GUIDELINES FOR MALARIA VECTOR CONTROL

World Health Organization

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Contents

Glossary v

Abbreviations xiii

Executive summary xiv

Recommendations xvi

1. Introduction 1

1.1 Background 1
1.2 Objectives 1
1.3 Scope 2
1.4 Outcomes 2
1.5 Target audience 3
1.6 Funding 3
1.7 Management of conflicts of interest 3
1.8 Methods used to formulate recommendations 4
1.9 Dissemination 9
1.10 Updating 10
1.11 User feedback 10

2. Malaria and related entomological and vector control concepts 11

2.1 Etiology 11
2.2 Vectors and their behaviour and distribution 12
2.3 Background and rationale for vector control 14

3. Recommendations on malaria vector control 17

3.1 Prevention, mitigation and management of insecticide resistance 21
3.2 Vector control across different malaria transmission settings 30

4. Recommendations on core interventions 34

4.1 Insecticide-treated nets (ITNs) 34
4.2 Indoor residual spraying (IRS) 45

5. Recommendations on supplementary interventions **48**

5.1 Larval source management (LSM) 48

6. Recommendations on personal protection measures **52**

6.1 Topical repellents, insecticide-treated clothing and spatial/airborne repellents 52

7. Other interventions **56**

7.1 Space spraying 56

7.2 Housing improvements 57

8. Special situations **58**

8.1 Residual transmission 58

8.2 Epidemics and humanitarian emergencies 58

8.3 Migrant populations and populations engaged in high-risk activities 60

9. Implementation challenges **61**

9.1 Acceptability, participation and ethical considerations 61

9.2 Equity, gender and human rights 63

9.3 Resource implications and prioritization 64

9.4 Human resources and entomological capacity 65

10. Monitoring and evaluation of vector control **67**

10.1 Quality assurance of vector control interventions 67

11. Research agenda to support future updates **70**

References **72**

Annexes **79**

Annex 1. Persons involved in development of the Guidelines 80

Annex 2. Overview of WHO guideline development process 87

Annex 3. Criteria used in the Evidence-to-Decision Framework 89

Annex 4. GRADE tables assessing the certainty of evidence 90

Glossary

The majority of the following definitions are from the WHO publication on malaria terminology, which is subject to periodic update. For the latest edition, please see: www.who.int/malaria/publications/atoz/malaria-terminology/en/. Definitions not yet captured in the *WHO malaria terminology* document are indicated with an asterisk.

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.*
biological insecticide*	Pesticides made from natural materials that are meant to kill or control insects. These natural source materials may include animals, plants, bacteria or minerals.
biting rate	Average number of mosquito bites received by a host in a unit 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.*

coverage, universal	Access to and use of appropriate interventions by the entire population at risk of malaria.
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; usually quantified as the proportion of mosquitoes resting indoors; used in assessing the effect of indoor residual spraying *Note: Contrasts with exophily.*
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 blood 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; usually quantified as the proportion of mosquitoes resting outdoors versus indoors; used in estimating outdoor transmission risks. *Note: Contrasts with endophily.*

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).
infectivity*	Ability of a *Plasmodium* strain to establish an infection in an anopheline mosquito species and undergo development until the mosquito has sporozoites in its salivary glands.
insecticide	Chemical product (natural or synthetic) that kills insects: Ovicides kill eggs; larvicides (larvacides) kill larvae; pupacides kill pupae; adulticides kill adult mosquitoes. Residual insecticides remain active for an extended period. *Note: WHO maintains a prequalification listing of vector control products (1).*
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: i) habitat modification, which is a permanent alteration of the environment, e.g. land reclamation; ii) habitat manipulation, which is a recurrent activity, e.g. flushing of streams; iii) larviciding, which is the regular application of biological or chemical insecticides to water bodies; and iv) 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.*
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 (parasite prevalence)	Proportion of a specified population with malaria infection at one time.
malaria incidence	Number of newly diagnosed malaria cases during a defined period in a specified population.
malariogenic potential*	The risk of malaria transmission; the product of receptivity, vulnerability and mosquito infectivity.

malarious area	Area in which transmission of malaria is occurring or has occurred during the preceding three years.
net, insecticide-treated*	Mosquito net that repels, disables or kills mosquitoes that come into contact with the insecticide on the netting material. The three categories of insecticide-treated net are: • C*onventionally treated net:* a mosquito net that has been treated by dipping it into a WHO-recommended insecticide. To ensure its continued insecticidal effect, the net should be re-treated periodically. • *Long-lasting insecticidal net:* a factory-treated mosquito net made of netting material with insecticide incorporated within or bound around the fibres. The net must retain its effective biological activity for at least 20 WHO standard washes under laboratory conditions and three years of recommended use under field conditions. • *Pyrethroid-PBO net:* a mosquito net that includes both a pyrethroid insecticide and the synergist piperonyl butoxide. To date, pyrethroid-PBO nets have not met required thresholds to qualify as long-lasting insecticidal nets. *Note: Untreated mosquito nets can also provide substantial protection against mosquito bites, but they have less effect against vectorial capacity and transmission rates.*
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.*

Public health intervention*	A public health intervention is any effort or policy that attempts to improve mental and physical health on a population level. Common types of interventions include screening programmes, vaccination, food and water supplementation, and health promotion. Common issues that are the subject of public health interventions include obesity, drug, tobacco and alcohol use, and the spread of infectious diseases such as malaria. An effort or policy may meet the criteria of a public heath intervention if it prevents disease on both the individual and community level and has a positive impact on public health. For malaria vector control tools, technologies and approaches designed to prevent disease at the community level (e.g. IRS and ITNs), demonstration of public health value is required for WHO to issue a policy recommendation.
public health value*	A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans. *Note: Public health value = epidemiological impact*
receptivity	Receptivity of an ecosystem to transmission of malaria. *Note: A receptive ecosystem should have e.g. the presence of competent vectors, a suitable climate and a susceptible population.*
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.
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).*

synergist*	A substance that does not itself have insecticidal properties, but that, when mixed and applied with insecticides of a particular class, considerably enhances their potency by inhibiting an enzyme that normally acts to detoxify the insecticide in the insect system.
transmission 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 malaria transmission following the implementation in time and space of a widely effective malaria programme. *Note: The sources of and risks for 'residual transmission' may vary by location, time and the existing components of the current 'effective malaria programme'.*
transmission, seasonal	Transmission that occurs only during some months of the year and is markedly reduced during other months.
transmission, stable	Epidemiological type of malaria transmission characterized by a steady prevalence pattern, with little variation from one year to 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.* • Principal vector: The species of *Anopheles* mainly responsible for transmitting malaria in any particular circumstance. *Note: Principal vectors may overlap seasonally or alternate in importance.* • Secondary or subsidiary vector: Species of *Anopheles* thought to play a lesser role in transmission than the principal vector; capable of maintaining malaria transmission at a reduced level.
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.* *Note: vector control interventions include tools, technologies and approaches.*
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.
vulnerability	The frequency of influx of infected individuals or groups and/or infective anopheline mosquitoes. *Note: Also referred to as 'importation risk'. The term can also be applied to the introduction of drug resistance in a specific area.*

Source: *WHO malaria terminology (2)* except where indicated by an asterisk (*)

Abbreviations

ANC	antenatal care
CIDG	Cochrane Infectious Diseases Group
EIR	entomological inoculation rate
EPI	expanded programme on immunization
GMP	Global Malaria Programme
GRADE	grading of recommendations assessment, development and evaluation
IRM	insecticide resistance management
IRS	indoor residual spraying
ISO	International Organization for Standardization
ITN	insecticide-treated net
ITPS	insecticide-treated plastic sheeting
IVM	integrated vector management
LLIN	long-lasting insecticidal net
LSM	larval source management
MPAC	Malaria Policy Advisory Committee
PBO	piperonyl butoxide
PICO	population, participants or patients; intervention or indicator; comparator or control; outcome
PQ	prequalification (WHO)
RCT	randomized controlled trial
VCAG	Vector Control Advisory Group
VCTEG	Technical Expert Group on Malaria Vector Control
WHO	World Health Organization

Executive summary

Vector control is a vital component of malaria prevention, control and elimination strategies because it can be highly effective in providing personal protection and/or reducing disease transmission. This 1st edition of the World Health Organization (WHO) *Guidelines for malaria vector control* has been prepared in accordance with the latest WHO standard methods for guideline development. It is a consolidated document that incorporates: i) new recommendations based on systematic reviews of the available evidence on the effectiveness of most, but not yet all, vector control interventions; and ii) existing recommendations developed previously based on expert opinion. Reviews on other interventions are ongoing, and the findings will be added to later editions of the *Guidelines*. The primary aim of consolidating the available evidence and recommendations was to condense the large, yet fragmented volume of available guidance into an up-to-date and coherent resource for national malaria programmes and their implementing partners. In cases where readers observe inconsistencies with earlier WHO publications, the *Guidelines* should be considered to supersede prior guidance.

The *Guidelines* cover core interventions, supplementary interventions, personal protection measures and other interventions. Core interventions for malaria vector control are applicable for all populations at risk of malaria in most epidemiological and ecological settings, namely: i) deployment of insecticide-treated nets (ITNs) that are prequalified by WHO, which in many settings are long-lasting insecticidal nets (LLINs); and ii) indoor residual spraying (IRS) with a product prequalified by WHO. Once high coverage with one core intervention has been achieved, supplementary interventions – namely the deployment of chemical or biological larvicides – can be used in addition to the core interventions in specific settings and circumstances.

The evidence base for larval source management through habitat modification and habitat manipulation was not considered in the preparation of this edition of the *Guidelines*, but will be covered in a future edition once available evidence has been systematically reviewed. For biological control with larvivorous fish, the evidence base was found to be insufficient to support a recommendation for use as an intervention with public health impact.

Personal protection measures considered in development of the *Guidelines* were topical repellents, insecticide-treated clothing and indoor spatial/airborne repellents. The evidence base for these interventions was deemed insufficient to support their recommendation for use as interventions with public health value. However, due to the likely protection of users from mosquito bites and, in turn, malaria infection, the use of topical repellents and insecticide-treated clothing are considered to be public health interventions. WHO is investigating a process and associated evaluation endpoints to develop evidence-based policy recommendations on these and other public health interventions designed to provide personal protection.

Space spraying (i.e. insecticide applied through: thermal fogging; cold aerosol distribution by handheld or backpack sprayers, ground vehicles or aerial means; or repetitious spraying by two or more sprays in quick succession) should not be undertaken for malaria vector control. The evidence base for housing improvement as an approach for malaria prevention and control is currently under review, and recommendations in this area will be included in an update to the *Guidelines*.

Recommendations

Malaria vector control

MALARIA BURDEN REDUCTION AND ELIMINATION

Priority should be given to delivering 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 intervention.

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

Universal coverage with effective vector control using a core intervention (ITNs or IRS) is recommended for all populations at risk of malaria in most epidemiological and ecological settings. The population at risk of malaria may increase or decrease as a result of changes in malariogenic potential of a given geographical area.

Good practice statement [1]

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

Good practice statement

Once high coverage with a core intervention has been achieved, recommended supplementary interventions with proven public health value may be deployed in specific settings and circumstances. The decision to

[1] Statements reflecting consensus of the guidelines development group, but not supported by a systematic evidence review.

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

Good practice statement

In areas[2] with ongoing local malaria transmission (irrespective of both the pre-intervention and current level of transmission), vector control interventions should not be scaled back. Universal coverage with effective malaria vector control of all inhabitants of such areas should be pursued and maintained.

Good practice statement

In areas[2] where transmission has been interrupted, the scale-back of vector control should be based on a detailed analysis that includes assessment of the receptivity and vulnerability, active disease surveillance system, and capacity for case management and vector control response.

Good practice statement

Core interventions

INSECTICIDE-TREATED NETS

Pyrethroid-only LLINs prequalified by WHO are recommended for deployment as a core intervention in all malaria-endemic settings.

Strong recommendation as an intervention with public health value, high-certainty evidence

Pyrethroid-PBO nets prequalified by WHO are conditionally recommended for deployment instead of pyrethroid-only LLINs where the principal malaria vector(s) exhibit pyrethroid resistance that is: a) confirmed, b) of intermediate level,[3] and c) conferred (at least in part) by a monooxygenase-based resistance mechanism, as determined by standard procedures.

Conditional recommendation as an intervention with public health value, moderate-certainty evidence

[2] The minimum size of an area is determined by the availability of reliable disaggregated disease surveillance data and feasibility for making decisions on vector control implementation. The area is not necessarily based on administrative boundaries.

[3] Defined as 10–80% mosquito mortality in standard WHO susceptibility tests or CDC bottle bioassays

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

Good practice statement

Recipients of ITNs 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

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

Good practice statement

Old ITNs should only be collected where there is assurance that: i) communities are not left uncovered, i.e. new ITNs are distributed to replace old ones; and ii) there is a suitable and sustainable plan in place for safe disposal of the collected material.

