interest

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<u>Summary of Declarations of Interest</u>

Dr Mark Coosemans is employed by the Institute of Tropical Medicine of Antwerp, Belgium, and has received a grant from the Bill and Melinda Gates Foundation for the impact of repellents for malaria prevention in Cambodia, as well as repellents for the study from SC Johnson. This work was conducted from 2012-2014. He has also received six grants for the evaluation of public health pesticides from WHOPES since 2007 some of which will run through 2018.

Dr Jeffrey Hii is employed by the Malaria Consortium and has received remuneration for consulting services from WHO and from the Ministry of Health, East Timor, for work conducted in 2017. He has held a grant from

SC Johnson, which ceased in 2017, to evaluate transfluthrin and received financial support from Bayer Crop Science to attend the 4th Bayer Vector Control Expert Meeting in 2017. He holds an ongoing WHO/TDR research grant which has focused on studying magnitude and identifying causes for residual transmission in Thailand and Vietnam (completed), and will be used to study the impact of socio-ecological systems and resilience (SESR)-based strategies on dengue vector control in schools and neighbouring household communities in Cambodia (awaiting ethical approval).

The WHO Secretariat assessed the interests declared by the experts. WHO is of the opinion that these declarations do not constitute conflicts of interest and that the considered experts could participate subject to the public disclosure of their interests.

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*According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single malaria-related company exceeds 10,000 USD in a calendar year. Likewise, a shareholding in any one malaria-related company in excess of 1,000 USD would also constitute a “significant shareholding”.

Last updated: 11 November 2017

Annex 2. WHO guideline development process

Stage/primary contributor	**Step**
PLANNING	
WHO Member State, WHO country office or public/private entity	Request guidance on a topic
WHO Technical Unit	Determine if a guideline is needed; review existing WHO and external guidelines Obtain approval for guideline development from the director of the relevant technical unit at WHO Discuss the process with the Guideline Review Committee (GRC) Secretariat and with other WHO staff with experience in developing guidelines Form the WHO Guideline Steering Group Identify sufficient resources; determine the timeline
WHO Guideline Steering Group	Draft the scope of the guideline; begin preparing the planning proposal Identify potential members of the Guideline Development Group (GDG) and its Chair Obtain declarations of interest and manage any conflicts of interest among potential GDG members
WHO Guideline Steering Group and Guideline Development Group	Formulate key questions in PICO format; prioritize outcomes
WHO Guideline Steering Group	Finalize the planning proposal and submit it to the GRC for review
Guideline Review Committee	Review and approve the planning proposal
DEVELOPMENT	
Systematic review team	Perform systematic reviews of the evidence for each key question Evaluate the quality of the evidence for each important outcome, using GRADE as appropriate
WHO Guideline Steering Group	Convene a meeting of the GDG
Guideline Development Group	Formulate recommendations using the GRADE framework
WHO Guideline Steering Group	Draft the guideline document
External Review Group	Conduct external peer review
PUBLISHING AND UPDATING	
WHO Guideline Steering Group and editors	Finalize the guideline document; perform copy-editing and technical editing; submit the final guideline to the GRC for review and approval
Guideline Review Committee	Review and approve the final guideline
WHO Guideline Steering Group and editors	Finalize the layout; proofread Publish (online and in print as appropriate)

WHO Technical Unit and Programme Manager	Disseminate, adapt, implement, evaluate
WHO Technical Unit	Update

GDG: Guideline Development Group; GRADE: Grading of Recommendations Assessment, Development and Evaluation; GRC: Guideline Review Committee; PICO: population, intervention, comparator, and outcome.

Annex 3. GRADE tables assessing the quality of evidence

CORE	
1.	ITNs ALONE 1.1 What is the current effect of ITNs (compared to no nets, and to untreated nets)?
2.	INDOOR RESIDUAL SPRAYING 2.1 What is the effect of indoor residual spraying alone? 2.2 What is the effect of IRS compared to ITNs?
3.	COMBINING IRS WITH ITNs 3.1 Is the combined use of IRS and ITNs more effective in reducing malaria transmission than the use of ITNs alone?
Supplementary	
4.	LARVICIDING 4.1 Does larviciding (with insecticide, insect growth regulators, microbial agents, or oils) control malaria?
5.	LARVIVOROUS FISH 5.1 In malaria transmission settings, are larvivorous fish effective for malaria control?
6.	SPACE SPRAYING 6.1 In malaria transmission settings, is space spraying effective for malaria control alone or in combination with core interventions, compared to any of the core interventions?
7.	REPELLENTS 7.1 Do topical repellents reduce malaria? 7.2 Do impregnated clothes reduce malaria? 7.3 Do spatial repellents reduce malaria?

1. Insecticide Treated Nets

Question: What is the current effect of ITNs (compared to no nets, and to untreated nets)?

Recommendation				
Insecticide-treated nets are recommended as a malaria prevention and control intervention.				
Strength of Recommendation				
For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
STRONG				

Overall Quality of Evidence for all Critical Outcomes			
High	Moderate	Low	Very Low
HIGH			

Balance of Desirable and Undesirable Effects	
Desirable	Undesirable
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 identified in systematic review May play an as yet undetermined role in pyrethroid 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.

Rationale for the Recommendation
ITNs generate significant desirable effects in terms of reducing deaths, clinical disease and infections compared to no nets (HIGH certainty evidence). Undesirable effects of ITNs are considered to be trivial.

Remarks
IMPLEMENTATION CONSIDERATIONS Universal coverage should be maintained in endemic settings. MONITORING AND EVALUATION Improved post-distribution monitoring of nets is needed: durability, usage, coverage. RESEARCH PRIORITIES Resistance management: Determine the effectiveness of next-generation nets and insecticides in areas where resistance to pyrethroids is high Determine the comparative effectiveness of different net types Determine the effectiveness of nets in situations of residual/outdoor transmission Determine the role of ITN use in transmission ‘hotspots’ and elimination settings Generate evidence for assessing the impact of insecticide resistance on key outcomes (malaria mortality, clinical disease and prevalence of infection)

Evidence-to-Decision Framework – ITNs versus No Nets

PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Malaria has significant effects on individuals (especially children under 5, pregnant women and other groups with little or no acquired immunity) and communities.							
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
There is unlikely to be any significant variability in the values individuals and communities place on reduced malaria mortality, clinical disease, incidence and prevalence.							
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Absolute costs compared to no intervention may be high, but are of the same order of magnitude as costs of alternative interventions.							
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ITNs are generally distributed to ALL households in a mass campaign approach designed to achieve universal access.							
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
ITNs are generally acceptable to most recipients, despite some small inconveniences.							
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
ITNs are a cornerstone of malaria prevention and control in many countries.							

Should insecticide-treated nets or curtains vs. no nets be used for preventing malaria?						
Population: People at risk of malaria **Intervention:** Insecticide-treated nets or curtains **Comparison:** No nets **Setting:** Burkina Faso 1996; Cambodia 2002, Ghana 1995; Côte d'Ivoire 2000; Kenya 1988, 1995 and 1998; Myanmar 1999; Sierra Leone 1993; Pakistan 1991; United Republic of Tanzania 1996 **Source:** Original review: Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev 2004, Issue 2. Art. No.: CD000363. doi: 10.1002/14651858.CD000363.pub2. Supplemented with new literature search and compilation of GRADE tables						
Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Risk with no nets	Risk with insecticide-treated nets or curtains				
All-cause mortality	33 per 1000	27 per 1000 (25 to 29)	Rate Ratio 0.83 (0.77 to 0.89)	129 714 (5 RCTs)	⨁⨁⨁⨁ HIGH[1]	
P. falciparum uncomplicated episodes	178 per 1000	96 per 1000 (86 to 107)	Rate Ratio 0.54 (0.48 to 0.60)	32 699 (5 RCTs)	⨁⨁⨁⨁ HIGH[1]	
P. falciparum uncomplicated episodes (cumulative incidence)	137 per 1000	60 per 1000 (43 to 85)	Risk Ratio 0.44 (0.31 to 0.62)	10 964 (2 RCTs)	⨁⨁⨁◯ MODERATE[1,2]	
P. falciparum prevalence	120 per 1000	83 per 1000 (65 to 107)	Risk Ratio 0.69 (0.54 to 0.89)	17 860 (5 RCTs)	⨁⨁⨁⨁ HIGH[1]	
P. vivax uncomplicated episodes (cumulative incidence)	149 per 1000	91 per 1000 (71 to 114)	Risk Ratio 0.61 (0.48 to 0.77)	10 972 (2 RCTs)	⨁⨁⨁◯ MODERATE[1,2]	
P. vivax prevalence	130 per 1000	130 per 1000 (98 to 174)	Risk Ratio 1.00 (0.75 to 1.34)	9900 (2 RCTs)	⨁⨁◯◯ LOW[1,2,3]	
Any *Plasmodium spp.* uncomplicated episodes	256 per 1000	128 per 1000 (72 to 231)	Rate Ratio 0.50 (0.28 to 0.90)	5512 (1 RCT)	⨁⨁◯◯ LOW[1,4,5]	
Severe malaria episodes	15 per 1000	8 per 1000 (6 to 12)	Rate Ratio 0.56 (0.38 to 0.82)	31 173 (2 RCTs)	⨁⨁⨁⨁ HIGH[1]	
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)						

Notes

[1]Not downgraded for indirectness: For most included studies, it is unclear whether insecticide resistance was present. We judge that there is no convincing evidence that insecticide resistance would significantly affect the impact of ITNs on the included epidemiological outcomes. A previous review that included entomological outcomes showed that the difference in mosquito mortality risk using ITNs compared to untreated nets modestly decreased as insecticide resistance increased (Strode 2014). However, mosquito mortality risk remained significantly higher for ITNs than for untreated nets, regardless of the resistance status.

[2]Downgraded by 1 for indirectness: Most of the data were provided by a trial in two refugee camps in Pakistan. The second trial was in Myanmar and provided data only for children under 10 years of age. It is not clear how confidently the information can be applied to other populations.

[3]Downgraded by 1 for imprecision: The CI includes both a sizable increase and decrease in prevalence.

[4]Not downgraded for imprecision: The smallest effect size is still a sizable reduction of 56 episodes per 1000 child-years.