Good practice statement

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

Good practice statement

INDOOR RESIDUAL SPRAYING

IRS deploying a product prequalified by WHO is recommended as a core intervention in all malaria-endemic settings. DDT has not been prequalified; it may be used for IRS if no equally effective and efficient alternative is available, and if it is used in line with the Stockholm Convention on Persistent Organic Pollutants.

Strong recommendation as an intervention with public health value, low-certainty evidence

Supplementary interventions

LARVICIDING

The regular application of biological or chemical insecticides to water bodies (larviciding) is recommended as a supplementary intervention in areas where high coverage with a core intervention has been achieved, where aquatic habitats of the principal malaria vector(s) are few, fixed and findable, and where its application is both feasible and cost-effective.

Conditional recommendation as an intervention with public health value, low-certainty evidence

Personal protection measures

TOPICAL REPELLENTS

Deployment of topical repellents is not recommended as an intervention with public health value; however, topical repellents may be beneficial as an intervention to provide personal protection.

*Conditional recommendation **against** deployment as an intervention with public health value, low-certainty evidence*

INSECTICIDE-TREATED CLOTHING

Use of insecticide-treated clothing is not recommended as an intervention with public health value; however, insecticide-treated clothing may be beneficial as an intervention to provide personal protection in specific population groups.

*Conditional recommendation **against** deployment as an intervention with public health value, low-certainty evidence*

Other interventions

SPACE SPRAYING

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

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

1. Introduction

1.1 BACKGROUND

Malaria remains an important cause of illness and death in children and adults throughout the world, with 87 countries reporting one or more cases of malaria in 2017. Malaria control requires an integrated approach, including prevention (with an emphasis on vector control, plus chemoprevention), early diagnosis and prompt effective treatment. The WHO *Guidelines for the treatment of malaria* were first developed in 2006 and have been revised periodically, with the most recent edition published in 2015. To date there has been no equivalent comprehensive guidelines 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 in this 1st edition of the *Guidelines for malaria vector control* are based on a firm evidence base for certain interventions, whereas for other interventions, major information gaps necessitated formulation of guidance based on expert opinion. The *Guidelines* will therefore remain under regular review; updates are envisioned on an ongoing basis as new evidence becomes available.

The recommendations and their rationale presented in the main body of this document are brief so as to facilitate quick reference. More detail on the underlying evidence base is provided in a series of annexes.

1.2 OBJECTIVES

The objectives of the *Guidelines* are:

1. to provide evidence-based recommendations on the appropriate choice(s) of vector control options for malaria prevention and control;
2. to inform and guide technical decisions on the effective implementation of each of the vector control options currently available for malaria prevention and control;

3. to support the development by WHO Member States of evidence-based national malaria vector control policies and strategies;
4. to facilitate uptake of WHO guidance by bringing together a large number of existing guidance documents on malaria vector control into one document; and
5. to inform a research agenda to support revision of the *Guidelines* by identifying gaps in evidence that are constraining the development of guidance or weakening current recommendations.

1.3 SCOPE

The *Guidelines* provide evidence-based recommendations pertaining to vector control tools, technologies and approaches (collectively termed "interventions") that are currently available for malaria prevention and control, and for which sufficient evidence on their efficacy is available to support systematic reviews. For areas where evidence is currently weak or absent, the development of guidance relies on expert opinion to a considerable extent. The vector control recommendations presented in the *Guidelines* are based on a consideration of the evidence gained from randomized controlled trials (RCTs) and other types of trials and studies, as well as the technical knowledge and experience of the Guidelines Development Group, Guidelines Steering Group and External Review Group (the latter of which was comprised of members of the Malaria Policy Advisory Committee (MPAC)) **(Annex 1)**.

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.

1.4 OUTCOMES

The *Guidelines* commence by providing general recommendations on malaria vector control, followed by more specific recommendations on individual interventions and good practice statements on their deployment. The interventions are divided into categories of core, supplementary, personal protection, and other interventions. Core interventions are those that have demonstrated public health value and are broadly applicable for populations at risk of malaria in most epidemiological and ecological settings. Supplementary interventions are those that are applicable for specific populations, situations or settings and hence are not broadly applicable. Personal protection measures have the primary function of

protecting individual users, although they may have some as yet unproven public health value. Other interventions with potential public health value are also presented. For some interventions, the evidence base is currently under review. The outcome of these revisions will inform the formulation of revised or new recommendations, to be incorporated into the *Guidelines*.

1.5 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 in malaria-endemic countries. The *Guidelines* are also intended for use 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. They are also intended to guide researchers and those interested in the outcomes of research to address the evidence gaps that are constraining the development of guidance or weakening current recommendations.

1.6 FUNDING

The *Guidelines*, developed by the WHO Global Malaria Programme, were funded through an 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.

1.7 MANAGEMENT OF CONFLICTS OF INTEREST

All members of the Guidelines Development Group and the Expert Review Group made declarations of interest, which were managed in accordance with standard WHO procedures and cleared by the Office of Compliance, Risk Management and Ethics. The WHO Guidelines Steering Group and the Chair of the Guidelines Development Group were satisfied that there had been a transparent declaration of interests. No case necessitated the exclusion of any Guidelines Development Group or Expert Review Group members. 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 Guidelines Development Group, the Guidelines Steering Group and the External Review Group, as well as a summary of the declarations of interest are listed in **Annex 1**.

1.8 METHODS USED TO FORMULATE RECOMMENDATIONS

The *Guidelines* were prepared in accordance with latest standard WHO methods for guideline development *(3)*. Types of outcome measures assessed in the evidence reviews included: rate of all-cause child mortality; incidence rate of malaria; incidence rate of severe malaria episodes; rate of clinical malaria; rate of uncomplicated episodes of *P. falciparum*; malaria incidence; parasite prevalence (also specifically *P. falciparum* and *P. vivax* prevalence); anaemia prevalence; entomological inoculation rate (EIR); density of immature vector stages; and, number of larval sites positive for immature vector stages.

The WHO guideline development process involves planning; conducting a 'scoping' and needs assessment; establishing an internal WHO Guidelines Steering Group and an external Guidelines Development Group; formulating key questions in PICO format; commissioning evidence reviews; applying Grading of Recommendations Assessment, Development and Evaluation (GRADE) to the certainty of evidence; and making recommendations. This methodology (see **Annex 2**) ensures that the link between the evidence base and the recommendations is transparent.

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

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

- providing inputs as to the scope of the *Guidelines*;
- assisting the Guidelines 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 certainty of 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 document prior to submission to the Guidelines Review Committee.

The Guidelines Development Group established for these *Guidelines* consisted of 13 members that included: relevant technical experts; intended end-users (programme managers and health professionals responsible for adopting, adapting and implementing the *Guidelines*); other representatives from malaria-endemic countries; and experts in assessing evidence and developing evidence-based guidelines. The Chair of the Guidelines Development Group and several of its members had expertise in ensuring that equity, human rights, gender and social determinants are taken into consideration in efforts to improve public health outcomes.

The Guidelines 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 criteria to arrive at a recommendation for or against an intervention; these are listed in **Annex 3** along with accompanying descriptions.

The Evidence-to-Decision Framework summaries for each of the recommendations contained in the *Guidelines* are presented alongside the GRADE tables in **Annex 4**. Selected external reviewers, consisting of persons interested in the subject of the *Guidelines* and individuals who would be affected by the recommendations, conducted a peer review of the draft *Guidelines* document to inform revisions prior to its submission to the Guidelines Review Committee for approval.

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 of Northern Ireland and Great Britain was commissioned to undertake systematic reviews and assess the certainty of evidence for each priority question. This included new systematic reviews on the combined deployment of IRS with ITNs; and space spraying. Existing

systematic reviews covering larviciding, the deployment 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.

Each search was independently assessed by two review authors. Included studies were described, assessed, and data presented as specified in the protocol using *Covidence* and *Review Manager 5* software. GRADE formulation and application of subgroup analysis was carried out by the review author teams, with oversight from the CIDG editorial team, including the Co-ordinating Editor, three Editors, and the SIDG Statistician.

In formulating its recommendations, the Guidelines Development Group also considered additional evidence that was deemed unsuitable for inclusion and analysis under the Cochrane systematic review process, particularly in developing the Evidence-to-Decision Frameworks (**Annex 4**). IRS is a core intervention for malaria prevention and control that has been used successfully in malaria-endemic countries for decades, but is an intervention for which few RCTs have been conducted. Therefore, the availability of data suitable for use in a Cochrane-style meta-analysis is limited. A separate systematic review of the large body of evidence generated from the IRS implementation trials and from national control programmes will be conducted to further strengthen the evidence base to support recommendations pertaining to this core intervention.

Pre-existing WHO recommendations and guidance relevant to malaria, and specifically to vector control, were also reviewed and in some cases revised by the Guidelines Development Group.

Certainty of evidence

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

TABLE 1
The four classes of certainty of evidence used in GRADE

CERTAINTY OF EVIDENCE	INTERPRETATION
High	The Group is very confident in the estimate of effect and considers that further research is very unlikely to change this confidence.
Moderate	The Group has moderate confidence in the estimate of effect and considers that further research is likely to have an important impact on that confidence and may change the estimate.
Low	The Group has low confidence in the estimate of effect and considers 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.

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 shown in boxes in each respective section (light green); an evidence box (light grey) is also presented for each recommendation. The complete GRADE tables and additional references are provided in **Annex 4**.

Formulation of recommendations

The systematic reviews, GRADE tables and other relevant materials were provided to all members of the Guidelines Development Group. Recommendations were formulated after considering the certainty of evidence, the balance of benefits and harms, values and preferences, and the feasibility of the intervention (**Table 2**). Values and preferences were taken into account through discussions on the relative value beneficiaries place on the outcomes of the intervention, and on the relative acceptability

of the intervention to the beneficiaries. Although cost is a critical factor in setting national vector control policies and was broadly considered in the recommendation formulation process, explicit analyses of the costs and cost-effectiveness of the various interventions did not form part of the Cochrane reviews conducted for this 1st edition of the *Guidelines*. Expanded evidence-based recommendations on resource implications will be developed and incorporated into a revised version of the *Guidelines*.

The Guidelines Development Group discussed the proposed wording of each recommendation at in-person meetings and through e-mail correspondence and teleconferencing, and rated the strength of each recommendation in accordance with the four-point scale presented in **Table 1**. The guideline development process aimed to generate group consensus; voting on specific points was available as an option to finalize recommendations on which no consensus could be reached. The final draft was circulated to the Guidelines Development Group and the External Review Group (**Annex 1**). Comments from external reviewers were incorporated into the revised *Guidelines* as appropriate.

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

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

Types of guidance

Two types of guidance are presented in the *Guidelines*.

- *Intervention recommendations*: These recommendations were formulated by the panel using the GRADE approach, supported by systematic reviews of the evidence, with formal assessment of the certainty of evidence.

- *Good practice statements*: These statements reflect a consensus among the panel that the net benefits of adherence to the statement are large and unequivocal, and that the implications of the statement are common sense. These statements have usually been taken or adapted from existing recommendations or guidance initially developed through broad consultation, such as through the WHO Technical Expert Group on Malaria Vector Control (VCTEG) or MPAC. These statements are made to reinforce the basic principles of good management practice for implementation.

Strength of recommendations

Each intervention recommendation was classified as strong or conditional using 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.

1.9 DISSEMINATION

The *Guidelines* will be published electronically in PDF format on the WHO website. Using electronic rather than hardcopy versions is a less expensive and faster way to provide up-to-date guidance to Member States and their implementing partners. The English language version will be made available first, with French and Spanish translations to follow soon after. 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 webinars and through regional, subregional and country meetings, as appropriate. Member States will be supported by WHO in the development and update of national strategies based on these *Guidelines*.

1.10 UPDATING

Updates to the *Guidelines* will be undertaken as soon as possible once new evidence for interventions with an existing policy recommendation becomes available, or as the Vector Control Advisory Group (VCAG) assesses new vector control tools, technologies or approaches, their public health value is validated and a WHO policy recommendation supporting their deployment has been formulated *(4)*. Periodic monitoring and evaluation of the use of the *Guidelines* by Member States will be conducted by means of malaria programme reviews and other technical support missions.

1.11 USER FEEDBACK

User feedback on the 1st edition of the *Guidelines* will be collected as part of all dissemination activities both informally and by directing users to the generic WHO GMP email address: vcguidelines@who.int. In addition, an online survey will be conducted to capture user experiences prior to major revisions to the *Guidelines.*

2. Malaria and related entomological and vector control concepts

2.1 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*) most commonly infect humans. *P. falciparum* and *P. vivax* are the most prevalent species and *P. falciparum* is the most dangerous. A fifth species, *P. knowlesi* (a species of *Plasmodium* that primarily infects non-human primates) is increasingly being reported in humans inhabiting forested regions of some countries of South-East Asia and the Western Pacific regions, and in particular on the island of Borneo.