[5]Downgraded by 2 for indirectness: The evidence comes from one trial only, which was conducted in Myanmar and in which participants were exclusively children under 10 years of age. It is not clear how confidently the information can be applied to other populations.

Should insecticide-treated nets or curtains vs. untreated nets be used for preventing malaria?

Population: People at risk of malaria
Intervention: Insecticide-treated nets or curtains
Comparison: Untreated nets
Setting: Cameroon 1992 (Moyou-Somo 1995); Colombia 1993 (Kroeger 1995); Ecuador 1992 (Kroeger 1995); Gambia 1993 (D'Alessandro 1995); Gambia 1985 (Snow 1987); Madagascar 1994 (Rabarison 1995); Nicaragua 1996 (Kroeger 1999); Peru Amazon 1992 (Kroeger 1995); Peru Coast 1993 (Kroeger 1995); Thailand 1988 (Kamol-Ratanakul 1992); Thailand 1991 (Luxemburger 1994); Venezuela 2000 (Magris 2007)
Source: Original review: Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev 2004, Issue 2. Art. No.: CD000363. doi: 10.1002/14651858.CD000363.pub2. Supplemented with new literature search and compilation of GRADE tables

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Risk with untreated nets	Risk with insecticide-treated nets and curtains				
All-cause mortality	19 per 1000	13 per 1000 (7 to 23)	Rate Ratio 0.67 (0.36 to 1.23)	32 721 (2 RCTs)	⨁⨁⨁◯ MODERATE[1,2]	
P. falciparum uncomplicated episodes	180 per 1000	104 per 1000 (77 to 142)	Rate Ratio 0.58 (0.43 to 0.79)	2084 (5 RCTs)	⨁⨁⨁⨁ HIGH[1,3]	
P. falciparum prevalence	85 per 1000	69 per 1000 (58 to 82)	Risk Ratio 0.81 (0.68 to 0.97)	300 (4 RCTs)	⨁⨁⨁⨁ HIGH[1]	
P. vivax uncomplicated episodes	143 per 1000	104 per 1000 (73 to 150)	Rate Ratio 0.73 (0.51 to 1.05)	1771 (3 RCTs)	⨁⨁◯◯ LOW[1,2,4]	
P. vivax uncomplicated episodes (cumulative incidence)	168 per 1000	97 per 1000 (50 to 191)	Risk Ratio 0.58 (0.30 to 1.14)	17 910 (3 RCTs)	⨁⨁◯◯ LOW[1,2,5,6]	
P. vivax prevalence	85 per 1000	44 per 1000 (11 to 173)	Risk Ratio 0.52 (0.13 to 2.04)	300 (1 RCT)	⨁◯◯◯ VERY LOW[1,7,8]	
Any *Plasmodium spp.* uncomplicated episodes (cumulative incidence)	69 per 1000	32 per 1000 (12 to 88)	Risk Ratio 0.47 (0.17 to 1.28)	7082 (2 RCTs)	⨁⨁⨁◯ MODERATE[1,2,5]	
Any *Plasmodium spp.* prevalence	104 per 1000	18 per 1000 (5 to 55)	Risk Ratio 0.17 (0.05 to 0.53)	691 (1 RCT)	⨁◯◯◯ VERY LOW[1,9,10]	

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

Notes

[1]Not downgraded for indirectness: For most included studies, it is unclear whether insecticide resistance was present. We judge that there is no convincing evidence that insecticide resistance would significantly affect the impact of ITNs on the included epidemiological outcomes. A previous review that included entomological outcomes showed that the difference in mosquito mortality risk using ITNs compared with untreated nets modestly decreased as insecticide resistance increased (Strode 2014). However, mosquito mortality risk remained significantly higher for ITNs than for untreated nets, regardless of the resistance status.
[2]Downgraded by 1 for imprecision: The CI includes both a sizable decrease and an increase in the absolute number of events.
[3]Not downgraded for inconsistency: Despite significant heterogeneity (I^2 statistic value of 75%), each trial consistently shows an effect that favours ITNs.

[4]Downgraded by 1 for indirectness: The three studies had restrictive participant inclusion criteria. The largest weighted study included only children from a displaced persons camp in Thailand. The second study included only migrant workers also in Thailand. The third included only children under 10 years of age in Venezuela. It is not clear how confidently the information can be applied to other populations.
[5]Not downgraded for risk of bias: Although the lack of participant blinding could potentially influence the likelihood of reporting a fever, this is not deemed likely to seriously affect the results of the studies.
[6]Downgraded by 1 for inconsistency: There is substantial heterogeneity between study findings, with no overlap in CIs between the two largest weighted studies.
[7]Downgraded by 2 for imprecision: The CI includes both a sizable decrease and increase in the absolute number of events. Additionally, the small sample size and low number of events are insufficient for confidently estimating the effect size.
[8]Downgraded by 2 for indirectness: The results come from only one study, conducted only in children living in displaced persons camps in Thailand. It is not clear how confidently the information can be applied to other populations.
[9]Downgraded by 1 for imprecision: The small sample size and low number of events are insufficient for confidently estimating the effect.
[10]Downgraded by 2 for indirectness: The results come from only one study, conducted only in children living in the Amazon rainforest. It is not clear how confidently the information can be applied to other populations.

2. Indoor Residual Spraying

Questions:

2.1 What is the effect of indoor residual spraying alone?

2.2 What is the effect of IRS compared to ITNs?

Recommendation
IRS is recommended for populations at risk of malaria in most epidemiological and ecological scenarios. IRS is one of the core interventions currently recommended for malaria vector control and should continue to be so.

Rationale for the Recommendation
The certainty of the evidence subjected to systematic review is graded LOW. Only a single RCT was graded. The VCTEG 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 VCTEG 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.

Strength of Recommendation

For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
STRONG				

Overall Quality of Evidence for all Critical Outcomes			
High	Moderate	Low	Very Low
		LOW	

Balance of Desirable and Undesirable Effects

Desirable	Undesirable
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 identified in systematic review May play an as yet undetermined role in pyrethroid insecticide resistance development in *Anopheles* vectors Requires householders to grant permission for spray team to enter house Requires householders to remove personal items from houses prior to spraying (e.g. foodstuffs) Some insecticide formulations (e.g. DDT) leave unsightly residue on sprayed surfaces

Remarks

IMPLEMENTATION CONSIDERATIONS
Decisions on selection of insecticide to be used will depend on the resistance profile of the local vector population.
High (universal) coverage should be maintained.
The primary vector should be endophilic.
Implementation of the intervention should be timely.

MONITORING AND EVALUATION
Residual activity of the insecticide(s)

RESEARCH PRIORITIES
Impact of IRS in urbanized areas with changing housing designs
Impact 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)

Evidence-to-Decision Framework – Indoor Residual Spraying

PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Malaria has significant effects on individuals (especially children under 5, pregnant women and other groups with little or no acquired immunity) and communities.							
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
There is unlikely to be any significant variability in the values individuals and communities place on reduced malaria incidence and prevalence.							
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Absolute costs compared to no intervention may be high, but are of the same order of magnitude as costs of alternative interventions.							
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
IRS is applied to ALL households in a targeted area.							
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
IRS is generally acceptable to most recipients, despite some small inconveniences.							
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
IRS is currently successfully implemented in many countries.							

In malarial areas, is indoor residual spraying effective?						
Population: People at risk of malaria **Intervention:** Indoor residual spraying **Comparison:** No indoor residual spraying **Setting:** Three RCTs in United Republic of Tanzania, Pakistan and India assessed the impact of IRS versus no IRS on malaria. **Source:** Original review: Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. Cochrane Database Syst Rev. 2010;4:CD006657. doi:10.1002/14651858.CD006657.pub2. Supplemented with new literature search and compilation of GRADE tables						
Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Risk with no IRS	Risk with IRS				
Areas with intense malaria transmission (EIR >1)						
Incidence of malaria in children under 5 years	65 per 100 child-years	56 per 100 child-years (50 to 61)	Rate Ratio 0.86 (0.77 to 0.95)	884 (1 RCT)[a]	⨁⨁◯◯ LOW[1,2]	
Parasite prevalence in children under 5 years	68 per 100 child-years	63 per 100 child-years (55 to 73)	Risk Ratio 0.94 (0.82 to 1.08)	452 (1 RCT)[a]	⨁⨁◯◯ LOW[1,2]	
Areas with unstable malaria (EIR <1)						
Incidence of malaria in all ages	5 per 100	1 per 100 (0 to 1)	Risk Ratio 0.12 (0.04 to 0.31)	18 261 (1 RCT)[b,c]	⨁⨁◯◯ LOW[3,4,5]	
Parasite prevalence in children aged 5–15 years	11 per 100	3 per 100 (2 to 4)	Risk Ratio 0.24 (0.17 to 0.34)	2359 (1 RCT)[b,c]	⨁⨁◯◯ LOW[4,5,6]	
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).						

Notes

[a]Curtis 1998

[b]Rowland 2000

[c]Misra 1999

[1]Downgraded by 1 for indirectness: The outcome is heavily dependent on the setting. All data contributing to this outcome come from only one study, which generates uncertainty.

[2]Downgraded by 1 for imprecision: Wide CIs.

[3]Misra 1999 reported on this outcome as well. Incidence of malaria in all ages showed an effect favouring the intervention; however, the magnitude of the effect is much smaller (RR 0.69; 95% CI 0.64–0.73). This result is not cluster-adjusted, and therefore it has not been pooled with Rowland (2000).

[4]Downgraded by 1 for indirectness: The outcome is heavily dependent on the setting. All data contributing to this outcome come from only one study, which generates uncertainty.

[5]Downgraded by 1 for imprecision: Wide CIs.

[6]Misra 1999 reported on this outcome as well. Incidence of malaria in all ages showed an effect favouring the intervention; however, the magnitude of the effect is much smaller (RR 0.72; 95% CI 0.54–0.95). This result is not cluster-adjusted, and therefore it has not been pooled with Rowland (2000).

What is the comparative effectiveness of IRS compared to ITNs?						
Population: People at risk of malaria **Intervention:** Indoor residual spraying **Comparison:** Insecticide-treated nets **Setting:** Two RCTs in United Republic of Tanzania and India assessed the impact of IRS versus ITNs on malaria. **Source:** Original review: Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. Cochrane Database Syst Rev. 2010;4:CD006657. doi:10.1002/14651858.CD006657.pub2. Supplemented with new literature search and compilation of GRADE tables						
Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Risk with ITNs	Risk with IRS				
Areas with intense malaria transmission (EIR >1)						
Incidence of malaria in children under 5 years	63 per 100 child-years	55 per 100 child-years (49 to 62)	Rate Ratio 0.88 (0.78 to 0.98)	818 (1 RCT)[a]	⨁⨁◯◯ LOW[1,2]	
Parasite prevalence in children under 5 years	60 per 100 child-years	64 per 100 child-years (55 to 74)	Risk Ratio 1.06 (0.91 to 1.22)	449 (1 RCT)[a]	⨁⨁◯◯ LOW[1,2]	
Areas with unstable malaria (EIR <1)						
Incidence of malaria in all ages	2 per 100	3 per 100 person-years (3 to 4)	Rate Ratio 1.48 (1.37 to 1.60)	88 100 (1 RCT)[b]	⨁⨁◯◯ LOW[3,4]	
Parasite prevalence in all ages	0 per 100	0 per 100 (0 to 0)	Risk Ratio 1.70 (1.18 to 2.44)	52 934 (1 RCT)[b]	⨁⨁◯◯ LOW[3,4]	
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).						

Notes

[a]Curtis 1998

[b]Misra 1999

[1]Downgraded by 1 for indirectness: The outcome is heavily dependent on the setting. All data contributing to this outcome come from only one study, which generates uncertainty.

[2]Downgraded by 1 for imprecision: Wide CIs.

[3]Downgraded by 1 for indirectness: The outcome is heavily dependent on the setting. All data contributing to this outcome come from only one study, which generates uncertainty.

[4]Downgraded by 1 for imprecision: Wide CIs.

3. Combining Insecticide Residual Spraying with ITNs

3.1 Is the combined use of IRS and ITNs more effective in reducing malaria transmission than the use of ITNs alone?

Recommendations
Malaria control and elimination programmes should prioritize the delivery of either LLINs or IRS at high 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. Addition of IRS with a non-pyrethroid insecticide to high ITN coverage is recommended where pyrethroid resistance is potentially compromising the effectiveness of ITNs. In areas where no operational implication of pyrethroid resistance has been confirmed, IRS in addition to high ITN coverage is not recommended. Pyrethroid IRS is not recommended in combination with ITNs.

Strength of Recommendation				
For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
	CONDITIONAL			

Overall Quality of Evidence for all Critical Outcomes			
High	Moderate	Low	Very Low
	MODERATE		

Balance of Desirable and Undesirable Effects	
Desirable	Undesirable
None identified in systematic review. In areas of confirmed pyrethroid resistance, IRS with a non-pyrethroid insecticide is expected to increase effectiveness against malaria.	None identified in systematic review. Cost of combining two interventions will significantly increase commodity and operational costs

Rationale for the Recommendation
The systematic review did not provide evidence of a benefit of adding IRS in situations where ITNs are already being used. MODERATE certainty of evidence. Non-pyrethroid IRS in addition to ITNs is potentially useful as an insecticide resistance management approach in areas of high pyrethroid resistance. Evidence for any additional benefit in such situations is required.

Remarks
IMPLEMENTATION CONSIDERATIONS The degree of pyrethroid resistance and its impact on the effectiveness of ITNs Vector resistance status to the proposed IRS active ingredient In resource-constrained situations, it is unlikely to be financially feasible to deploy both core interventions together. Current practice shows that in these situations, when non-pyrethroid IRS is deployed, subsequent ITN mass distributions are not conducted. MONITORING AND EVALUATION Entomological surveillance, including population densities, EIRs and behaviour, is required. Insecticide resistance status and investigations of cross-resistance Quality control of the IRS and ITNs Coverage (access and use) of ITNs Coverage of IRS RESEARCH PRIORITIES The evidence base for combining non-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.

Evidence-to-Decision Framework – IRS in addition to ITNs

PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Malaria has significant effects on individuals (especially children under 5, pregnant women and other groups with little or no acquired immunity) and communities.							
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
The systematic review found no substantial desirable effects; however, there are certain contexts where a moderate anticipated desirable effect may be seen.							
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
There is unlikely to be any significant variability in the values individuals and communities place on reduced malaria incidence and prevalence.							
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	**Does not favour either the intervention or the comparison**	Probably favours the intervention	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Absolute costs compared to no intervention may be high, but are of the same order of magnitude as costs of alternative interventions.							
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
Adding IRS to ITNs will incur significant additional costs.							
COST EFFECTIVENESS	Favours the comparison	**Probably favours the comparison**	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
There is no evidence of additional benefit in adding IRS to ITNs.							
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
IRS and ITNs are generally acceptable to most recipients, despite some small inconveniences.							
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
IRS and ITN programmes are currently successfully implemented in many countries.							

Is the combination of IRS and ITNs more effective in reducing malaria transmission than ITNs alone?

Population: People at risk of malaria
Intervention: Indoor residual spraying + ITNs
Comparison: Insecticide-treated nets
Setting: The four studies were conducted in sub-Saharan African countries, with one study in southern Benin (Corbel 2012), one in the west lowlands of Eritrea (Keating 2011), one in the upper river region of Gambia (Pinder 2015), and one in north-west Tanzania (West 2014). The former three regions experience seasonal transmission, while north-west Tanzania has perennial transmission with two peak seasons.
Source: Choi L, Pryce J, Garner P. The combination of indoor residual spraying with insecticide-treated nets versus insecticide-treated nets alone for preventing malaria (Protocol). Cochrane Database Syst Rev. 2017;6:CD012688. doi:10.1002/14651858.CD012688.

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Risk with ITNs alone	Risk with IRS + ITNs				
Malaria incidence	60 episodes per 100 child-years	70 episodes per 100 child-years (55 to 88)	Rate Ratio 1.17 (0.92 to 1.46)	5249 child-years (2 RCTs)	⨁⨁⨁◯ MODERATE[1]	
Malaria prevalence	18 per 100	19 per 100 (14 to 25)	Odds Ratio 1.04 (0.73 to 1.48)	34 530 (4 RCTs)	⨁⨁◯◯ LOW[1,2]	
Entomological inoculation rate	117 infectious bites per 100 people per year	67 infectious bites per 100 people per year (30 to 146)	Rate Ratio 0.57 (0.26 to 1.25)	(2 RCTs)[a]	⨁◯◯◯ VERY LOW[1,3,4]	
Anaemia prevalence (haemoglobin <8g/dl)	5 per 100	5 per 100 (4 to 6)	Odds Ratio 1.04 (0.83 to 1.30)	12 940 (2 RCTs)	⨁⨁⨁◯ MODERATE[1]	

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). The assumed risk of the comparison group is calculated from the total number of events / total number of participants in the control arms contributing to the meta-analysis. The assumed risk of EIR is taken from baseline measurements of a study conducted in Tanzania (West 2014).

Notes

[a] This outcome was measured in West (2014) with traps (320 CDC light traps per month) and in Corbel (2012) with human landing catches (128 person nights per cluster).
[1]Downgraded by 1 for imprecision: Wide CIs.
[2]Downgraded by 1 for inconsistency: Moderate heterogeneity with I^2 statistic value of 47% not explained by subgroup analysis (net use and insecticide mode of action).
[3]Downgraded by 1 for inconsistency: Large differences in effect estimates in the two studies, from RR 0.78 to RR 0.17. This heterogeneity is also evident in a third study evaluating EIR as an adjusted rate difference, 2010: 2.67 (1.89–2.74); 2011: 0.20 (0.14–0.27) (Pinder 2015).
[4]Downgraded by 2 for imprecision: Very wide CIs.

4. Larviciding

4.1 Does larviciding (with insecticide, insect growth regulators, microbial agents, or oils) control malaria?

Recommendation				
Larviciding could be recommended for malaria control as a supplementary intervention in specific settings where the application is both feasible and cost-effective. These settings are generally areas where aquatic habitats are few, fixed and findable. Larviciding is likely to be 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 expert technical opinion and knowledge.				
Strength of Recommendation				
For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
	CONDITIONAL			

Overall Quality of Evidence for all Critical Outcomes			
High	Moderate	Low	Very Low
		LOW	
Balance of Desirable and Undesirable Effects			
Desirable		Undesirable	
None identified in systematic review		None identified in systematic review May affect non-target fauna Communities may not accept its application to sources of drinking water or water used for other domestic purposes	
Rationale for the Recommendation			
Larviciding is used for malaria control in several countries, including Somalia and Sudan; however, certainty of the evidence of epidemiological effects is low or very low.			
Remarks			

Evidence-to-Decision Framework – Larviciding

PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Malaria has significant effects on individuals (especially children under 5, pregnant women and other groups with little or no acquired immunity) and communities.							
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
The systematic review found no substantial desirable effects; however, there are certain contexts where a moderate anticipated desirable effect may be seen.							
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
Certainty of the evidence of effects for large aquatic habitats is determined to be very low. For small aquatic habitats, it is determined to be moderate. Combined certainty is judged to be low, with a significant lack of evidence in some settings that may consider larviciding.							
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
There is unlikely to be any significant variability in the values individuals and communities place on reduced malaria incidence and prevalence.							
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
Larviciding will always be more costly than no larviciding. The cost of larviciding depends on the setting and ranges from moderate to large.							
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
Certainty varies according to type of aquatic habitat.							
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
For governments, larviciding is generally perceived as acceptable, but for other stakeholders (donors?) it may not be.							
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility varies from place to place, and the panel considered that the evidence presented in the systematic review may be biased, as sites selected for trials were selected based on their suitability/feasibility for larviciding.							