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

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 interventions. Under conditions of 'stable malaria transmission', where populations are continuously exposed to a high frequency of malarial

inoculation,[4] partial immunity to clinical disease is acquired in early childhood which results in a reduced risk of developing severe malaria in older children. 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 in these endemic settings, although they may continue to have low densities of parasites in their blood and are capable of infecting mosquitoes. 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 both infection and severity of infection. 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 generally low level of transmission retards the acquisition of immunity such 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 EIR 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 of severe malaria if their infection is not detected promptly and treated effectively.

2.2 VECTORS AND THEIR BEHAVIOUR AND DISTRIBUTION

Malaria is transmitted through the bites of infective female *Anopheles* mosquitoes. There are more than 400 different species of *Anopheles* mosquito, of which around 40 are malaria vectors of major importance. **Annex 5** presents a list of principal vector species by WHO region, along with a brief description of the key ecological and behavioural characteristics relevant to control.

[4] Generally defined as an entomological inoculation rate (EIR) that exceeds 10 infective bites per person per year.

Anopheles mosquitoes lay their eggs in water. The eggs hatch to produce larvae, which undergo several moults before emerging from the pupal stage as adult mosquitoes. Different species of *Anopheles* mosquito have their own preferred aquatic habitats; for example, some prefer small, shallow collections of fresh water such as puddles and animal hoof prints, whereas others prefer large, open water bodies including lakes, swamps and rice fields.

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

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

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

It is important to note that while an individual species of *Anopheles* will characteristically exhibit certain biting and resting behaviours, these are not absolute; subpopulations and individuals may exhibit different behaviours depending on a combination of intrinsic genetic factors, availability of preferred hosts and availability of suitable resting sites. Environmental and climatic factors, including rainfall, moonlight, wind speed, etc., as well

as the deployment of vector control interventions can all influence biting and resting behaviours. For example, the highly efficient African malaria vector *Anopheles gambiae* s.s. is generally considered to be human-biting, indoor-biting and indoor-resting, but it can also exhibit more zoophilic and exophagic tendencies. *Anopheles arabiensis* is a species that generally exhibits an outdoor biting and resting habit, but may exhibit indoor biting and resting tendencies, depending on the availability of alternative hosts.

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

2.3 BACKGROUND AND RATIONALE FOR VECTOR CONTROL

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

Nowadays, it is well established that effective vector control programmes can make a major contribution towards advancing human and economic development. Aside from direct health benefits, reductions in vector-borne diseases enable greater productivity and growth, reduce household poverty, increase equity and women's empowerment, and strengthen health systems *(6)*. Despite the clear evidence in broad support of vector control efforts, the major vector-borne diseases combined still account for around 17% of the estimated global burden of communicable diseases, claiming more than 700 000 lives every year *(7)*. Recognizing the great potential to enhance efforts in this area, WHO led the development of the *Global vector control response 2017–2030*, which is outlined in the subsequent section.

The control of malaria, unlike that of most other vector-borne diseases, has seen a major increase in financial resources since 2000, leading to a significant reduction in the global burden. Between 2000 and 2015, the infection prevalence of *P. falciparum* in endemic Africa was halved and the incidence of clinical disease fell by 40% *(8)*. Malaria control interventions averted an estimated 663 (credible interval (CI) 542–753) million clinical cases in Africa, with ITNs making the largest contribution (68% of cases averted). IRS contributed an estimated 13% (11–16%), with a larger proportional contribution where intervention coverage was high *(7)*.

Global vector control response 2017–2030

In 2017, the World Health Assembly welcomed the *Global vector control response 2017–2030 (6)* and adopted a resolution to promote an integrated approach to the control of vector-borne diseases. The approach builds on the concept of integrated vector management (IVM),[5] 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 in full alignment with Sustainable Development Goal 3.3. The 2030 targets are: to reduce mortality due to vector-borne diseases globally by at least 75% (relative to 2016); to reduce case incidence due to vector-borne diseases globally by at least 60% (relative to 2016); and to prevent epidemics of vector-borne diseases in all countries. Detailed national and regional priority activities and associated interim targets for 2017–2022 have also been defined.

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) innovation for the development of new tools, technologies and approaches and increased basic and applied research to underpin optimized 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.

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

Effective and sustainable vector control is achievable only with sufficient human resources, an enabling infrastructure and a functional health system. Countries should conduct a vector control needs assessment *(9)* 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) that are aligned with IVM: i) strengthening inter- and intra-sectoral action and collaboration; ii) engaging and mobilizing communities; iii) enhancing vector surveillance and monitoring and evaluation of interventions; and iv) scaling up and integrating tools and approaches.

In some settings, vector control interventions can reduce transmission and disease burden of more than one disease. Examples include 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 possibly yellow fever where their vectors and distributions overlap. However, programmes should avoid an approach that overlays multiple interventions to compensate for deficiencies in implementation of any one intervention; this may divert resources and attention away from reaching the full impact of existing interventions and lead to resource wastage.

The decision to use a vector control intervention in a particular setting or situation should be based on clear evidence of its epidemiological efficacy. Implementation must be to a high standard and aim to achieve and maintain universal coverage of at-risk populations. Covering at-risk populations with evidence-based and cost-effective vector control interventions offers the greatest immediate opportunity to reduce infections and disease.

3. Recommendations on malaria vector control

UNIVERSAL COVERAGE

Universal coverage with effective vector control using a core intervention (ITNs or IRS) is recommended for all populations at risk of malaria in most epidemiological and ecological settings. The population at risk of malaria may increase or decrease as a result of changes in malariogenic potential.

Good practice statement

Universal health coverage means that all individuals and communities receive the health services they need without suffering financial hardship. It includes the full spectrum of essential, quality health services, from health promotion to prevention, treatment, rehabilitation and palliative care. In the context of malaria, universal coverage is defined as access to and use of appropriate interventions by the entire population at risk of malaria. The *Global Technical Strategy for Malaria 2016–2030* states that it is essential for malaria programmes to "ensure universal access to malaria prevention, diagnosis and treatment" (Pillar 1). This strategy includes effective vector control as a major component, with a significant budgetary allocation.

The core vector control interventions applicable for all populations at risk of malaria in most epidemiological and ecological settings are: i) deployment of ITNs that are prequalified by WHO, which in many settings are LLINs; and ii) IRS with a product prequalified by WHO. The exception to this is DDT, which has not been prequalified. This insecticide may be used for IRS if no equally effective and efficient alternative is available, and if it is used in line with the Stockholm Convention on Persistent Organic Pollutants. Since 2000, 78% of the malaria clinical cases averted through interventions have been due to insecticidal vector control, namely through the widespread scale-up of ITNs and IRS. Universal coverage of vector control interventions is generally considered best practice to obtain optimal impact.

BOX 1.
Summary of evidence from Cochrane systematic review

IRS compared to ITNs:

Two RCTs were included in the systematic review. Studies were conducted in an area with intense transmission (United Republic of Tanzania) and an area with unstable transmission (India).

- IRS may lead to a greater reduction in malaria incidence than ITNs in areas of intense transmission.
  (Rate Ratio: 0.88; 95% CI (0.78–0.98); one study; low certainty evidence)
- There may be little or no difference in parasite prevalence between IRS and ITNs in areas of intense transmission.
  (Odds Ratio: 1.06; 95% CI (0.91–1.22); one study; low certainty evidence)
- IRS may reduce malaria incidence to a lesser extent than ITNs in areas of unstable transmission.
  (Rate Ratio: 1.48; 95% CI (1.37–1.60); one study; low certainty evidence)
- There may be little or no difference in parasite prevalence between IRS and ITNs in areas of unstable transmission.
  (Odds Ratio: 1.70; 95% CI (1.18–2.44); one study; low certainty evidence)

In terms of the relative effectiveness of IRS compared to ITNs, there was only low certainty evidence available for areas of intense transmission and for areas with unstable transmission. It was therefore not possible to arrive at a definite conclusion on their comparative effectiveness. WHO therefore currently views these two core interventions as of equal effectiveness and there is no general recommendation to guide selection of one over the other. Preferences of national malaria programmes, beneficiaries or donors are usually based on operational factors, such perceived or actual implementation challenges (see **Section 9**) and the requirement for insecticide resistance prevention, mitigation and management (see **Section 3.1**). Financial considerations such as cost and cost-effectiveness are also major drivers of decision-making, and selection of malaria vector control interventions should thus be embedded into a prioritization process that considers the cost and effectiveness all available malaria interventions and aims at achieving maximum impact with the available resources. Evaluations of the relative cost and cost-effectiveness of ITNs and IRS are ongoing to inform revision of the *Guidelines*.

CORE INTERVENTIONS

Priority should be given to delivering 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 intervention.

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

BOX 2.
Summary of evidence from Cochrane systematic review

IRS in addition to ITNs:

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

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

A review conducted in 2014 on the deployment of IRS in combination with ITNs (specifically pyrethroid-only LLINs) provided evidence that, in settings where there is high coverage with ITNs and where these remain effective, IRS may have limited utility in reducing malaria morbidity and mortality. WHO guidance was developed accordingly to emphasize the need for good-quality implementation of either ITNs or IRS, rather than deploying both in the same area *(10)*. However, the combination of these interventions

may be considered for resistance prevention, mitigation or management should sufficient resources be available (see the following text and **Section 3.1**). Given the resource constraints across malaria endemic countries, the deployment of a second core vector control intervention on top of high coverage with an existing core vector control intervention should only be considered as part of a broader prioritization analysis aimed at achieving maximum impact with the available resources. In many settings, a switch from one to the other core intervention, rather than their combination, is likely to be the only financially feasible option

COMBINATION OF INSECTICIDE-TREATED NETS AND INDOOR RESIDUAL SPRAYING

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

Good practice statement

Insecticide resistance threatens the effectiveness of insecticidal interventions and hence is a key consideration in determining which vector control interventions to select to ensure impact of is maximised. One approach to the prevention, mitigation and management of vector insecticide resistance is the co-deployment (or combination) of interventions with different insecticides (see **Section 3.1**). Therefore, WHO guidance developed based on the 2014 review differentiated between the effect of combined interventions on malaria morbidity and mortality versus the utility of this approach in a resistance management strategy *(9)*. A summary of the conclusions (with slight updates for clarity) used to develop the above recommendations is as follows:

1. In settings with high ITN coverage where these remain effective, IRS may have limited utility in reducing malaria morbidity and mortality. However, IRS may be implemented as part of an insecticide resistance management (IRM) strategy in areas where there are ITNs *(11)*.
2. If ITNs and IRS are to be deployed together in the same geographical location, IRS should be conducted with a non-pyrethroid insecticide.

3. Malaria control and elimination programmes should prioritize the delivery of 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 intervention.

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

5. All programmes in any transmission setting that decide to prioritize the combined deployment of ITNs and IRS over other potential use of their financial resources should include a rigorous programme of monitoring and evaluation (e.g. a stepped wedge introduction of the combination) in order to confirm whether the additional inputs are having the desired impact. Countries that are already using both interventions should similarly undertake an evaluation of the effectiveness of the combination versus either ITNs or IRS alone.

These findings and conclusions were substantiated by a systematic review of the evidence (currently under peer review) that was conducted in preparing the *Guidelines (12)*. However, subsequently released results from a study in one setting in Sudan showed that pyrethroid-only ITNs plus IRS with a non-pyrethroid reduced malaria incidence to a greater extent than ITNs alone in an area with pyrethroid resistance *(13)*. An update to the systematic review will be required as additional evidence is currently being generated.

Moreover, the approach of combining interventions for resistance management was developed largely based on experience with agricultural pest management, and the evidence base from public health remains weak.

3.1 PREVENTION, MITIGATION AND MANAGEMENT OF INSECTICIDE RESISTANCE

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

The development of resistance in malaria vectors has so far been moderate overall. Monitoring insecticide resistance in malaria vectors

has revealed that, between 2010 and 2016, the frequency of pyrethroid resistance increased significantly in *An. funestus s.l.* (32% increase in resistance frequency), moderately in *An. gambiae s.l.* (13% increase) and only slightly in other malaria vectors (5% increase) *(14)*. Between 2010 and 2017, 68 of the 87 countries reporting one or more malaria cases in 2017 have reported resistance to at least one insecticide, and 57 of those countries have reported resistance to two or more classes of insecticide. WHO maintains a global insecticide resistance database and an online mapping tool that consolidate information on the status of the insecticide susceptibility of *Anopheles* mosquitoes in malaria-endemic countries *(15)*.

To date, there is no evidence of operational failure of vector control programmes as a direct result of increasing frequency of pyrethroid resistance pyrethroid resistance *(13, 16)*. Based on past experience, however, it is likely that operational failure will eventually occur if effective IRM strategies are not designed and implemented. Ideally, such strategies should be implemented before resistance arises. The overarching concepts of such resistance management strategies were outlined in the *Global plan for insecticide resistance management in malaria vectors* (GPIRM) in 2012 *(10)*.

The GPIRM defines key technical principles for addressing insecticide resistance, as follows:

- Insecticides should be deployed 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 over consecutive years; 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 ITNs in the near term, they should not generally be deployed for IRS in areas with ITNs.
- IRM principles and methods should be incorporated into all vector control programmes, not as an option, but as a core component of programme design.
- The agricultural sector should try to avoid using classes of insecticide that are widely used for public health and should collaborate with vector control authorities in an intersectoral approach.

- Routine monitoring of insecticide resistance is essential to 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.

The subsequent section of the *Guidelines* builds on the original GPIRM recommendations in order to provide more detailed guidance on potential IRM approaches currently available to countries, as guided by resistance monitoring data (see **Figure 1**).

Approaches

Historically, the most common way insecticides have been deployed to control malaria vectors has been through 'sequential use'.[6] In essence, this is when a single insecticide class is used continuously or repeatedly until resistance has rendered it less effective or ineffective, after which a switch is made to an insecticide with a different mode of action to which there is no (or less) resistance. In theory, this may allow for an eventual switch back to the original insecticide class if resistance decreases to the point that it is no longer detectable by means of bioassays. Practical examples of such reversion are rare and tend to be short-lived when they do occur. This practice of sequential use, however, is not considered good practice for malaria vector control as it counters the proactive resistance management approach outlined in the GPIRM. Options to implement such a proactive IRM strategy are limited.

All WHO prequalified ITNs contain a pyrethroid insecticide, either alone or combined with the synergist PBO, while one net contains a pyrethroid and a pyrrole *(1)*.[7] IRS formulations are prequalified from four out of five insecticide classes currently covered by a WHO policy recommendation. As of February 2019, no DDT product has been prequalified and none is under assessment.

Based on experience in agriculture, resistance management approaches have been proposed with the aim of preventing or delaying the emergence of resistance by removing selection pressure or by killing resistant

[6] This is likely due to: i) the limited number of insecticide classes historically available for malaria vector control, especially for ITNs; ii) the limited evidence base available to demonstrate impact of resistance and clear outcomes from resistance management approaches; and c) insufficient consideration given to the need to prevent or slow the development of resistance in order to preserve the effectiveness of available interventions.

[7] A pyrrole is a broad-spectrum insecticide that acts on the insect's stomach and through contact.

mosquitoes. These include mixtures of insecticides, mosaic spraying, rotations of insecticides and deployment of multiple interventions in combination.

- *Mixtures* are formulations that combine two or more insecticides with different modes of action. Mixtures are widely used as drug treatments in co-formulated combination therapy. Effective deployment of a mixture requires that the presence of resistance to all insecticides in the mixture is rare, so that any individual that survives exposure to one insecticide is highly likely to be killed by the other insecticide or insecticides. Ideally, all insecticides in a mixture should have a similar residual life and remain bioavailable over time; in practice, this is difficult to achieve, particularly for vector control products that are meant to last for a number of years, such as LLINs. An ITN product containing a pyrethroid and a pyrrole insecticide received a WHO interim recommendation after having been evaluated under the former WHOPES in phase I and II trials as a pyrethroid-only net *(17)*; WHO will require data on the epidemiological impact of this product in order to enable assessment of its public health value and develop a WHO policy recommendation. ITNs with a pyrethroid and a juvenile hormone mimic[8] have been developed, and one product is under WHO evaluation. A mixture of a pyrethroid and a neonicotinoid insecticide for IRS was recently prequalified by WHO.
- *Rotations* involve switching between insecticides with different modes of action at pre-set time intervals, irrespective of resistance frequencies. The theory is that resistance frequencies will decline (or at least not increase) during the period of non-deployment of insecticides with a specific mode of action.
- *Mosaics* involve the deployment of insecticides of different modes of action in neighbouring geographical areas. The optimal spatial scale (size of areas) for mosaics has yet to be determined, and rotations are generally considered to be more practical and feasible.
- *Combinations* expose the vector population to two classes of insecticides with differing modes of action through the co-deployment of different interventions in the same place. For instance, pyrethroid-only LLINs combined with a non-pyrethroid IRS (where both are at high coverage) is a potential approach to IRM, although there is little evidence to indicate that such a combination of interventions will lead to additional epidemiological impact relative to one intervention deployed at high coverage (see above).

[8] A juvenile hormone mimic can inhibit development of adult characteristics or can interrupt reproductive maturation in adult insects.

For public health vector control, there is still little evidence and no consensus on the best IRM approach or approaches to apply in a given situation. A 2013 review of experimental and modelling studies on insecticide, pesticide and drug resistance concluded that mixtures generally lead to the slowest evolution of resistance *(18)*. However, more recently, an exploration of overlaps between agriculture and public health found that – owing to caveats and case specificity – there is only weak evidence of one IRM approach being better than another and that the standard practice of using insecticides until resistance emerges before switching to an alternative (i.e. sequential use) may be equally effective under certain circumstances. More research is thus needed to compare resistance management approaches in the field *(19)*, and to improve understanding of the biological mechanisms that are likely to favour different approaches in different situations *(20, 21)*.

Evidence-based planning

Given the heavy reliance on insecticidal interventions – primarily ITNs and IRS – insecticide resistance of local vectors is a key consideration in vector control planning and implementation. Ideally, IRM practices should be implemented as part of routine operations prior to the emergence of resistance, rather than waiting for resistance to develop and for control failure to be suspected or confirmed. However, pyrethroid resistance is common and widespread in major malaria vectors and resistance to the three other main insecticide classes used in malaria vector control has been detected across most regions of the world *(13)*. A pragmatic approach must be taken that seeks to select appropriate vector control interventions based on the insecticide resistance profile of the major malaria vectors in the target area. To outline how resistance will be monitored and managed, countries should develop and implement national plans in accordance with the WHO *Framework for a national plan for monitoring and management of insecticide resistance in malaria vectors (22)*. These plans should be revisited regularly to consider new information and to integrate new tools, technologies and approaches, once these are supported by WHO policy recommendations and have been prequalified.

To assist countries in the selection of ITN or IRS product classes, **Tables 4** and **5** indicate whether the different product classes with a current WHO recommendation are considered optimal, acceptable or not recommended based on the resistance status (frequency), intensity and mechanisms of local vectors *(23)*. One major caveat is that vector control interventions are seldom selected on the basis of resistance data alone. Such selection should also consider other influential factors specific to the local context, such as appropriateness of the intervention for housing structures, population acceptance or compliance, and available capacity

for deployment. Cost and availability of products can also be major factors affecting resistance management. Implementation of IRM should not come at the expense of reductions in vector control coverage for populations at risk of malaria.

The tables below define the suitability of different product classes based on available resistance information, but do not seek to prescribe the use of individual product classes or specific products. Where the combination of ITNs and IRS is appropriate, the selection of the non-pyrethroid IRS product should be guided by **Table 5**, based on insecticide resistance data. It is envisaged that as the public health value of additional interventions and product classes is validated and policy recommendations are developed, these tables will be updated accordingly through revision of the *Guidelines*. Modifications of methods to assess insecticide resistance[9] may also be considered once the new evidence in this area becomes available.

To inform the decision-making process, resistance monitoring should ideally be conducted at sufficient sites that are representative of the eco-epidemiological setting(s) throughout the area for which intervention(s) are to be deployed. Resistance monitoring data should be collected for all principal malaria vectors at least annually; if data are available for multiple time points, the most recent should to be considered the most relevant. Resistance to each insecticide class being deployed or intended to be deployed should be tested so as to adequately guide selection of interventions and establish a baseline of information for new classes. However, implementation of resistance management or mitigation approaches need not wait until comprehensive data are available from resistance monitoring across the entire target area. Due to limited resources for monitoring (and potentially few mosquitoes for testing), there is likely to be the need to generalize data to larger areas of operational significance.

Examination of spatio-temporal trends in insecticide resistance is currently ongoing to inform the development of further guidance on the optimal frequency and extent of monitoring required to inform vector control decision-making. Further information on insecticide resistance monitoring and more broadly on entomological surveillance is included in the WHO reference manual on malaria surveillance, monitoring and evaluation, which outlines priority data across different transmission settings *(24)*.

[9] Such as cone bioassays with different ITNs using local vector populations as a proxy for comparative bioefficacy

FIGURE 1.

Overview of the process and outcomes for insecticide resistance monitoring in malaria vector mosquitoes. Includes measures of: i) phenotypic resistance frequency via discriminating concentration bioassays, ii) resistance intensity via intensity concentration bioassays, and iii) resistance mechanisms via synergist-insecticide bioassays, molecular and biochemical assays. *Source: excerpt from (22).*

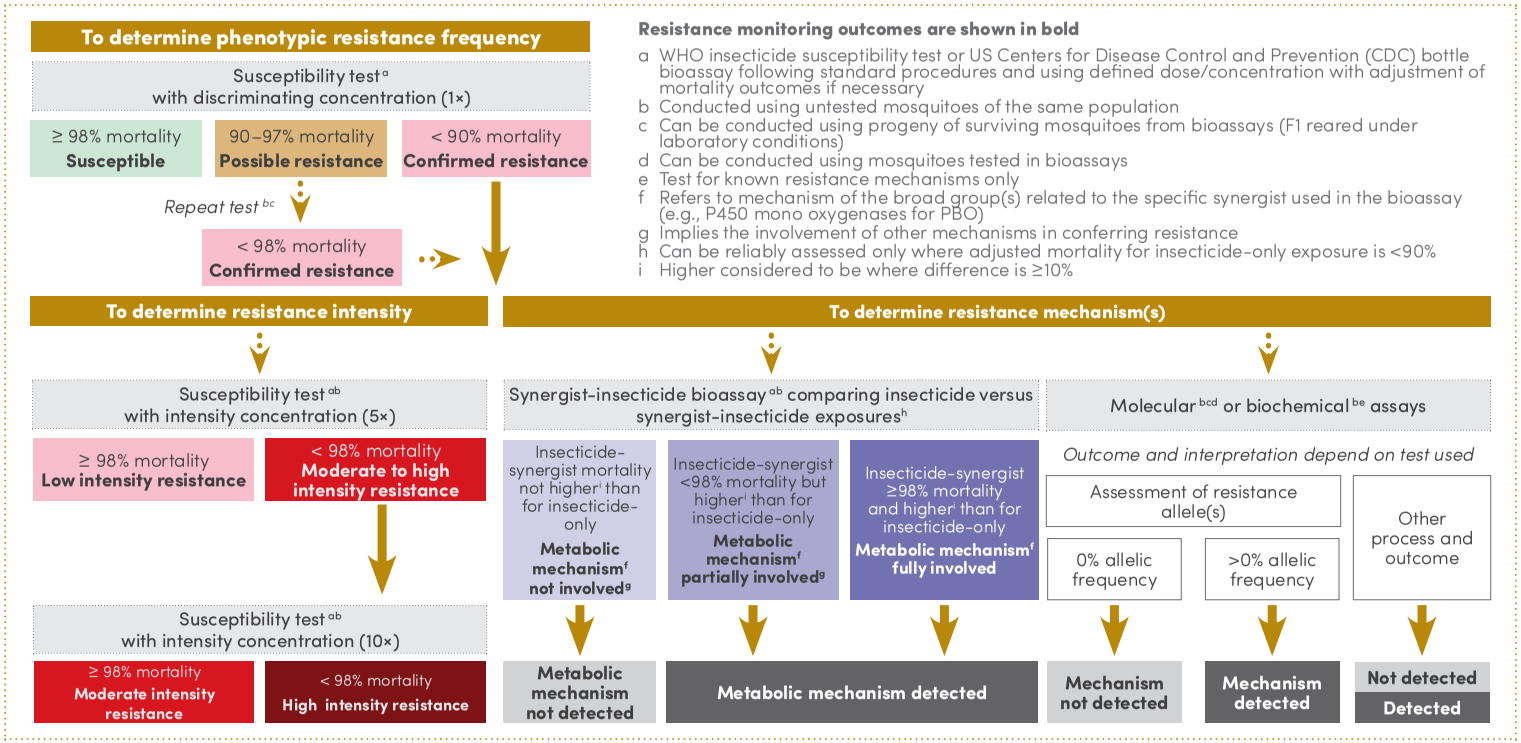

TABLE 4.

Selection of ITN product class based on outcomes from insecticide resistance monitoring in principal malaria vector(s), for areas in which ITNs are the core malaria vector control intervention

Options are indicated as:

optimal (++), acceptable (+), or deployment not supported by data (-).

INTERVENTION	PRODUCT CLASS	PYRETHROID INSECTICIDE(S) RESISTANCE					
		PRIMARY MEASURES		SECONDARY MEASURES			
		Resistance status		Resistance intensity		Resistance mechanism(s)	
		No confirmed resistance[1]	Confirmed resistance[2]	Moderate or low intensity[3]	High intensity[2]	P450s not detected and/or shown to not be involved	P450s detected and/or shown to be fully or partially involved
Resistance outcomes (see Figure 1 and *(22)*)		●	●	●	●	●	●●
ITN	Pyrethroid-only nets	++	+	+	+	+	+
	Pyrethroid plus synergist nets i.e. PBO nets	– [4]	++ [5]	+	+	– [4]	++

Dark grey shading indicates that criteria specified for both resistance status and resistance mechanisms should be fulfilled for this to be considered optimal.