Should larviciding vs no larviciding be used for controlling malaria?						
Population: Anyone at risk of malaria **Intervention:** Larviciding with insecticides, insect growth regulators, microbial larvicides, or oils **Comparison:** Not receiving larviciding interventions as described above. Any co-interventions must be received in both control and intervention arms. **Setting:** Studies were conducted in Kenya (Fillinger 2009), Gambia (Majambere 2010), United Republic of Tanzania (Maheu-Giroux 2013) and Sri Lanka (Yapabandara 2001). **Source:** Choi L, Wilson A. Larviciding to control malaria (Protocol). Cochrane Database Syst Rev. 2017;7:CD012736. doi:10.1002/14651858.CD012736						
Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Risk with no larviciding	Risk with larviciding				
Habitats exceeding 1km^2 in area						
Malaria incidence	23 episodes per 100 child-years	37 episodes per 100 child-years (30 to 46)	Odds Ratio 1.97 (1.39 to 2.81)	1793 child-years (1 non-randomized crossover trial)	⨁◯◯◯ VERY LOW[1,2]	
Parasite prevalence	14 per 100	19 per 100 (7 to 44)	Odds Ratio 1.49 (0.45 to 4.93)	3574 (1 non-randomized crossover trial)	⨁◯◯◯ VERY LOW[1,3]	
Habitats <1km^2 in area						
Malaria incidence	23 episodes per 100 child-years	5 episodes per 100 person-years (4 to 6)	Rate Ratio 0.20 (0.16 to 0.25)	4649 person-years (1 RCT)	⨁⨁⨁◯ MODERATE[4,5]	
Parasite prevalence	12 per 100	9 per 100 (7 to 11)	Odds Ratio 0.72 (0.58 to 0.89)		⨁⨁◯◯ LOW[6,7]	
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). The assumed risk of the comparison group is calculated from the total number of events / total number of participants in the control arms contributing to the meta-analysis.						

Notes

[1]Downgraded by 1 for inconsistency: Both comparisons indicate an effect favouring no larviciding, but there is considerable quantitative heterogeneity (I^2 statistic = 81%).

[2]Downgraded by 1 for imprecision: Wide CIs.

[3]Downgraded by 2 for imprecision: Very wide CIs.

[4]Downgraded by 1 for imprecision: There is a large effect combined with a low number of events, which creates uncertainty around the point estimate.

[5]An additional study measured incidence but reported it as new infections and so therefore was not combinable. However, the study showed a large effect consistent with the findings above (RR 0.44; 95% CI 0.23–0.82) (Fillinger 2009). In GRADE assessment, the point estimate of 0.44 is very low certainty of evidence.

[6]Observational studies, so GRADE assessment starts at 'low', therefore no further downgrading required for risk of bias.

[7]An additional study measured prevalence but reported it as a slide positivity rate and so therefore was not combinable. However, the study showed a large effect consistent with the findings above; pooled RR 0.07; 95% CI 0.04–0.13 (Yapabandara 2001). In GRADE assessment, the point estimate of 0.07 is moderate certainty of evidence.

5. Larvivorous Fish

5.1 In malaria transmission settings, are larvivorous fish effective for malaria control?

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

Strength of Recommendation

For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
		NO RECOMMENDATION		

Overall Quality of Evidence for all Critical Outcomes			
High	Moderate	Low	Very Low
NO STUDIES INCLUDED			

Balance of Desirable and Undesirable Effects

Desirable	Undesirable
None identified in the systematic review Fish can serve as an additional source of nutrition	None identified in the systematic review

Rationale for the Recommendation
There is insufficient evidence to support an effect of larvivorous fish on malaria transmission or disease outcomes. The VCTEG recognizes that there are specific settings in which the intervention is currently implemented, and in these specific settings programme staff consider it to be effective. In some of the settings where larvivorous fish are used, programmatic evidence exists; however, this was not determined appropriate for inclusion in the systematic review due to unsuitable study design or other concerns. The VCTEG acknowledges that there may be data at country/programme level that the VCTEG is not aware of.

Remarks
IMPLEMENTATION CONSIDERATIONS There is evidence that this intervention is only appropriate for mosquito aquatic habitats that are large, permanent and few. There is a need for local capacity for breeding fish, maintaining fish and monitoring aquatic habitats. MONITORING AND EVALUATION There is a need to summarize the characteristics of settings in which this intervention might be applicable. RESEARCH PRIORITIES Well-designed epidemiological studies (not larval density) should be conducted in areas where programmes include larvivorous fish in order to provide the evidence base.

Evidence-to-Decision Framework – Larvivorous Fish

PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Malaria has significant effects on individuals (especially children under 5, pregnant women and other groups with little or no acquired immunity) and communities.							
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
No included studies for epidemiological outcomes. Studies included in the review measured larval outcomes only (very low certainty).							
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
There is unlikely to be any significant variability in the values individuals and communities place on reduced densities of mosquito immatures.							
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
Varies, but likely to be high as it requires considerable logistical investment.							
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
Information on the logistical and other resource requirements for introducing larvivorous fish is available in Use of fish for malaria control. Cairo: World Health Organization Regional Office for the Eastern Mediterranean; 2003. WHO-EM/MAL/289/E/G.							
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
For communities, larvivorous fish are generally perceived as acceptable, but for other stakeholders (donors?) they may not be.							
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

Does the introduction of larvivorous fish contribute to malaria control?						
Population: People at risk of malaria **Intervention:** Larvivorous fish **Comparison:** No larvivorous fish **Setting:** Studies were undertaken in Sri Lanka (two studies), India (three studies), Ethiopia (one study), Kenya (two studies), Sudan (one study), Grande Comore Island (one study), Republic of Korea (two studies), Indonesia (one study) and Tajikistan (two studies). These studies were conducted in a variety of settings, including localized water bodies (such as wells, domestic water containers, fishponds and pools (seven studies), river bed pools below dams (two studies), rice field plots (four studies) and water canals (two studies). **Source:** Walshe DP, Garner P, Abdel-Hameed Adeel AA, Pyke GH, Burkot T. Larvivorous fish for preventing malaria transmission. Cochrane Database Syst Rev. 2017 (in press). Updated with three new studies contributing to the secondary outcomes related to larval populations						
Outcome	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				
	Control	Larvivorous fish				
Clinical malaria (incidence)	-	-	-	No studies	No studies	
Entomological inoculation rate	-	-	-	No studies	No studies	
Density of adult malaria vectors	-	-	-	No studies	No studies	
Density of immature stages of vectors in aquatic habitats Quasi-experimental studies	-	-	Not pooled. Variable effects reported	12 studies	⨁◯◯◯ VERY LOW[1-9]	
Larval sites positive for immature stages of the vectors Quasi-experimental studies			Not pooled. Positive effects reported	5 studies	⨁◯◯◯ VERY LOW[1,2,10,11,12]	
* The basis for the assumed risk (for example the median control group risk across studies) is provided in the notes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).						

Notes

[1]Downgraded by 2: The included studies were non-randomized controlled trials.

[2]No serious risk of bias: All studies suffered from additional problems, such as a small number of sites sampled, but these were not deemed adequate to further downgrade the evidence.

[3]No serious inconsistency: Seven studies found substantial reductions in immature vector densities at the intervention sites (Haq 2013; Howard 2007; Kim 2002; RTDC 2008; Sitaraman 1976; Yu 1989; Zvantsov 2008). For Zvantsov 2008, the effect of *P. reticulata* was not sustained in one site, even after reintroduction of fish.

[4]No serious indirectness: These seven studies introduced larvivorous fish into household water sources in India (Haq 2013; Sitaraman 1976), ponds in Kenya (Howard 2007), and rice fields in Republic of Korea (Kim 2002; Yu 1989) and Tajikistan (RTDC 2008; Zvantsov 2008). The longest follow-up was in India and still showed benefit at 12 months (Haq 2013). In one study from India (Sitaraman 1976), the duration of effect seemed to be influenced by the number of fish introduced. For Zvantsov 2008, the effect of *P. reticulata* was not sustained in one site, even after reintroduction of fish.

[5]No serious imprecision: Although statistical significance was not reported, the effects in some studies appear large (Haq 2013; Howard 2007; Kim 2002; RTDC 2008; Sitaraman 1976; Yu 1989; Zvantsov 2008).

[6]Downgraded by 1 for inconsistency: Effects were variable. Large effects were observed in water canals in Sudan (Mahmoud 1985), but only until 9 months post-intervention. Effects on immature vector populations in Central Java were dependent on vector species (Nalim 1988). No effect in ponds in Kenya stocked once with fish or restocked every two weeks with fish at follow-up (13 weeks). Some effect in water canals in Kenya restocked with fish every 2 weeks at follow-up (13 weeks) (Imbahale 2011a).

[7]No serious indirectness: These three studies introduced larvivorous fish into ponds in Kenya (Imbahale 2011a), ponds in Sudan (Mahmoud 1985) and rice fields in Central Java (Nalim 1988). The longest follow-up was in Central Java (6 years) but showed different effects upon different vector species. In one study from Kenya, the effect seemed to be influenced by the type of site, as an effect was observed in water canal sites but not in pond sites.
[8]Downgraded by 1 for inconsistency: Effects were variable. In one study, no major difference between control and experimental groups was detected at final follow-up (120 days), but the area under the curve suggested a more rapid decline in larvae in the experimental group (Kusumawathie 2008a). In one study, control and experimental groups were not matched at baseline (experimental group higher). However, substantively lower values were detected in the intervention arm at follow-up (1 year) (Kusumawathie 2008b).
[9]No serious indirectness: Two studies introduced larvivorous fish into river bed pools below dams in Sri Lanka (Kusumawathie 2008a; Kusumawathie 2008b). The longest follow-up still showed benefit at 1 year post-intervention in one study. However, control and experimental groups were not matched at baseline (experimental group higher) in all studies.
[10]No serious indirectness: This study introduced larvivorous fish into household water sources in Ethiopia (Fletcher 1992). Benefit was still shown at follow-up (1 year).
[11]No serious inconsistency: Both studies found substantial reductions in immature vector density at the intervention sites (Menon 1978; Sabatinelli 1991).
[12]No serious indirectness: These two studies introduced larvivorous fish into household water sources in Grande Comore Island (Sabatinelli 1991) and India (Menon 1978). The longest follow-up was in Grande Comore Island and still showed benefit at 1 year post-intervention.

6. Space Spraying

6.1 In malaria transmission settings, is space spraying effective for malaria control alone or in combination with core interventions, compared to any of the core interventions?

Recommendation
In the absence of high-quality evidence on the effectiveness of space spraying, and considering other factors including cost and anticipated cost-effectiveness, core malaria vector control interventions (ITNs and IRS) should normally be prioritized over space spraying in the majority of settings.