[1] for all major vector species to all pyrethroid insecticides tested

[2] for at least one major vector species to at least one pyrethroid insecticide

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

[4] may be considered acceptable instead of pyrethroid-only nets if this will not compromise coverage (e.g. total cost of the delivered PBO net is equal to or less than that of a pyrethroid-only net)

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

TABLE 5.

Selection of IRS product class based on outcomes from insecticide resistance monitoring in principal malaria vector(s), for areas in which IRS is the core malaria vector control intervention

Options are indicated as:

optimal (++), acceptable (+), or deployment not supported by data (-).

INTERVENTION	PRODUCT CLASS	INSECTICIDE RESISTANCE TO THE CLASS OF INSECTICIDE IN THE IRS PRODUCT					
		PRIMARY MEASURES		SECONDARY MEASURES			
		Resistance status		Resistance intensity		Resistance mechanism(s)	
		No confirmed resistance to insecticide class[1]	Confirmed resistance to insecticide class[2]	Moderate or low intensity resistance[3]	High intensity resistance[2]	Mechanisms known to confer resistance to class not detected	Mechanisms known to confer resistance to class detected
Resistance outcomes (see Figure 1 and *(22)*)							
IRS[7]	Organophosphate, organochlorine[6], carbamate or pyrethroid formulations	++	-	- [4]	-	++	- [5]
	Fast-acting insecticide formulations (with comparable entomological effectiveness to the above product class, i.e. neonicotinoids)	++	-	- [4]	-	++	- [5]

[1] for all major vector species to all insecticides tested of the insecticide class(es) used in the IRS product

[2] for at least one major vector species to at least one insecticide of the insecticide class used in the IRS product

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

[4] may be considered acceptable if there is also confirmed resistance to all other insecticide classes in available IRS products

[5] may be considered acceptable if mechanisms are detected that are known to confer resistance to all other insecticide classes in available IRS products

[6] note that while DDT may have some utility for malaria vector control, as of 18 September 2018, there were no DDT IRS formulations prequalified by WHO

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

3.2 VECTOR CONTROL ACROSS DIFFERENT MALARIA TRANSMISSION SETTINGS

Understanding the degree of risk of malaria transmission in a given geographic area provides the foundation for the design of cost-effective intervention programmes to decrease malaria burden, eliminate transmission and prevent re-establishment of malaria. The risk of malaria transmission is the product of receptivity, vulnerability (i.e. importation risk) and mosquito infectivity, and is referred to as the malariogenic potential. The receptivity of an ecosystem to malaria transmission is determined by the presence of competent vectors, a suitable climate and a susceptible human population. Vulnerability refers to the rate of importation of parasites through the movement of infected individuals or, occasionally, infected anopheline vectors. Infectivity, or vector susceptibility, depends on the compatibility between the anopheline vector and the infecting strain of *Plasmodium*.

National malaria programmes should undertake stratification by malariogenic potential in order to: differentiate receptive from non-receptive areas; identify receptive areas in which malaria transmission has already been curtailed by current interventions; distinguish between areas with widespread transmission and those in which transmission occurs only in discrete foci; and determine geographical variations and population characteristics that are associated with vulnerability *(25)*.

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

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

In areas[10] with ongoing local malaria transmission (irrespective of both the pre-intervention and the current level of transmission), the scale-back of vector control should not be undertaken. Universal coverage with effective malaria vector control of all persons in such areas should be pursued and maintained.

Good practice statement

In areas where transmission has been interrupted, the scale-back of vector control should be based on a detailed analysis that includes assessment of the receptivity and vulnerability, active disease surveillance system, and capacity for case management and vector control response.

Good practice statement

Access to effective vector control interventions will need to be maintained in the majority of countries and locations where malaria control has been effective. This includes settings with ongoing malaria transmission, as well as those in which transmission has been interrupted but in which some level of receptivity and vulnerability remains. Malaria elimination is defined as the interruption of local transmission (reduction to zero incidence of indigenous cases) of a specified malaria parasite species in a defined geographical area as a result of deliberate intervention activities. Following elimination, continued measures to prevent re-establishment of transmission are usually required *(24)*. Interventions are no longer required once eradication has been achieved. Malaria eradication is defined as the permanent reduction to zero of the worldwide incidence of infection caused by all human malaria parasite species as a result of deliberate activities.

A comprehensive review of historical evidence and mathematical simulation modelling undertaken for WHO in 2015 indicated that the scale-back of malaria vector control was associated with a high probability of malaria resurgence, including for most scenarios in areas where malaria transmission was very low or had been interrupted. Both the historical review and the simulation modelling clearly indicated that the risk of resurgence was significantly greater at higher EIRs and case importation rates, and lower coverage of active case detection and case management *(26)*.

[10] The minimum size of an area is determined by the availability of reliable disaggregated disease surveillance data and feasibility for decisions on vector control implementation. The area is not necessarily based on administrative boundaries.

During the pre-elimination and elimination phases, ensuring universal access to vector control for at-risk populations remains a priority, even though the size and specific identity of the at-risk populations may change as malaria transmission is reduced.

As malaria incidence falls and elimination is approached, increasing heterogeneity in transmission will result in foci with ongoing transmission in which vector control should be enhanced. Such foci may be due to particularly intense vectorial capacity, lapsed prevention and treatment services, changes in vectors or parasites that make the current strategies less effective, or reintroduction of malaria parasites by the movement of infected people or, more rarely, infected mosquitoes. Guidance on entomological surveillance across the continuum from control to elimination is provided elsewhere *(23)*.

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

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

Supplementary interventions such as larval source management (LSM) can be used in addition to the core interventions in specific settings and circumstances. Recommendations on larviciding with chemical or biological insecticides are outlined in a subsequent chapter. The VCAG on new tools, technologies and approaches is currently evaluating a number of new interventions that have the potential to address residual transmission (http://www.who.int/vector-control/vcag/). Implementation of supplementary interventions should be in accordance with the principles outlined in the *Global vector control response 2017–2030 (6)*.

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

SUPPLEMENTARY INTERVENTIONS

Once high coverage with a core intervention has been achieved, recommended supplementary interventions with proven public health value may be deployed as a public health intervention in specific settings and circumstances. The decision to deploy a supplementary vector control intervention should only be taken after conducting a prioritization analysis across malaria interventions, not just vector control, to ensure maximum impact of any additional resources.

Good practice statement

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

4. Recommendations on core interventions

4.1 INSECTICIDE-TREATED NETS (ITNS)

WHO recommends ITNs – which in many settings should be LLINs – 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. ITNs can produce a 'community effect' whereby even members of the community who do not sleep under a net gain some protection due to the effect of the treated nets on mosquito longevity (and therefore vectorial capacity). Large-scale field trials *(27, 28)* and transmission models *(29, 30)* suggest that absolute coverage of ≥50% of effectively treated nets is expected to result in community-wide protection of non-users in most settings and that, within these, further gains are realized as coverage increases. A community effect of ITNs has, however, not been observed in all settings *(31, 32)*. WHO GMP has initiated a systematic review of the evidence base on the 'community effect' of ITNs to further investigate observed presence/absence of this effect depending on contextual factors and study designs, as well as the relationship between coverage and community-level impact in different transmission settings where this effect has been observed.

Two main ITN classes are currently covered by a WHO policy recommendation:

- Pyrethroid-only nets, including LLINs: This product class covers both conventionally treated nets that rely on periodic re-treatment of nets by dipping into an insecticide formulation, and factory-treated LLINs made of netting material with insecticide incorporated within or bound around the fibres. LLINs are defined as retaining their effective biological activity for at least 20 WHO standard washes under laboratory conditions and three years of recommended use under field conditions.
- Pyrethroid-PBO net: This product class contains both a pyrethroid insecticide and the synergist piperonyl butoxide (PBO).

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

Pyrethroid-only nets

PYRETHROID-ONLY NETS

Pyrethroid-only LLINs prequalified by WHO are recommended for deployment as a core intervention in all malaria-endemic settings.

Strong recommendation as a public health intervention, high-certainty evidence

BOX 3
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 individual RCTs; 12 studies compared ITNs with untreated nets, and 11 studies compared ITNs with no nets. Based on WHO regions, 12 studies were conducted in Africa (Burkina Faso, Cote d'Ivoire, Cameroon, Gambia (two studies), Ghana, Kenya (three studies), Madagascar, Sierra Leone, United Republic of Tanzania), six in the Americas (Colombia, Ecuador, Nicaragua (two studies), Peru and Venezuela) and four in South-East Asia (India, Myanmar, Thailand (two studies)) and one in the Eastern Mediterranean (Pakistan).

ITNs versus no ITNs:

- ITNs reduce the rate of all-cause child mortality compared to no nets

  (Rate Ratio: 0.83; 95% CI (0.77–0.89); five studies; high certainty evidence)
- ITNs reduce the rate of uncomplicated episodes of *P. falciparum* compared to no nets

  (Rate Ratio: 0.54; 95% CI (0.48–0.60); five studies; high certainty evidence)
- ITNs reduce the prevalence of *P. falciparum* infection compared to no nets

  (Rate Ratio: 0.69; 95% CI (0.54–0.89); five studies; high certainty evidence)

- ITNs may have little or no effect on the prevalence of *P. vivax* infection compared to no nets

  (Risk Ratio: 1.00; 95% CI (0.75–1.34); two studies; low certainty evidence)
- ITNs reduce the incidence rate of severe malaria episodes compared to no nets

  (Rate Ratio: 0.56; 95% CI (0.38–0.82); two studies; high certainty evidence)

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, compared to no nets, ITNs are effective in reducing the rate of all-cause child mortality, the rate of uncomplicated episodes of *P. falciparum*, the incidence rate of severe malaria episodes, and the prevalence of *P. falciparum*. ITNs may also reduce the prevalence of *P. vivax*, but here the evidence of an effect is less certain.

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

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

The current WHO policy recommendation for ITNs applies only to those mosquito nets that have a current WHO PQ listing and that contain only an insecticide of the pyrethroid class[11] (categorized as 'pyrethroid-only LLINs') *(3)*. For ITNs that currently do not have a policy recommendation, including nets treated with another class of insecticide either alone or in addition to a pyrethroid insecticide, WHO will determine the data requirements for assessing their public health value based on technical advice from the VCAG. In 2017, a separate recommendation applicable to pyrethroid nets treated with a synergist ('pyrethroid-PBO nets') was formulated based on the latest available evidence *(33)*.

Pyrethroid-PBO nets

PYRETHROID-PBO NETS

Pyrethroid-PBO nets prequalified by WHO are conditionally recommended for deployment instead of pyrethroid-only LLINs where the principal malaria vector(s) exhibit pyrethroid resistance that is: a) confirmed, b) of intermediate level,[12] and c) conferred (at least in part) by a monooxygenase-based resistance mechanism, as determined by standard procedures.

Conditional recommendation as a public health intervention, moderate-certainty evidence

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

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

[12] Defined as 10–80% mortality in standard WHO susceptibility tests or CDC bottle bioassays

PBO nets affect their relative efficacy. A non-inferiority design for experimental hut studies with entomological endpoints is being explored by WHO as a means to provide clarity in this respect.

Epidemiological data from one cluster RCT indicated that a pyrethroid-PBO net product had additional public health value compared to a pyrethroid-only LLIN product in an area where the principal malaria vector(s) had confirmed pyrethroid resistance of moderate intensity conferred (at least in part) by monooxygenase-based resistance mechanism, as determined by standard procedures. On the basis of the current evidence, WHO has concluded and recommended the following:

1. Based on the epidemiological findings and the need to deploy products that are effective against pyrethroid-resistant mosquitoes, pyrethroid-PBO nets are being given a conditional endorsement as a new WHO class of vector control products.
2. National malaria control programmes and their partners should consider the deployment of pyrethroid-PBO nets in areas where the principal malaria vector(s) have pyrethroid resistance that is: a) confirmed, b) of intermediate level (as defined above), and c) conferred (at least in part) by a monooxygenase-based resistance mechanism, as determined by standard procedures. Deployment of pyrethroid-PBO nets must only be considered in situations where coverage with effective vector control (primarily LLINs or IRS) will not be reduced; the primary goal must remain the achievement and maintenance of universal coverage for all people at risk of malaria.
3. 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.
4. Pyrethroid-PBO nets should not be considered a tool that can alone effectively manage insecticide resistance in malaria vectors. It is an urgent task to develop and evaluate ITNs treated with non-pyrethroid insecticides and other innovative vector control interventions for deployment across all settings, in order to provide alternatives for use in a comprehensive IRM strategy.

Further details are available in the full document online *(32)*. The conditional recommendation will be updated based on a systematic review published in late 2018 (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012776.pub2/full), once data from an ongoing second study with epidemiological outcomes have been assessed by the VCAG.

Achieving and maintaining universal coverage with ITNs for malaria prevention and control

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

Good practice statement

Recipients of ITNs 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

In December 2017, WHO published updated recommendations on achieving and maintaining universal coverage with LLINs *(34)*. These recommendations were developed and revised based on expert opinion through broad consultation, including multiple rounds of reviews by the MPAC. Below, these recommendations have been summarized and slightly revised to clarify that these recommendations are not specific to LLINs, but apply to ITNs in general.