Strength of Recommendation

For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
			CONDITIONAL	

Overall Quality of Evidence for all Critical Outcomes			
High	Moderate	Low	Very Low
			VERY LOW

Balance of Desirable and Undesirable Effects	
Desirable	Undesirable
No desirable effects identified by systematic review	No undesirable effects identified by systematic review

Rationale for the Recommendation
Only observational studies were available, graded as VERY LOW certainty evidence. 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. The high costs and limited anticipated cost-effectiveness of this intervention dissuade against its use.

Remarks
IMPLEMENTATION CONSIDERATIONS Specialist technical equipment required RESEARCH PRIORITIES Demonstrate evidence of impact, particularly in emergency situations, through design of high-quality trials

Evidence-to-Decision Framework – Space Spraying

PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Malaria has significant effects on individuals (especially children under 5, pregnant women and other groups with little or no acquired immunity) and communities.							
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
There is unlikely to be any significant variability in the values individuals and communities place on reduced malaria incidence and prevalence.							
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**Don't know**
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favours the comparison	**Probably favours the comparison**	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
The evidence reviewed did not consider cost-effectiveness, but the expert opinion of the VCTEG is that it probably favours the comparison.							
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
This intervention is politically acceptable, but may be less so for other stakeholders.							
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

No GRADE table produced, as no suitable studies identified

Should insecticide space spraying versus no insecticide space spraying be used for preventing malaria transmission?						
Population: Anyone living in a malarious area **Intervention:** Insecticide space spraying **Comparison:** No insecticide space spraying **Setting:** Malaria-endemic countries and regions **Source:** Pryce J, Choi L, Malone D. Insecticide space spraying for preventing malaria transmission (Protocol). Cochrane Database Syst Rev. 2017;6:CD012689. doi:10.1002/14651858.CD012689						
Outcome	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Assumed risk	Corresponding risk				

7. Topical and Spatial Repellents

7.1 Do topical repellents reduce malaria?

7.2 Do impregnated clothes reduce malaria?

7.3 Do spatial repellents reduce malaria?

Recommendation				
Use of topical repellents for malaria prevention is not currently recommended as a public health intervention. Topical repellents may be beneficial as a tool to provide personal protection against malaria in specific population groups.				
Strength of Recommendation				
For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
			CONDITIONAL	

Overall Quality of Evidence for all Critical Outcomes			
High	Moderate	Low	Very Low
		LOW	

Balance of Desirable and Undesirable Effects	
Desirable	Undesirable
No desirable effects identified in systematic review	

Rationale for the Recommendation
The systematic review assessed the evidence of a benefit from the use of topical repellents as a malaria prevention tool in a public health setting to be LOW certainty. Based on expert opinion and in line with current WHO recommendations, topical repellents may still be useful in providing personal protection against malaria.
Remarks
RESEARCH PRIORITIES Investigations of the potential public health value of topical repellents in specific settings and target populations

Evidence-to-Decision Framework – Topical Repellents

PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Malaria has significant effects on individuals (especially children under 5, pregnant women and other groups with little or no acquired immunity) and communities.							
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
There is unlikely to be any significant variability in the values individuals and communities place on reduced malaria incidence and prevalence.							
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Topical repellents are not long-lasting and have to be applied regularly; therefore, costs are likely to be moderate–high.							
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favours the comparison	**Probably favours the comparison**	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
The evidence reviewed did not consider cost-effectiveness, but the expert opinion of the VCTEG is that it probably favours the comparison.							
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
The impact of topical repellents on health equity depends on the distribution channel (public versus private) and the specific target population.							
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
This intervention is politically acceptable, but may be less so for other stakeholders.							
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
The VCTEG considers this to be a difficult intervention to implement through public-sector channels.							

In malarial areas, are topical repellents effective in preventing malaria?

Population: People at risk of malaria
Intervention: Topical repellent
Comparison: No repellent
Setting: Six studies investigated the impact of topical repellent compared to placebo or no treatment (Chen-Hussey 2013; Hill 2007; McGready 2001; Rowland 2004; Sangoro 2014b; and Sluydts 2016). In total, 34 281 participants were included in the treatment arms and 33 016 in the control arms. The studies were conducted in a variety of countries: Lao People's Democratic Republic (Chen-Hussey 2013), Bolivia (Hill 2007), Thailand (McGready 2001), Pakistan (Rowland 2004), United Republic of Tanzania (Sangoro 2014b) and Cambodia (Sluydts 2016). A variety of repellents and concentrations were used: 15% DEET (Chen-Hussey 2013; Sangoro 2014b); 20% DEET (McGready 2001); 30% PMD (Hill 2007); 20% DEET and 0.5% permethrin (Rowland 2004); and picaridin (20% picaridin for adults and 10% picaridin for children) (Sluydts 2016). Three studies used LLINs as co-interventions (Chen-Hussey 2013; Hill 2007; Sangoro 2014b). Most studies included all children and adults in the population; however, one study included only pregnant women (McGready 2001).
Source: Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ. Mosquito repellents for malaria prevention (Protocol). Cochrane Database Syst Rev. 2015;4:CD011595. doi:10.1002/14651858.CD011595.

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Risk with placebo or no treatment	Risk with topical repellent				
Clinical malaria (*P. falciparum*)	39 per 1000	25 per 1000 (15 to 41)	Rate Ratio 0.65 (0.40 to 1.07)	4450 (3 studies)	⨁◯◯◯ VERY LOW[1,2,3]	
Parasitaemia (*P. falciparum*)	15 per 1000	12 per 1000 (9 to 17)	Rate Ratio 0.84 (0.64 to 1.12)	13 310 (4 studies)	⨁⨁◯◯ LOW[4,5]	
Clinical malaria (*P. vivax*)	36 per 1000	48 per 1000 (36 to 64)	Rate Ratio 1.32 (0.99 to 1.76)	3996 (2 studies)	⨁⨁◯◯ LOW[6,7]	
Parasitaemia (*P. vivax*)	18 per 1000	19 per 1000 (14 to 25)	Rate Ratio 1.07 (0.80 to 1.41)	9434 (3 studies)	⨁⨁◯◯ LOW[7,8]	

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

Notes

[1]Downgraded by 1 for risk of bias: Sangoro 2014b used alternate allocation and reported a baseline imbalance; random sequence generation and allocation concealment were not described by Rowland 2004 or Sluydts 2016; and Sluydts 2016 did not have a placebo so the intervention was not blinded.

[2]Downgraded by 1 because of the large heterogeneity between the three trials: The I^2 statistic, which quantifies the proportion of the variation in the point estimates due to among-study differences, was considered substantial at 50%. The subgroup analysis explained the heterogeneity to some extent, but we do not believe that there is enough evidence to suggest there was a true subgroup effect, given that there was no heterogeneity in the outcome parasitaemia caused by *P. falciparum* when studies with and without LLINs were also analysed.

[3]Downgraded by 1 for imprecision: The sample size is too small, the CIs are wide, the pooled effect (0.40 to 1.07) overlaps a relative risk (RR) of 1.0 (no effect) and presents an estimate of effect ranging between beneficial and harmful.

[4]Downgraded by 1 for risk of bias: Hill 2007 used alternate allocation and reported a baseline imbalance; random sequence generation and allocation concealment were not described by McGready 2001 or Sluydts 2016.

[5]Downgraded by 1 for imprecision: The sample size is too small, the CIs are very wide, the pooled effect (0.62 to 1.12) overlaps a relative risk (RR) of 1.0 (no effect) and presents an estimate of effect ranging between beneficial and harmful.

[6]Downgraded by 1 for risk of bias: Random sequence generation and allocation concealment were not described by Rowland 2004 or Sluydts 2016; Sluydts 2016 was not placebo-controlled and the intervention was not blinded.

[7]Downgraded by 1 for imprecision: The CIs are very wide, the pooled effect (0.80 to 1.41) overlaps a relative risk (RR) of 1.0 (no effect) and presents an estimate of effect ranging between beneficial and harmful.

[8]Downgraded by 1 for risk of bias: Random sequence generation and allocation concealment were not described by McGready 2001 or Sluydts 2016

8. Insecticide-Treated Clothing

Recommendation				
Use of insecticide-treated clothing for malaria prevention is not currently recommended as a public health intervention. Insecticide-treated clothing may be beneficial as a tool to provide personal protection against malaria in specific population groups (refugees, military).				
Strength of Recommendation				
For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
			CONDITIONAL	

Overall Quality of Evidence for all Critical Outcomes			
High	Moderate	Low	Very Low
		LOW	
Balance of Desirable and Undesirable Effects			
Desirable		Undesirable	
Evidence of an effect on clinical *P. falciparum* and *P. vivax* malaria in specific population groups		No undesirable effects identified in systematic review	
Rationale for the Recommendation			
The systematic review identified some LOW quality evidence of an effect on clinical *P. falciparum* and *P. vivax* malaria in specific population groups. No evidence was available on epidemiological effects in the general at-risk population.			
Remarks			
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			

Evidence-to-Decision Framework – Insecticide-Treated Clothing

PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Malaria has significant effects on individuals (especially children under 5, pregnant women and other groups with little or no acquired immunity) and communities.							
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
There is unlikely to be any significant variability in the values individuals and communities place on reduced malaria incidence and prevalence.							
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Clothing will require regular re-treatment; therefore, costs are likely to be moderate–high.							
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favours the comparison	**Probably favours the comparison**	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
The evidence reviewed did not consider cost-effectiveness, but the expert opinion of the VCTEG is that it probably favours the comparison.							
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
The impact of insecticide-treated clothing on health equity depends on the distribution channel (public versus private) and the specific target population.							
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
The VCTEG considers this to be a difficult intervention to implement through public-sector channels as a public health measure.							

Does insecticide-treated clothing provide protection against malaria?						
Population: People at risk of malaria **Intervention:** Insecticide-treated clothing **Comparison:** Placebo or no treatment **Setting:** ITCs were investigated in trials conducted in refugee camps in Pakistan and in military personnel based in the Colombian Amazon. **Source:** Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ. Mosquito repellents for malaria prevention (Protocol). Cochrane Database Syst Rev. 2015;4:CD011595. doi:10.1002/14651858.CD011595.						
Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Risk with placebo or no treatment	Risk with insecticide-treated clothing				
Clinical malaria (*P. falciparum*)	35 per 1000	17 per 1000 (10 to 29)	Rate Ratio 0.49 (0.29 to 0.83)	997 (2 studies)	⨁⨁◯◯ LOW[1,2]	
Clinical malaria (*P. vivax*)	116 per 1000	74 per 1000 (47 to 117)	Rate Ratio 0.64 (0.40 to 1.01)	997 (2 studies)	⨁⨁◯◯ LOW[41,2]	
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).						