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

Mass campaigns should distribute 1 ITN for every 2 persons at risk of malaria. However, for procurement purposes, the calculation to determine the number of ITNs required needs to be adjusted at the population level, since many households have an odd number of members. Therefore a ratio of 1 ITN for every 1.8 persons in the target population should be used to estimate ITN requirements, unless data to inform a different quantification ratio are available. In places where the most recent population census is more than five years old, countries can consider including a buffer (e.g. adding 10% after the 1.8 ratio has been applied) or using data from previous ITN campaigns to justify an alternative buffer amount. Campaigns should also normally be repeated every three years,

unless available empirical evidence justifies the use of a longer or shorter interval between campaigns. In addition to these data-driven decisions, a shorter distribution interval may also be justified during humanitarian emergencies, as the resulting increase in population movement may leave populations uncovered by vector control and potentially increase their risk of infection as well as the risk of epidemics.

Continuous distribution through ANC and EPI channels should remain functional before, during and after mass distribution campaigns. School-based distribution should be discontinued in campaign years to avoid over-supply of ITNs. In areas where school-based distributions are operating at scale and achieve high coverage, these distributions may even be sufficient to replace mass distribution campaigns.

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

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

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

- **ANC, EPI and other child health clinics:** These should be considered high-priority continuous ITN distribution channels in countries where these services are used by a large proportion of the population at risk of malaria, as occurs in much of sub-Saharan Africa.
- **Schools, faith- and community-based networks, and agricultural and food-security support schemes:** These can also be explored as channels for ITN distribution in countries where such approaches are feasible and equitable. Investigating the potential use of these distribution channels in complex emergencies is particularly important.

- **Occupation-related distribution channels:** In some settings, particularly in Asia, the risk of malaria may be strongly associated with specific occupations (e.g. plantation and farm workers and their families, miners, soldiers and forest workers). In these settings, opportunities for distribution through channels such as private sector employers, workplace programmes and farmers' organizations may be explored.
- **Private or commercial sector channels:** These can be important channels for supplementing free ITN distribution through public sector channels. Access to ITNs can also be expanded by facilitating the exchange of vouchers or coupons provided through public sector channels for a free or subsidized ITN at participating retail outlets. ITN products distributed through the private sector should be regulated by the national registrar of pesticides in order to ensure that product quality is in line with WHO recommendations.

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

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

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

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

Countries should generate data on defined standard indicators of coverage and access rates in order to ascertain whether 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 are: i) the proportion of households with at least one ITN; ii) the proportion of the population with access to an ITN within their household; and iii) the proportion of the population reporting having slept under an ITN the previous night (by age (<5 years; 5–14 years; 15+ years), gender and access to ITN).

Management of old ITNs

COLLECTION AND DISPOSAL OF OLD ITNS

Old ITNs should only be collected where there is assurance that: i) communities are not left uncovered, i.e. new ITNs are distributed to replace old ones; and ii) there is a suitable and sustainable plan in place for safe disposal of the collected material.

Good practice statement

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

Good practice statement

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

Strong recommendation, high-certainty evidence

Currently, LLINs and the vast majority of their packaging (bags and baling materials) are made of non-biodegradable plastics *(35)*. The large-scale deployment of LLINs has given rise to questions as to the most appropriate and cost-effective way to deal with the resulting plastic waste, particularly given that most endemic countries currently do not have the resources to manage LLIN collection and waste disposal programmes.

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

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

1. LLINs entering domestic use in Africa each year contribute approximately 100 000 tonnes of plastic and represent a per capita rate of plastic consumption of 200 grams per year. This is substantial in absolute terms, but constitutes only approximately 1% to 5% of the total plastic consumption in Africa and thus is small compared to other sources of plastic and other forms of plastic consumption.
2. The plastic from LLINs is treated with a small amount of pyrethroid insecticide (less than 1% per unit mass for most products), and plastic packaging is therefore considered a pesticide product/container.
3. Old LLINs and other nets may be used for a variety of alternative purposes, usually due to perceived ineffectiveness of the net, loss of net physical integrity or presence of another net.
4. 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.
5. LLIN collection was not implemented on a large scale or sustained in any of the pilot study countries. It may be feasible to recycle LLINs, but it is not practical or cost-effective at this point, as there would need to be specialized adaptation and upgrading of recycling facilities before insecticide-contaminated materials could be included in this process.
6. Two important and potentially hazardous practices are: i) routinely removing LLINs from bags at the point of distribution and burning discarded bags and old LLINs, which can produce highly toxic fumes including dioxins, and ii) discarding old LLINs and their packaging in water, as they may contain high concentrations of residual insecticides that are toxic to aquatic organisms, particularly fish.
7. Insecticide-treated plastics can be incinerated safely in high-temperature furnaces, but suitable facilities are lacking in most countries. Burial away from water sources and preferably in non-permeable soil is an appropriate method to dispose of net bags and old LLINs in the absence of a suitable high-temperature incinerator.

8. In most countries, ministries of environment (national environment management authorities) are responsible for setting up and enforcing laws/regulations to manage plastic waste broadly. Although some countries have established procedures for dealing with pesticide-contaminated plastics, it is unrealistic to expect national malaria control and elimination programmes to single-handedly address the problem of managing waste from LLINs. Environmental regulations; leadership and guidance from national environmental authorities; and oversight from international agencies, such as the United Nations Environment Programme, are all necessary.

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

If such plastic material (with packaging an issue at the point of distribution and old LLINs an intermittent issue at household level when the net is no longer in use) is left in the community, it is likely to be re-used in a variety of ways. While the insecticide-exposure entailed by this kind of re-use has not yet been fully studied, the expected negative health and environmental impacts of leaving it in the community are considered less than amassing the waste in one location and/or burning it in the open air.

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

4.2 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 product that has a WHO PQ listing is a core intervention for deployment in malaria-endemic locations. DDT, which has not been prequalified, may be used for IRS if no equally effective and efficient alternative is available, and if it is used in line with the Stockholm Convention on Persistent Organic Pollutants.

INDOOR RESIDUAL SPRAYING

IRS deploying a product prequalified by WHO is recommended as a core intervention in all malaria-endemic settings. DDT has not been prequalified; it may be used for IRS if no equally effective and efficient alternative is available, and if it is used in line with the Stockholm Convention on Persistent Organic Pollutants.

Strong recommendation as a public health intervention, 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)

When carried out correctly, IRS has historically been shown to be a powerful intervention to reduce adult mosquito vector density and longevity and, therefore, to reduce malaria transmission. However, few RCTs have been conducted on IRS and so the availability of data suitable for use in a Cochrane-style meta-analysis is limited. The Guidelines Development Group determined that the data from these randomized trials, as well as the large body of evidence generated from other studies, warranted the continued recommendation of IRS as a core intervention for malaria prevention and control. A systematic review of evidence from non-randomized studies will be undertaken to further underpin this recommendation or modify it as appropriate.

Insecticide formulations for IRS *(1)* fall into five major insecticide classes with three modes of action,[13] based on their primary target site in the vector:

Sodium channel modulators

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

Acetylcholinesterase inhibitors

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

Nicotinic acetylcholine receptor competitive modulators

- Neonicotinoids: clothianidin

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

IRS products using four of these insecticide classes have been pre-qualified by WHO; as of February 2019, there were no DDT IRS formulations prequalified. The products listed have been prequalified based on their safety, quality and entomoligical efficacy, which includes evaluation of their mortality effect on mosquitoes when applied to a range of interior surfaces of dwellings found in malaria-endemic areas. Residual efficacy needs to continue for at least three months after the application of the insecticide to the substrate, usually cement, mud or wood *(36)*. Insecticides are available in various formulations to increase their longevity on different surfaces.

IRS is considered an appropriate intervention where:

- the majority of the vector population feeds and rests inside houses;
- the vectors are susceptible to the insecticide that is being deployed;
- people mainly sleep indoors at night;
- the malaria transmission pattern is such that the population can be protected by one or two rounds of IRS per year;
- the majority of structures are suitable for spraying; and
- structures are not scattered over a wide area, resulting in high transportation and other logistical costs.

5. Recommendations on supplementary interventions

5.1 LARVAL SOURCE MANAGEMENT (LSM)

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

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

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

LARVICIDING

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 high coverage with a core intervention has been achieved, where aquatic habitats are few, fixed and findable, and where its application is both feasible and cost-effective.

Conditional recommendation as a public health intervention, low-certainty evidence

BOX 5
Summary of evidence from Cochrane systematic review

Larviciding versus no larviciding:

Four studies were included in the systematic review, of which only one was an RCT; the remaining three studies were non-randomized. Studies were undertaken in Gambia, Kenya, Sri Lanka and United Republic of Tanzania.

Larviciding applied to mosquito aquatic habitats exceeding 1km² 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 1km² in area:

- Larviciding probably reduces malaria incidence compared to no larviciding

  (Rate Ratio: 0.20; 95% CI (0.16–0.25); one study; moderate certainty evidence)
- Larviciding may reduce parasite prevalence compared to no larviciding

  (Odds Ratio: 0.72; 95% CI (0.58–0.89); two studies; low certainty evidence)

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 and specific evidence confirming that such measures can reduce malaria incidence in the local setting.

The WHO 2013 operational manual on LSM *(37)* concludes that LLINs and IRS remain the backbone of malaria vector control, but LSM represents an additional (supplementary) strategy for malaria control in Africa. Larviciding will generally be most effective in areas where larval habitats are few, fixed and findable, and likely less feasible in areas where the aquatic habitats are abundant, scattered and variable. Determination of whether or not specific habitats are suitable for larviciding should be based on assessment by an entomologist. The WHO operational manual focuses on sub-Saharan Africa, but the principles espoused are likely to hold for other geographic regions that fit the same criteria. The following settings are potentially the most suitable for larviciding as a supplementary measure implemented alongside the core interventions:

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

LARVIVOROUS FISH

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

No recommendation, insufficient evidence

BOX 6

Summary of evidence from Cochrane systematic review

Larvivorous fish versus no larvivorous fish:

Fifteen studies were included in the systematic review. Studies were undertaken in Comoros, Ethiopia, India (three studies), Indonesia, Kenya, Republic of Korea (two studies), Sri Lanka (two studies), Sudan, and Tajikistan (two studies).

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

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

The studies were not suitable for a pooled analysis.

- It is unknown whether larvivorous fish reduce the density of immature vector stages compared to no larvivorous fish
  (unpooled data; 12 studies; very low certainty evidence)
- Larvivorous fish may reduce the number of larval sites positive for immature vector stages compared to no larvivorous fish
  (unpooled data; five studies; low certainty evidence)

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

6. Recommendations on personal protection measures

6.1 TOPICAL REPELLENTS, INSECTICIDE-TREATED CLOTHING AND SPATIAL/AIRBORNE REPELLENTS

Topical repellents, insecticide-treated clothing and spatial/airborne repellents have all been proposed as potential methods for malaria prevention in areas where the mosquito vectors bite or rest outdoors, or bite in the early evening or early morning when people are not within housing structures. They have also been proposed for specific population groups, such as those who live or work away from permanent housing structures (e.g. migrants, refugees, internally displaced persons, military personnel) or those who work outdoors at night. In these situations, the effectiveness of the core interventions (ITNs or IRS) may be reduced. Repellents have also been proposed for use in high-risk groups, such as pregnant mothers. Despite the potential to provide individual protection against bites from malaria vectors, the deployment of the above personal protective methods in large-scale public health campaigns has been limited, at least partially due to the scarcity of evidence of their public health value. Daily compliance and appropriate use of the repellents seem to be major obstacles to achieving such potential impact *(38)*. Individuals' use of the intervention to achieve personal protection faces the same obstacles.

TOPICAL REPELLENTS

Deployment of topical repellents for malaria prevention is not recommended as an intervention with public health value; however, topical repellents may be beneficial as an intervention to provide personal protection against malaria.

*Conditional recommendation **against** deployment as an intervention with public health value, low-certainty evidence*

BOX 7.
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 among residents in Plurinational State of Bolivia, Cambodia, Lao People's Democratic Republic and United Republic of Tanzania, and in specific populations in Pakistan (refugees) and Thailand (pregnant women).

- It is unknown whether topical repellents have an effect on clinical malaria caused by *P. falciparum*

  (Risk Ratio: 0.65; 95% CI (0.40–1.07); three studies; very low certainty evidence)
- Topical repellents may or may not have a protective effect against *P. falciparum* parasitaemia

  (Risk Ratio: 0.84; 95% CI (0.64–1.12); four studies; low certainty evidence)
- Topical repellents may increase the number of clinical cases caused by *P. vivax*

  (Risk Ratio: 1.32; 95% CI (0.99–1.76); two studies; low certainty evidence)
- Topical repellents may or may not have a protective effect against *P. vivax* parasitaemia

  (Risk Ratio: 1.07; 95% CI (0.80–1.41); three studies; low certainty evidence)

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.