Notes

[1]Downgraded by 1 for risk of bias: Soto 1995 did not describe how randomization and allocation concealment were assured. Rowland 1999 did not describe the method used for allocation concealment.

[2]Downgraded by 1 for imprecision: The sample sizes and number of events are very small.

9. Spatial/Airborne Repellents

Recommendation
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 and published.

Strength of Recommendation				
For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
		NO RECOMMENDATION		

Overall Quality of Evidence for all Critical Outcomes			
High	Moderate	Low	Very Low
			VERY LOW

Balance of Desirable and Undesirable Effects	
Desirable	Undesirable
None identified in systematic review	None identified in systematic review

Rationale for the Recommendation
The systematic review identified only two studies with high risk of bias, imprecision and inconsistency, resulting in VERY LOW certainty of evidence of an effect.

Remarks
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

Evidence-to-Decision Framework – Spatial/Airborne Repellents

PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Malaria has significant effects on individuals (especially children under 5, pregnant women and other groups with little or no acquired immunity) and communities.							
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
There is unlikely to be any significant variability in the values individuals and communities place on reduced malaria parasitaemia.							
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
The impact of spatial/airborne repellents on health equity would depend on the population targeted.							
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
This intervention is politically acceptable, but may be less so for other stakeholders.							
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
Depends on the product formulation. Some formulations are longer lasting.							

In malarial areas, are spatial/airborne repellents effective in preventing malaria?						
Population: People at risk of malaria **Intervention:** Spatial/airborne repellent **Comparison:** Placebo or no spatial/airborne repellent **Setting:** Two studies were conducted in India (Narasanyamy, 1989; Tewari, 1990) and one was conducted in Haiti, Central America (Krogstad, 1975). **Source:** Pryce J, Choi L, Malone D. Insecticide space spraying for preventing malaria transmission (Protocol). Cochrane Database Syst Rev. 2017, Issue 6. CD012689. doi: 10.1002/14651858.CD012689.						
Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)	Importance of the outcome to decision-making
	Risk with placebo or no treatment	Risk with spatial/airborne repellent				
Parasitaemia (all species)	10 per 1000	2 per 1000 (0 to 18)	Rate Ratio 0.24 (0.03 to 1.72)	6683 (2 studies)	⨁◯◯◯ VERY LOW[1,2,3]	
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).						

Notes

[1]Downgraded by 1 for risk of bias: Hill 2014 was not blinded.

[2]Downgraded by 1 for imprecision: Hill 2014 was underpowered and reported very few events (1/3349 in the intervention and 11/3270 in the control), and the CIs ranged from no effect to large benefits. Both studies were underpowered.

[3]Downgraded by 1 for inconsistency: There is considerable unexplained heterogeneity between trials (I^2 statistic = 73%).

Annex 4. Previously issued WHO recommendations and guidance

Title	Type	Publication Date
Global Strategic Framework for Integrated Vector Management	Framework	2004
Insecticide-treated mosquito nets: a WHO position statement	Position Statement	2007
The role of larviciding for malaria control in sub-Saharan Africa	Interim Position Statement	2012
Handbook for Integrated Vector Management		2012
Global plan for insecticide resistance management in malaria vectors		2012
Achieving universal coverage with long-lasting insecticidal nets in malaria control	Recommendation	2013 (revised 2014)
WHO guidance note on capacity building in malaria entomology and vector control	Guidance Note	2013
Larval source management: a supplementary measure for malaria vector control. An operational manual.		2013
Control of residual malaria parasite transmission	Technical Note	2014
WHO guidance for countries on combining indoor residual spraying and long-lasting insecticidal nets	Guidance Note	2014
WHO recommendations on the sound management of old long-lasting insecticidal nets	Recommendation	2014
Indoor residual spraying: An operational manual for IRS for malaria transmission, control and elimination. Second edition.		2015
Risks associated with scale-back of vector control after malaria transmission has been reduced	Information Note	2015
Malaria vector control policy recommendations and their applicability to product evaluation	Information Note	2017
Achieving and maintaining universal coverage with long-lasting insecticidal nets for malaria control	Recommendations	2017
Conditions for deployment of mosquito nets treated with a pyrethroid and piperonyl butoxide	Recommendations	2017

Annex 5: Principal malaria vectors and information on key ecology and behaviours by WHO region

WHO Region	Ecological zone	Vector species	Breeding sites	Biting behaviour			Resting behaviour	Insecticide resistance	Remarks
				Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily		
AFRO	Coastal (W. Africa)	An. melas	Brackish water of lagoons and mangrove (Avicennia) belts	Zoophilic and anthropophilic	Indoors and outdoors	00:00 to dawn	Predominantly outdoors		
AFRO	Forest, Guinea savanna, Sudan savanna, Sahel (wetter, more humid)	An. gambiae s.s.	Shallow, open, sunlit pools: borrow pits, drains, brick pits, car tracks, ruts, hoofprints around ponds, wells. Also pools of receding rivers, backwater, rainwater filling in natural depressions, etc.	Predominantly anthropophilic	Predominantly indoors	00:00 to dawn	Indoors and outdoors		High diversity, incipient speciation?
AFRO	Northern Guinea savanna, Sudan savanna, Sahel (drier)	An. arabiensis	Small, temporary, sunlit, clear and shallow freshwater pools. Can include slow-flowing, partially shaded streams and a variety of large and small natural and man-made habitats and rice fields	More zoophilic than An. gambiae s.s.	More exophagic than An. gambiae s.s.	Early evening and early morning	Predominantly outdoors		Very variable behaviours
AFRO	All zones, except subdesert and coastal areas	An. funestus s.s.	Permanent, clear, fresh waters, slightly shaded, with floating or erect vegetation, and containing little organic matter or mineral salts: swamps, edges of lakes and ponds, pools in stream and river banks, rice fields (esp. Madagascar and Mali)	Highly anthropophilic	Indoors	00:00 to dawn, but generally later than An. gambiae	Predominantly indoors		Member of Funestus subgroup
AFRO	Forest and savanna	An. nili	Streams among debris and floating vegetation, swamps	Predominantly anthropophilic	Largely outdoors	00:00 to 01:00	Predominantly outdoors		
AFRO	Forest only	An. moucheti	Sides of water courses, esp. with Pistia and slow-moving water with vertical vegetation. Fish culture ponds	Predominantly anthropophilic	Partly indoors	00:00 to dawn	Predominantly indoors		
AFRO	Coastal (E. Africa)	An. merus	Crab holes, domestic wastes, marshes, rock pools and casual rainwater pools (NOT mangroves)	Zoophilic and anthropophilic	Indoors and outdoors	00:00 to 01:00 peak	Predominantly outdoors		
PAHO	Coastal and mountain fringe	An. albimanus	Open, sunlit, clear water, incl. rice fields. Fresh or brackish	May be zoophilic or anthropophilic	Predominantly outdoors	Evening and night	Predominantly outdoors (endophilic in Mexico, Central America)		
PAHO	Mountain fringe	An. albitarsis s.l.	Sunlit, clear, fresh water, incl. lagoons, lakes, rice fields	Zoophilic and anthropophilic	Indoors and outdoors	Evening and night	Predominantly outdoors		
PAHO	Coastal	An. aquasalis	Sunlit habitats containing emergent vegetation, both brackish and fresh, incl. stream pools, mangrove swamps, grass swamps, lagoons and ditches	Zoophilic and anthropophilic	Indoors and outdoors	Dusk and early evening	Predominantly outdoors		
PAHO	Above 600m	An. braziliensis							
PAHO	Savanna, plains, valleys, lowland forest and forest fringe	An. darlingi	Natural water bodies, incl. lagoons, lakes and particularly slow-flowing streams or rivers with shaded, clear water, and associated submerged vegetation such as bamboo roots	Anthropophilic	Indoors and outdoors	All night	Predominantly outdoors		Very adaptable to human behaviour
PAHO		An. freeborni	Clear seepage water, roadside pools, rice fields (margins), and similar habitats. Sunlit pools preferred, although larvae are occasionally found in shaded pools.	Zoophilic	Predominantly outdoors				
PAHO	Lowland	An. marajoara	Sunlit and clear or muddy water, incl. gold	Zoophilic and	Indoors and outdoors	Evening peak	Exclusively		Member of An.