INSECTICIDE-TREATED CLOTHING

Deployment of insecticide-treated clothing for malaria prevention is not recommended as an intervention with public health value; however, insecticide-treated clothing may be beneficial as an intervention to provide personal protection against malaria in specific population groups.

*Conditional recommendation **against** deployment as an intervention with public health value, low-certainty evidence*

BOX 8.
Summary of evidence from Cochrane systematic review

Insecticide-treated clothing versus placebo or untreated clothing:

Two RCTs were included in the systematic review. Studies were conducted in specific populations in Colombia (military personnel) and Pakistan (Afghan refugees).

- Insecticide-treated clothing may have a protective effect against clinical malaria caused by *P. falciparum*

  (Risk Ratio: 0.49; 95% CI (0.29–0.83); two studies; low certainty evidence)
- Insecticide-treated clothing may have a protective effect against clinical malaria caused by *P. vivax*

  (Risk Ratio: 0.64; 95% CI (0.40–1.01); two studies; low certainty evidence)

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).

SPATIAL/AIRBORNE REPELLENTS

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

No recommendation, very low-certainty evidence

BOX 9.
Summary of evidence from Cochrane systematic review

Spatial/airborne repellents versus placebo or no malaria prevention intervention:

Two RCTs were included in the systematic review. Studies were conducted in China and Indonesia.

- It is unknown whether spatial repellents protect against malaria parasitaemia

  (Risk Ratio: 0.24; 95% CI (0.03–1.72); two studies; very low certainty evidence)

There is very low certainty evidence that spatial or airborne repellents may have a protective efficacy against malaria parasitaemia. Therefore, no recommendation on the use of spatial/airborne repellents in the prevention and control of malaria can be made until more studies assessing malaria epidemiological outcomes have been conducted.

7. Other interventions

7.1 SPACE SPRAYING

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

SPACE SPRAYING

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

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

BOX 10.
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 has hampered a comprehensive assessment of this intervention. Review of the evidence indicated that it is unknown whether space spraying causes a reduction in incidence of malaria. Nevertheless, space spraying is often deployed in response to outbreaks of mosquito-borne disease. Due to the high visibility of this intervention, the decision to use this approach is usually made to demonstrate that the authorities are taking action in response to the outbreak. This practice should be strongly discouraged given the limited evidence of the intervention's effectiveness and the potential for wastage of resources. The Guidelines Development Group therefore felt it necessary to develop a clear recommendation against space spraying for malaria control.

7.2 HOUSING IMPROVEMENTS

Available evidence indicates that poor-quality housing and neglected peridomestic environments are risk factors for the transmission of malaria, arboviral diseases (e.g. dengue, yellow fever, chikungunya, Zika virus disease), Chagas disease and leishmaniasis *(39)*. Closing open eaves, screening doors and windows with fly screens or mosquito netting, and filling holes and cracks in walls and roofs reduce the mosquitoes' entry points into houses. Together with metal roofs, ceilings, and finished interior walls, these modifications may reduce transmission of malaria and other vector-borne diseases.

A recent review indicated that housing quality is an important risk factor for malaria infection across the spectrum of malaria endemicity in sub-Saharan Africa *(40)*. However, specific evidence-based recommendations on housing and vector-borne diseases are still needed. To this end, the WHO Department of Public Health, Environmental and Social Determinants of Health is currently developing housing and health guidelines. To support the development of these guidelines, WHO has commissioned a systematic review of housing and vector-borne diseases by the CIDG. Once available, the outcomes of this review will be presented to the Guidelines Development Group with a view to formulating evidence-based recommendations for inclusion in both the housing and the malaria vector control guidelines.

8. Special situations

8.1 RESIDUAL TRANSMISSION

WHO acknowledges that even full implementation of core interventions will not be sufficient to completely halt malaria parasite transmission across all settings *(41)*. Some residual malaria parasite transmission will occur, even with universal access to and usage of ITNs or in areas with high IRS coverage. Residual transmission occurs as a result of a combination of human and vector behaviours, for example, when people reside in or visit forest areas or do not sleep in protected houses, or when local mosquito vector species exhibit one or more behaviours that allow them to avoid 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 greatly improved knowledge of the bionomics of the different sibling species within malaria vector species complexes, and new interventions and strategies in order to effectively address residual transmission. While this knowledge is being gained and interventions are being developed, national malaria control programmes must prioritize the effective implementation of current interventions to reduce transmission to the lowest level possible. At the same time, they should collaborate with academic or research institutions to generate local evidence on the magnitude of the problem of residual transmission of malaria, including information on human and vector behaviours, and the effectiveness of existing and novel interventions.

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

8.2 EPIDEMICS AND HUMANITARIAN EMERGENCIES

In the acute phase of a humanitarian emergency, the first priorities for malaria control are prompt and effective diagnosis and treatment. Vector control also has the potential to play an important role in reducing

transmission. However, the evidence base on the effectiveness of vector control interventions deployed in these settings is weak *(42)*.

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

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

Effective case management can be supplemented with distribution of ITNs, first targeting population groups most susceptible to developing severe malaria, but with the ultimate goal of achieving and maintaining 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.

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

Another intervention with potential for deployment in emergency situations is the long-lasting insecticide impregnated blanket or topsheet. Blankets or lightweight topsheets are often included in emergency relief kits. One advantage of blankets and topsheets is that they can be used anywhere people sleep (e.g. indoors, outdoors, any type of shelter).

However, as with ITPS, the evidence base regarding the effectiveness of this approach is currently limited. Data from community RCTs of long-lasting pyrethroid-treated wash-resistant blankets and topsheets would be required to determine public health value and develop specific policy recommendations for deployment as public health interventions.

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

8.3 MIGRANT POPULATIONS AND POPULATIONS ENGAGED IN HIGH-RISK ACTIVITIES

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

9. 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 *(43)*:

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

9.1 ACCEPTABILITY, PARTICIPATION AND ETHICAL CONSIDERATIONS

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

ITNs are generally acceptable to most communities. In many malaria-endemic countries, untreated nets were in use for many years prior to the introduction of ITNs and, even where there is not a long history of their use, they have become familiar tools for preventing mosquito bites. Individuals often appreciate the extra privacy afforded by a net, as well as its

effectiveness in controlling other nuisance insects. In very hot climates, ITNs may be less acceptable, as they are perceived to reduce air flow, making it too hot to allow for a comfortable sleep. In areas where mosquito densities are low or where malaria transmission is low, individuals and communities may perceive less benefit in using nets.

Community acceptance of IRS is critical to the programme's success, particularly as it involves disruption to the household, requiring householders to remove certain articles and allow spray teams to enter all rooms of the house. Repeated, frequent spraying of houses over extended periods can lead to refusal by householders. Reduced acceptance has been an impediment to effective IRS implementation in various parts of the world *(44)*.

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

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

WHO acknowledges that appropriate policy-making often requires explicit consideration of ethical matters in addition to scientific evidence. However, the ethical issues relevant to vector-borne disease control and research have not previously received the analysis necessary to further improve public health programmes. Moreover, WHO Member States lack specific guidance in this area. The Seventieth World Health Assembly *(45)* requested the Director-General "to continue to develop and disseminate normative guidance, policy advice and implementation guidance that provides support to Member States to reduce the burden and threat of vector-borne diseases, including to strengthen human-resource capacity

and capability for effective, locally adapted, sustainable and ethically sensitive vector control; to review and provide technical guidance on the ethical aspects and issues associated with the implementation of new vector control approaches in order to develop mitigating strategies and solutions; and to undertake a review of the ethical aspects and related issues associated with vector control implementation that include social determinants of health, in order to develop mitigating strategies and solutions to tackle health inequities." As a first step towards developing appropriate guidelines within the next two years, a scoping meeting was convened by WHO to identify the ethical issues associated with vector-borne diseases *(46)*. Further work has been undertaken to develop guidance. Once available, it will be reflected 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 deployment of insecticides (and growing vector resistance to insecticides), and research on and/or deployment of new vector control technologies. Genetically modified mosquitoes are one such innovation that presents potential challenges, including how to prevent their spread beyond the intended geographical target areas and limit potential effects on the local fauna. WHO has established a robust evaluation process for new vector control interventions *(47)* in order to ensure that these are fully and properly assessed prior to any WHO recommendation for their deployment.

9.2 EQUITY, GENDER AND HUMAN RIGHTS

The aim of all of the work of WHO is to improve population health and decrease health inequities. Sustained improvements to physical, mental and social well-being require actions in which careful attention is paid to equity, human rights principles, gender and other social determinants of health. A heightened focus on equity, human rights, gender and social determinants is expressed in the WHO 13th General Programme of Work.

In pursuit of this outcome, WHO is committed to providing guidance on the integration of sustainable approaches that advance health equity, promote and protect human rights, are gender-responsive and address social determinants into WHO programmes and institutional mechanisms; promoting disaggregated data analysis and health inequality monitoring; and providing guidance on the integration of sustainable approaches that advance health equity, promote and protect human rights, are gender-responsive and address social determinants into WHO's support at country level *(48)*.

WHO advocates for universal coverage with recommended vector control interventions. As such, malaria vector control is expected to be implemented without discrimination on the basis of age, sex, ethnicity, religion or other 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.

9.3 RESOURCE IMPLICATIONS AND PRIORITIZATION

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

At present, the most recent systematic review of the cost and cost-effectiveness of vector control interventions was published in 2011, drawing on studies published between 1990 and 2010 *(49)*. The body of evidence collated was based on the use of ITNs/LLINs and IRS in a few sites in sub-Saharan Africa. The authors found large variations in the costs of intervention delivery, which reflected not only the different contexts but also the various types of costing methodologies employed; these studies were rarely undertaken alongside clinical and epidemiological evaluations. The review reported that, while ITNs/LLINs and IRS were consistently found to be cost-effective across studies, evidence to determine their comparative cost-effectiveness was insufficient. WHO GMP is working with partners to

update the evidence review on the cost and cost-effectiveness evidence of the vector control interventions covered in the *Guidelines*.

Cost-effectiveness analysis – the comparison of the costs and outcomes of alternative interventions – can be a helpful tool for measuring the magnitude of additional health gained per additional unit of resources spent. WHO offers a series of tools to facilitate country-level cost-effectiveness analysis, notably through the CHOICE project *(50)*. Using the cost-effectiveness ratio in combination with cost-effectiveness thresholds, as applied in the above-mentioned review, provides some indication of the value for money of an intervention. Value for money, however, should not be used as a standalone criterion for decision-making, but rather used alongside other considerations, including affordability and budget impact analysis, among others *(51)*. The development of further guidance to inform resource use will be a focus in preparing explicit recommendations on resource use as part of the GRADE tables, using work by other WHO departments as a guide *(52)*. Given that resource considerations are highly context-specific and hence unlikely to be detailed enough to inform the prioritization of resources for vector control at country level, further work to guide country-level decision-making is also foreseen, but will be outside the scope of this global guidance document.

9.4 HUMAN RESOURCES AND ENTOMOLOGICAL CAPACITY

The *Global vector control response 2017–2030 (6)* 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 *(8)* will help to appraise current capacity, define what is needed to conduct proposed activities, identify opportunities for improved efficiencies in vector control, and guide resource mobilization.

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

and institutional capacity within programmes should be formulated. The plan should identify any additional resources and associated costs involved in achieving the desired objectives and set out clear terms of reference for the different staffing positions required.

Capacity-building priorities for established staff should be defined through a comprehensive training needs assessment led by the Ministry of Health and aligned with available WHO guidance *(53)*.

10. Monitoring and evaluation of vector control

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

Monitoring and evaluation of vector control interventions is covered in detail in the WHO reference manual on malaria surveillance, monitoring and evaluation *(23)*. In addition, a brief synopsis of quality assurance is provided below.

10.1 QUALITY ASSURANCE OF VECTOR CONTROL INTERVENTIONS

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

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

The WHO Model Quality Assurance System for Procurement Agencies *(54)* details the quality assurance steps and processes involved in procuring pharmaceutical products and diagnostics, but the principles are equally applicable to vector control products.

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

- sourcing only products with a WHO PQ listing for deployment against malaria vectors;
- requesting the supplier/manufacturer to provide a Certificate of Analysis for each batch of the product actually being supplied;
- pre-shipment inspection and sampling according to WHO guidance and/or International Organization for Standardization (ISO) standards, performed by an independent sampling agent;
- pre-shipment testing conducted by an independent quality control laboratory (WHO prequalified or ISO 17025 or Good Laboratory Practice accredited) to determine that the product conforms to approved specifications according to the WHO/CIPAC test methods;
- testing on receipt in country (post-shipment quality control testing) should only be conducted if specific risks related to transport have been identified or specific concerns over potential product performance justify this additional expense;
- tender conditions should include provisions for free-of-cost replacement of shipments that fail quality control checks and disposal of failed lots;
- post-marketing surveillance may be required, depending on the product and context, to monitor performance over time in order to ensure that products continue to conform to their specifications and/or recommended performance as set by WHO.