WHO Region	Ecological zone	Vector species	Breeding sites	Biting behaviour			Resting behaviour	Insecticide resistance	Remarks
				Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily		
	species, associated with wetlands, secondary forests and human intervention		diggings	anthropophilic			exophilic(?)		Albitarsis complex
PAHO	Mountain fringe	An. nuneztovari s.l.	Sunlit and shaded, incl. fresh, clear, still or flowing water with floating or emergent vegetation: lagoons, lakes, slow-flowing rivers, fish ponds, gold mine dugouts, rain puddles, and temporary or permanent pools	Zoophilic and anthropophilic	Predominantly outdoors	18:00–20:00 (nuneztovari A); 22:00–02:00 nuneztovari B/C	Outdoors		
PAHO	Highland	An. pseudopunctipennis s.l.	Sun-exposed, shallow, clear, freshwater streams or river pools with abundant filamentous algae (incl. brackish)	Zoophilic and anthropophilic	Indoors and outdoors	All night	Predominantly outdoors		
PAHO	Coastal plains and river valleys	An. quadrimaculatus subgroup	Rice fields, first flooding	Zoophilic	Predominantly outdoors	All night, peaks at dusk and dawn	Outdoors		An. quadrimaculatus (sp. A), An. smaragdinus (sp. B) and An. diluvialis (sp. C)
EMRO	Savanna, plains, and valleys and coastal SW Arabia	An. arabiensis	Small, temporary, sunlit, clear, shallow, freshwater pools. Can include slow-flowing, partially shaded streams and a variety of large and small natural and man-made habitats and rice fields	More zoophilic than An. gambiae ss	More exophagic than An. gambiae s.s.	Early evening and early morning	Predominantly outdoors		Very variable behaviours
EMRO	Savanna, plains and valleys	An. atroparvus	Brackish and fresh water. Canals, ditches, river margins, pools in river beds and rice fields	Predominantly zoophilic	Indoors and outdoors		Outdoors (animal sheds and stables). Hibernates but will feed		Member of maculipennis subgroup
EMRO	Savanna, plains and valleys in South. Peri-urban areas in Yemen	An. culicifacies	Clean and polluted water, incl. irrigation ditches, rice fields, swamps, pools, wells, borrow pits	Zoophilic	Predominantly outdoors	21:00–04:00 in warmer months, crepuscular in cooler	Predominantly indoors		
EMRO	Mountain fringe Iran	An. d'thali							
EMRO	Savanna, plains and valleys in South	An. fluviatilis	Streams, springs, pools, marshes, irrigation channels. Fresh or saline		Indoors and outdoors	Peak before 00:00	Indoors and outdoors		
EMRO	Savanna, plains and valleys in West	An. labranchiae	Similar to atroparvus, but warmer waters and incl. rice fields (no sympatry)	Predominantly anthropophilic, but will also bite animals	Indoors and outdoors		Predominantly indoors, but also outdoors. Hibernates but will feed		Member of maculipennis subgroup
EMRO	Foothills	An. maculipennis s.s.							
EMRO	Savanna, plains and valleys, forest fringe	An. messeae	Shaded, clear, very slow-flowing or stagnant, fresh water, incl. lake margins and marshes. Very widespread	Predominantly zoophilic	Predominantly outdoors		Outdoors (animal sheds and stables). Hibernates (diapause)		Member of maculipennis subgroup
EMRO	Alluvial plains	An. pharoensis	Clear, stagnant, shallow water with thick	Zoophilic and	Predominantly	Peak biting in first 3h	Predominantly		Principal vector in

WHO Region	Ecological zone	Vector species	Breeding sites	Biting behaviour			Resting behaviour	Insecticide resistance	Remarks
				Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily		
			vegetation. Shade essential. Drains, irrigation channels, seepages, pools, borrow pits, especially rice fields	anthropophilic	outdoors (animal shelters)	after sunset. 2nd peak just before dawn	outdoors		Delta and Nile valley of Egypt
EMRO	Savanna, plains and valleys of Iraq and Afghanistan	*An. pulcherrimus*	Warm, sunny, stagnant habitats with abundant submerged vegetation, rice fields	Zoophilic and anthropophilic					
EMRO	Savanna, plains and valleys and foothills	*An. sacharovi*	Sunlit sites with emergent and/or floating vegetation. Swamps, marshes, margins of rivers, streams and springs, seepages, wadis, pools and ditches, and rice fields	Zoophilic and anthropophilic	Indoors and outdoors	20:00–21:00, but can bite in day in shade	Indoors (mostly) and outdoors		Member of maculipennis subgroup
EMRO	Desert fringe, responsible for 'oasis malaria' in Morocco, Algeria, Egypt	*An. sergentii*	Non-polluted, shallow sites that contain fresh water with a slow current, slight shade and emergent vegetation or algae, incl. streams, seepages, canals, irrigation channels, springs, rice fields	Zoophilic and anthropophilic	Predominantly outdoors	Peak 20:00–22:00	Predominantly outdoors		
EMRO	Alluvial plains	*An. stephensi*	Man-made habitats, incl. cisterns, wells, gutters, storage jars, drains. Also grassy pools and alongside rivers	Predominantly anthropophilic	Predominantly indoors, but will readily bite outdoors in summer	Peak before 00:00	Predominantly indoors		
EMRO	Alluvial plains	*An. superpictus*	Gravel or pebble river and stream beds in shallow, slow-flowing clear water in full sunlight, incl. small pools within or next to drying river beds, irrigation channels and storage tanks, rice fields, ditches, borrow pits and hoof prints	Zoophilic and anthropophilic	Predominantly outdoors		Predominantly outdoors		Potential vector in Europe, vector in Turkey and Syria
EURO	Savanna, plains in Europe and southern Russia	*An. atroparvus*	Brackish and fresh water. Canals, ditches, river margins, pools in river beds and rice fields	Predominantly zoophilic	Indoors and outdoors		Outdoors (animal sheds and stables). Hibernates but will feed		Member of maculipennis subgroup
EURO	Coastal Italy, Corsica, Croatia	*An. labranchiae*	Similar to *An. atroparvus*, but warmer waters and incl. rice fields (no sympatry)	Predominantly anthropophilic, but will also bite animals	Indoors and outdoors		Predominantly indoors, but also outdoors. Hibernates but will feed		Member of maculipennis subgroup
EURO	Mountainous areas in Europe and coastal areas	*An. maculipennis s.s.*	Cold waters in upland areas (but also with *An. messae* at sea level in running water)	Predominantly zoophilic					
EURO	Savanna, plains in Georgia	*An. melanoon*	Fresh water, incl. rice fields (N Italy) and marshes and swamps (Spain)	Predominantly zoophilic					
EURO	Forest and forest fringe, mountain fringe	*An. messeae*	Shaded, clear, very slow-flowing or stagnant, fresh water, incl. lake margins and marshes. Very widespread	Predominantly zoophilic	Predominantly outdoors		Outdoors (animal sheds and stables). Hibernates (diapause)		Member of maculipennis subgroup
EURO	Savanna, plains and valleys and coastal areas	*An. sacharovi*	Sunlit sites with emergent and/or floating vegetation. Swamps, marshes, margins of rivers, streams and springs, seepages, wadis, pools and ditches, and rice fields	Zoophilic and anthropophilic	Indoors and outdoors	20:00–21:00 but can bite in day in shade	Indoors (mostly) and outdoors		Member of maculipennis subgroup
EURO	Western Europe	*An. subalpinus*	Fresh or slightly saline water, swamps or	Predominantly	Predominantly				

WHO Region	Ecological zone	Vector species	Breeding sites	Biting behaviour			Resting behaviour	Insecticide resistance	Remarks
				Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily		
			ponds, rivers, rice fields	zoophilic	outdoors				
SEARO / WPRO	Savanna, plains and valleys	*An. aconitus*	Rice fields (active and fallow), shallow pools (rock, stream, seepage, flood) and slow-moving streams	Predominantly zoophilic	Indoors and outdoors	Dusk to midnight	Outdoors		Member of Funestus group
SEARO / WPRO	Savanna, plains and valleys	*An. annularis*	Clean, still water with abundant vegetation, especially ponds, swamps and rice fields	Predominantly zoophilic	Indoors and outdoors	Night	Indoors		Member of Annularis group
SEARO / WPRO	Forested mountains and foothills, cultivated forests, plantations (e.g. rubber) and forest fringes	*An. baimaii*	Small, shallow, usually temporary, mostly shaded bodies of fresh, stagnant (or very slow-flowing) water, incl. pools, puddles, small pits (e.g. gem pits), animal footprints, wheel ruts, hollow logs, streams and even wells located in primary, secondary evergreen or deciduous forests, bamboo forests and fruit or rubber plantations			22:00–02:00			Member of *dirus* complex
SEARO / WPRO	Forest and forest fringe, mountain fringe, oil palm plantations (Sabah)	*An. balabacensis*	Shaded temporary pools of stagnant fresh water, incl. puddles, animal footprints, wheel tracks, ditches and rock pools, edges of swamps, streams and rice fields, and less frequently in containers	Anthropophilic	Indoors and outdoors	Dusk and night	Indoors and outdoors		Member of *leucosphyrus* complex
SEARO / WPRO	Highland (except western Timor) and rubber plantations	*An. barbirostris*	Fresh, deep water. Swamps. Can be found in rice fields and pools, river and stream margins and pools, ditches, moats, lakes, permanent and temporary ground pools, rice fields, wells, canals, marshes, rock pools, ponds, springs, swamps and animal footprints	Predominantly zoophilic	Outdoors	All night	Mostly outdoors		Member of Barbirostris group (12 species)
SEARO / WPRO	Forest and forest fringe, plantations; mountain fringe	*An. cracens*		Anthropophilic and zoophilic (monkeys)	Outdoors	20:00–21:00			
SEARO / WPRO	Forested areas with perennial streams to deforested riverine ecosystems and irrigated areas	*An. culicifacies*	Irrigated canals, stream margins, seepages, borrow pits, hoof marks, rock pools, sandy pools near rice fields, rock quarries, newly dug pits, ponds, domestic wells, tanks and gutters. Fresh water, but can tolerate salinity	ABCD zoophilic, E anthropophilic	Indoors and outdoors	Dusk and night	Indoors and outdoors		Complex within Funestus group
SEARO / WPRO	Forested mountains and foothills, cultivated forests, plantations (e.g. rubber) and forest fringes	*An. dirus*	Small, shallow, usually temporary, mostly shaded bodies of fresh, stagnant (or very slow-flowing) water, incl. pools, puddles, small pits (e.g. gem pits), animal footprints, wheel ruts, hollow logs, streams and even wells located in primary, secondary evergreen or deciduous forests, bamboo forests and fruit or rubber plantations	Anthropophilic and zoophilic (cattle, monkeys)	Indoors and outdoors	20:00–23:00	Outdoors		Member of *dirus* complex
SEARO / WPRO	Oil palm plantations (Sarawak)	*An. donaldi*	Habitats with some emergent vegetation and heavy shade such as jungle pools, swamp forest, sedge swamps. Also overgrown drains, rice fields and river swamps		Enter houses to bite at night	Adults will bite during the day in shady locations			

WHO Region	Ecological zone	Vector species	Breeding sites	Biting behaviour			Resting behaviour	Insecticide resistance	Remarks
				Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily		
SEARO / WPRO	Coastal (Indo-Malay region)	*An. epiroticus*	Fresh, brackish and salt water, typically with full sunlight and mats of green algae on surface	Predominantly zoophilic	Indoors and outdoors	Indoors 01:00–02:00 and 03:00–05:00; outdoors 21:00–22:00 and 01:00–02:00			Formerly *An. sundaicus* sp A
SEARO / WPRO	Coastal Australasian region	*An. farauti*	Natural, rain-fed temporary pools to larger semi-permanent to permanent bodies of ground water, usually with some varying degree of floating or emergent vegetation	Predominantly anthropophilic	Indoors and outdoors	All night, but can bite in day	Indoors and outdoors		Member of *farauti* complex. 8 species. Punctulatus group
SEARO / WPRO	Foothills usually <600m	*An. flavirostris*	Clear, slow-moving, freshwater habitats that are typically partly shaded by surrounding overhead vegetation and with margins containing emergent plants or grasses, edges of seepage pools, slow-flowing, grassy river edges, canals and irrigation ditches; reported from natural wells and occasionally stagnant pools, and very rarely from rice fields or ponds	Predominantly zoophilic	Indoors and outdoors	22:00–03:00	Outdoors		Member of Minimus subgroup
SEARO / WPRO	Savanna, plains and valleys; forested hills and mountainous areas	*An. fluviatilis*	Slow-flowing streams or river margins, in direct or diffuse sunlight. Also reported from rice fields	Sp S anthropophilic, T&U zoophilic	Spp. T&U outdoors	19:00–21:00	Sp S indoors, T&U outdoors		Member of *fluviatilis* complex, Funestus group
SEARO / WPRO	Mountain fringe	*An. harrisoni*							
SEARO / WPRO	Forest and forest fringe, plantations	*An. introlatus*							
SEARO / WPRO	Coastal Australasian region	*An. koliensis*	More permanent collections of fresh water (NEVER brackish), such as irrigation ditches and ponds containing floating and emergent vegetation, temporary pools in open grassland and along the margins of jungle, mostly exposed to sunlight	Predominantly anthropophilic	Outdoors and indoors	Night (after midnight	Predominantly outdoors		Member of Punctulatus group. 12 sibling species
SEARO / WPRO	Forest, forest fringe, plantations; mountain fringe	*An. latens*	Shaded temporary pools and natural containers of clear or turbid water on the ground in forest areas. Also stump ground holes, sand pools, ground pools, flood pools, rock pools, stream pools, stream margins, seepage-springs, wheel tracks and elephant footprints	Predominantly anthropophilic	Indoors and outdoors	22:00–04:00	Outdoors		Member of *leucosphyrus* complex
SEARO / WPRO	Mountain fringe	*An. lesteri*	Freshwater ground pools, ditches, margins of streams and ponds, rice fields, marshes, swamps, lakes and other impounded waters	Anthropophilic and zoophilic		Dusk and night	Indoors (?)		Member of Hyrcanus group
SEARO / WPRO	Oil palm plantations (Sarawak)	*An. letifer*	Still, shaded, dark, acidic water with emergent vegetation or numerous leaves in the water, incl. freshwater swamps, jungle pools, large isolated stream pools.	Predominantly anthropophilic	Outdoors	Night			
SEARO / WPRO	Forest, forest fringe, plantations	*An. leucosphyrus*	Shaded temporary pools and natural containers of clear or turbid water on the ground in forest areas	Predominantly anthropophilic	Indoors and outdoors		Outdoors		Member of *leucosphyrus* complex
SEARO	Mountain fringe	*An. maculatus s.l.*	Clean water often exposed to direct sunlight,	Predominantly	Indoors and outdoors	18:00–21:00			Member of Maculatus

WHO Region	Ecological zone	Vector species	Breeding sites	Biting behaviour			Resting behaviour	Insecticide resistance	Remarks
				Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily		
/ WPRO			incl. ponds, lakes, swamps, ditches, wells, pools, margins along small slow-flowing streams, gravel pits along stream margins, seepages, springs, rice fields, foot and wheel prints, occasionally tree holes and bamboo stumps	zoophilic					subgroup
SEARO / WPRO	Forest and forest fringe, plantations, mountain fringe	*An. minimus s.l.*	Small to moderate-sized streams or canals with slow-running, clear and cool water, partially shaded and with grassy margins	Predominantly anthropophilic	Indoors and outdoors	22:00–04:00	Indoors and outdoors		Member of minimus subgroup within Funestus group
SEARO / WPRO	Predominantly lowlands, but up to 2250m. Also plantations and coastal Australasia	*An. punctulatus* group	Most species utilize earthen-bound (often non-porous, clay-like substrates) collections of fresh water that are exposed to direct sunlight either entirely or partially	Predominantly anthropophilic	Indoors and outdoors	Variable	Outdoors		Member of Punctulatus group. 12 sibling species. Bionomics highly variable among members. More research required
SEARO / WPRO	Predominantly lowlands, but up to 2250m. Also plantations and coastal Australasia	*An. punctulatus* complex	Small, scattered, shallow, sunlit (partial shade is tolerated) temporary pools of fresh water, sand or gravel ground pools in small streams and river beds, and occasionally rock pools		Indoors and outdoors	Around midnight	Predominantly outdoors		
SEARO / WPRO	Forested mountains and foothills, cultivated forests, plantations (e.g. rubber) and forest fringes	*An. scanloni*	Small, shallow, usually temporary, mostly shaded bodies of fresh, stagnant (or very slow-flowing) water, incl. pools, puddles, small pits (e.g. gem pits), animal footprints, wheel ruts, hollow logs, streams and even wells located in primary, secondary evergreen or deciduous forests, bamboo forests and fruit or rubber plantations			Dusk 18:00–19:00			Member of *dirus* complex
SEARO / WPRO	Savanna, plains and valleys	*An. sinensis*	Shallow, freshwater habitats with emergent and/or floating vegetation in open agriculture lands (mainly rice fields). Also stream margins, irrigation ditches, ponds, marshes, swamps, bogs, pits, stump ground holes, grassy pools, flood pools, stream pools, rock pools, seepage-springs and wheel tracks	Predominantly zoophilic	Outdoors	Dusk and night	Outdoors		Member of Hyrcanus group
SEARO / WPRO	Savanna, plains and valleys; Urban (Goa)	*An. subpictus*	Sp B coastal, brackish water. ACD riverine pools, rice fields. Clear and turbid waters, reported from highly polluted habitats, incl. sites contaminated with organic waste, e.g. waste stabilization ponds, street pools and drains; strong association with rice and irrigation	Predominantly zoophilic (sp B anthropophilic)	Indoors and outdoors		Predominantly indoors		*subpictus* complex. 4 sibling species
SEARO / WPRO	Urban (India, Sri Lanka)	*An. stephensi*	Man-made habitats, incl. cisterns, wells, gutters, storage jars, drains	Predominantly anthropophilic	Predominantly indoors, but will readily bite outdoors in summer	Peak before 00:00	Predominantly indoors		
SEARO / WPRO	Coastal (Indo-Malay region)	*An. sundaicus*	Sunlit habitats containing pooled stagnant water, algae and non-invasive vegetation;	Predominantly anthropophilic	Indoors and outdoors	20:00–03:00	Indoors and outdoors		*sundaicus* complex. 4 species

WHO Region	Ecological zone	Vector species	Breeding sites	Biting behaviour			Resting behaviour	Insecticide resistance	Remarks
				Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily		
			ponds, swamps, lagoons, open mangrove, rock pools and coastal shrimp or fish ponds, irrigated inland sea-water canals. An. epiroticus strong association with shrimp/fish aquaculture						
SEARO / WPRO	Savanna, plains and valleys, incl. rice fields DPRK and Rep. of Korea	*An. yatsushiroensis*							

Sources for Annex 4:

Sinka ME, Rubio-Palis Y, Manguin S, Patil AP, Temperley WH, Gething PW, et al. The dominant *Anopheles* vectors of human malaria in the Americas: occurrence data, distribution maps and bionomic précis. Parasit Vectors. 2010;3:72.

Sinka ME, Bangs MJ, Manguin S, Coetzee M, Mbogo CM, Hemingway J, et al. The dominant *Anopheles* vectors of human malaria in Africa, Europe and the Middle East: occurrence data, distribution maps and bionomic précis. Parasit Vectors. 2010;3:117.

Sinka ME, Bangs MJ, Manguin S, Chareonviriyaphap T, Patil AP, Temperley WH, et al. The dominant *Anopheles* vectors of human malaria in the Asia-Pacific region: occurrence data, distribution maps and bionomic précis. Parasit Vectors. 2011;4:89.

Walter Reed Biosystematics Unit [website] (www.WRBU.org).

Zahar AR. Vector bionomics in the epidemiology and control of malaria. Part I. The WHO African Region and the Southern WHO Eastern Mediterranean Region. Section I: Malaria vectors of the Afrotropical Region. General information. Section II: An overview of the malaria control problems & the recent malaria situation. Geneva: World Health Organization; 1985 (VBC/84.6 & MAP/84.3).

Zahar AR. Vector bionomics in the epidemiology and control of malaria. Part I. The WHO African Region and the Southern WHO Eastern Mediterranean Region. Section III: Vector bionomics, malaria epidemiology and control by geographical areas. (A) West Africa. Geneva: World Health Organization; 1985 (VBC/85.1 & MAP/85.1).

Zahar AR. Vector bionomics in the epidemiology and control of malaria. Part I. The WHO African Region and the Southern WHO Eastern Mediterranean Region. Section III: Vector bionomics, malaria epidemiology and control by geographical areas. (B) Equatorial Africa, (C) Southern Africa. Geneva: World Health Organization; 1985 (VBC/85.2 & MAP/85.2).

Zahar AR. Vector bionomics in the epidemiology and control of malaria. Part I. The WHO African Region and the Southern WHO Eastern Mediterranean Region. Section III: Vector bionomics, malaria epidemiology and control by geographical areas. (D) East Africa, (E) Eastern Outer Islands, (F) Southwestern Arabia. Geneva: World Health Organization; 1985 (VBC/85.3 & MAP/85.3).

Zahar AR. Vector bionomics in the epidemiology and control of malaria. Part II. The WHO European Region and the WHO Eastern Mediterranean Region. Volume II: Applied field studies. Section I: An overview of the recent malaria situation and current problems & Section II: Vector distribution. Geneva: World Health Organization; 1990 (VBC/90.1 & MAL/90.1).

Zahar AR. Vector bionomics in the epidemiology and control of malaria. Part II. The WHO European Region and the WHO Eastern Mediterranean Region. Volume II: Applied field studies. Section III: Vector bionomics, malaria epidemiology and control by geographical areas. (B) Asia West of India. Geneva: World Health Organization; 1990 (VBC/90.3 & MAL/90.3).