  For ITNs, this may require testing both physical durability and insecticidal efficacy. For IRS products, bioefficacy on sprayed surfaces of a different nature (e.g. mud, brick), as applicable, should be periodically tested according to WHO procedures when an insecticide is first introduced into a country. Subsequent measurement of insecticide decay on sprayed surfaces should be done only if necessary, as it will incur additional expense. Countries can make post-marketing surveillance a priority in cases where there are no country-specific data on certain LLIN or IRS products, or where anecdotal data on poor performance of certain products may exist. Agreement on the need and scope of the proposed activities should be reached by all in-country stakeholders, including the national regulatory authority. All evaluations should follow WHO guidance.

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

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

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

11. Research agenda to support future updates

During the development of this 1st 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 as part of revision to the *Guidelines*:

- To conduct a systematic review of data on IRS interventions from studies other than cluster RCTs. Despite its long tradition and the large body of associated operational experience, few RCTs have been conducted on IRS. The Guidelines Development Group agreed that the strength of the current recommendations on IRS, and their specifics, could be enhanced through a systematic review of additional data from non-randomized studies.
- To conduct additional systematic reviews on housing and on two LSM interventions, namely habitat modification and manipulation.
- To review current evidence on resource use and draft expanded GRADE tables that include this information as an initial step guiding the prioritization of interventions. This process should follow examples provided in other WHO guidance, such as the interim policy guidance on the use of delamanid in the treatment of multidrug-resistant tuberculosis *(51)*.
- To develop a chapter to guide the collection of cost data alongside research studies for inclusion in the trial design manual recently issued by WHO on behalf of the VCAG *(54)*. Collection of cost data early on in the process of evaluating new interventions will make a useful contribution to building an evidence base on resource use, which can be drawn on for subsequent editions of the Guidelines.
- To conduct a systematic review of cost and cost-effectiveness data on all vector control interventions in order to complement the evidence base upon which recommendations are developed and identify knowledge gaps in these areas.
- To identify basic resources associated with the recommendations, including health system resources (training, supervision, etc.) to support countries in developing their own resource need and budget impact assessments.

- To develop further guidance on the deployment of improved or interventions in special situations, for example, with the aim of controlling residual transmission and protecting specific populations with high occupational exposure to malaria.

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Annexes

ANNEX 1. PERSONS INVOLVED IN DEVELOPMENT OF THE GUIDELINES

The following outlines the constitution of the Guidelines Development Group, Guidelines Steering Group, and External Review Group. Also indicated are members of the systematic review production and management team and Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis subgroup, as well as the guidelines methodologist. Final compositions of these groups are shown as of the date of finalization of the Guidelines.

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- Dr Nathalie Roebbel, Department of Public Health, Environment and Social Determinants of Health, World Health Organization, Geneva, Switzerland
- Dr Matt Shortus, WHO Country Office, Lao People's Democratic Republic
- Dr Raman Velayudhan, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

Members of the External Review Group

The WHO Malaria Policy Advisory Committee (MPAC) served as the External Review Group and included:

- Professor Ahmed Adeel, Independent Consultant, United States of America
- Dr Evelyn Ansah, Director, Center for Malaria Research, Institute of Health Research, University of Health and Allied Sciences, Ghana
- Professor Thomas Burkot, Professor and Tropical Leader, Australian Institute of Tropical Health and Medicine, James Cook University, Australia
- Professor Graham Brown, Professor Emeritus, University of Melbourne, Australia
- Dr Gabriel Carrasquilla, Director of ASIESALUD, Fundación de Santa Fe de Bogota, Centre for Health Research, Colombia
- Dr Maureen Coetzee, Director, Wits Research Institute for Malaria, University of Witwatersrand, South Africa
- Professor Umberto d'Alessandro, Director, Medical Research Council Unit, Gambia
- Dr Abdoulaye Djimde, Head, Molecular Epidemiology and Drug Resistance Unit, Malaria Research and Training Center, University of Mali, Mali
- Professor Azra Ghani, Professor in Infectious Diseases, Epidemiology, Centre for Outbreak Analysis and Modelling, Imperial College, United Kingdom
- Professor Brian Greenwood, Manson Professor of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine, United Kingdom
- Dr Caroline Jones, Senior Social Scientist, KEMRI Wellcome Trust Research Programme, Kenya
- Dr Stephen Kachur, Chief, Malaria Branch, Centers for Disease Control and Prevention, United States of America
- Professor Kevin Marsh (Chair), Director, KEMRI Wellcome Trust Research Programme, Kenya
- Dr Kamini Mendis, Independent Consultant in malaria and tropical medicine, Sri Lanka

- Professor Gao Qi, Senior Professor, Jiangsu Institute of Parasitic Diseases and Suzhou University, People's Republic of China
- Dr Pratap Singhasivanon, Associate Professor, Department of Tropical Hygiene, Mahidol University, Thailand
- Dr Larry Slutsker, Director, Malaria and Neglected Tropical Diseases, Center for Malaria Control and Elimination, PATH, United States of America
- Dr Richard Steketee, Director, Malaria Control and Elimination, PATH, United States of America
- Dr Neena Valecha, Director, National Institute for Malaria Research, India
- Professor Dyann Wirth, Richard Pearson Strong Professor and Chair, Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, United States of America

Systematic review production and management team and GRADE analysis subgroup members

- Mr Leslie Choi, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Mr Joe Pryce, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Ms Marty Richardson, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Dr Vittoria Lutje, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Dr Deirdre Walshe, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Prof Paul Garner, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Guidelines methodologist

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

Declaration of interests

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

The relevant declared interests are summarized as follows:

Dr T. Burkot reported several potential conflicts of interest related to consulting payments, research support and non-monetary support, as follows: 1) consulting with Intellectual Ventures Global Good Fund (IVGGF), the non-profit arm of Intellectual Ventures Laboratory. IVGGF develops technologies and then gives away the rights to any technologies developed in exchange to organizations and companies that make the resulting products available for use in developing countries at minimal cost. Work was conducted from October 2014 to March 2015 for a total of US$ 20 000 paid directly to James Cook University; 2) consulting with IVGGF for a secondment in 2017 to develop a vector control strategy on mosquito-proof housing and methods to age-grade mosquitoes for a total of US$ 250 000 paid directly to James Cook University; 3) consulting with the non-profit Programme for Appropriate Technology in Health (PATH) in 2017 to support grant applications to evaluate new vector control tools in Africa for a total of US$ 32 000 paid directly to James Cook University; 4) consulting with IVGGF from 2017 to February 2018 to provide technical support on developing guidelines for testing new vector control strategies for a total of US$ 8940 paid directly to Dr Burkot; 5) consulting with PATH from 2017 to February 2018 to provide technical advice on field trials for mosquito-proof housing products for a total of US$ 9600 paid directly to Dr Burkot; 6) research support in a supervisory role provided to James Cook University for evaluation of a new malaria diagnostic test from October 2015 to March 2017 for a total of US$ 120 000; 7) research support in a supervisory role provided to James Cook University to undertake a malaria serologic survey in the Solomon Islands until June 2018 for a total amount of US$ 100 000; and, 8) non-monetary support to Vestergaard in a supervisory role to evaluate the impact of insecticide netting on malaria in Solomon Islands. Declarations 1–3 and 6–7 were considered financially significant (amount that exceeds US$ 5000), non-personal and related to the employment of Dr Burkot at James Cook University. Declarations 4 and 5 were considered financially significant and personal. Declaration 8 was considered financially insignificant and personal.

Dr M. Coetzee reported a potential conflict of interest related to a family member's consulting work with AngloGold Ashanti in 2016 to carry out mosquito surveys and determine insecticide resistance in order to inform vector control strategies by gold mining companies in Africa. The family member received US$ 6000 for this work. This declaration was considered significant and non-personal, and not likely to affect discussions on malaria vector control guidelines.

Professor M. Coosemans reported receiving a grant from the Bill & Melinda Gates Foundation for studying the impact of repellents for malaria prevention in Cambodia and also reported receiving repellent products for the study from SC Johnson for work conducted in 2012–2014. He also reported receiving six grants for the evaluation of public health pesticides from WHOPES since 2007, some of which will continue until 2018. The WHO Secretariat assessed this declared conflict of interest as part of the preparations for the VCTEG, in which Professor Coosemans participates and which served as the Guidelines Development Group. Upon review, it was decided that the declarations made did not constitute conflicts of interest in this context and that Professor Coosemans could participate in the meeting, subject to the public disclosure of his interests.

Dr J. Hii reported receiving remuneration for consulting services from WHO and from the Ministry of Health of Timor-Leste for work conducted in 2017. He reported holding a grant from SC Johnson (US$ 100 000 managed by Malaria Consortium) that ceased in 2017 for the evaluation of transfluthrin, and receiving travel and accommodation support from Bayer Crop Science to attend the 4th Bayer Vector Control Expert Meeting in 2017. He reported holding a WHO/TDR research grant that focused on studying the magnitude and identifying causes for residual transmission in Thailand and Viet Nam (completed in 2018), and reported a plan to study the impact of socio-ecological systems and resilience (SESR)-based strategies on dengue vector control in schools and neighbouring household communities in Cambodia, which in November 2017 was awaiting ethical approval. The WHO Secretariat assessed this declared conflict of interest as part of the preparations for the VCTEG, in which Dr Hii participates and which served as the Guidelines Development Group. Upon review it was decided that the declarations made did not constitute conflicts of interest in this context and that Dr Hii could participate in the meeting, subject to the public disclosure of his 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 the expert's organization, from any single malaria-related company exceeds US$ 10 000 in a calendar year. Likewise, a shareholding in any one malaria-related company in excess of US$ 1000 would also constitute a 'significant shareholding'.

ANNEX 2. OVERVIEW OF 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 guidelines document is needed; review existing WHO and external guidelines • Obtain approval for guidelines development from the director of the relevant technical department at WHO • Discuss the process with the Guidelines Review Committee (GRC) Secretariat and with other WHO staff with experience in developing guidelines • Form the WHO Guidelines Steering Group • Identify sufficient resources; determine the timeline
	WHO Guidelines Steering Group	• Draft the scope of the guidelines; begin preparing the planning proposal • Identify potential members of the Guidelines Development Group and its Chair • Obtain declarations of interest and manage any conflicts of interest among potential Guidelines Development Group members
	WHO Guidelines Steering Group and Guidelines Development Group	• Formulate key questions in PICO (Population, participants or patients; intervention or indicator; comparator or control; outcome) format; prioritize outcomes
	WHO Guidelines Steering Group	• Finalize the planning proposal and submit it to the GRC for review
	Guidelines Review Committee	• Review and approve the planning proposal

Development	Systematic review team	• Perform systematic reviews of the evidence for each key question • Evaluate the certainty of the evidence for each important outcome, using Grading of Recommendations Assessment, Development and Evaluation (GRADE) as appropriate
	WHO Guidelines Steering Group	• Convene a meeting of the Guidelines Development Group
	Guidelines Development Group	• Formulate recommendations using the GRADE framework
	WHO Guidelines Steering Group	• Draft the guidelines document
	External Review Group	• Conduct external peer review
Publishing and updating	WHO Guidelines Steering Group and editors	• Finalize the guidelines document; perform copy-editing and technical editing; submit the final guidelines to the GRC for review and approval
	Guidelines Review Committee	• Review and approve the final guidelines
	WHO Guidelines 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

GRADE: Grading of Recommendations Assessment, Development and Evaluation; GRC: Guidelines Review Committee; PICO: Population, participants or patients; intervention or indicator; comparator or control; outcome.

ANNEX 3. 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).

ANNEX 4. GRADE TABLES ASSESSING THE CERTAINTY OF EVIDENCE

The Annex gives the results of Grading and Recommendations, Assessment, Development and Evaluation (GRADE) based on responses to questions of importance to populations at risk of malaria (population, participants or patients; intervention or indicator: comparator or control; outcome: PICO) and the results recommendations. The GRADE system is a uniform, widely adopted approach based on explicit methods for grading the certainty of evidence in support of recommendations in health care. The method ensures a transparent link between the evidence and the recommendations.

The PICO questions addressed were as follows:

Core interventions		
A4.1	ITNs alone	What is the current effect of ITNs (compared to no nets, and to untreated nets)?
A4.2	IRS	a. What is the effect of IRS alone? b. What is the effect of IRS compared to ITNs?
A4.3	Combining IRS with ITNs	Is the combined deployment of IRS and ITNs more effective in reducing malaria transmission than the deployment of ITNs alone?
Supplementary interventions		
A4.4	Larviciding	Does larviciding (with insecticide, insect growth regulators, microbial agents, or oils) control malaria?
A4.5	Larvivorous fish	In malaria transmission settings, are larvivorous fish effective for malaria control?
Other interventions		
A4.6	Space spraying	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?
A4.7	Repellents	a. Do topical repellents reduce malaria? b. Does insecticide-treated clothing reduce malaria? c. Do spatial/airborne repellents reduce malaria?

A4.1 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 certainty 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 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) and to untreated nets (HIGH certainty evidence). Undesirable effects of ITNs are considered to be trivial.

Remarks

The evidence review followed the original 2003 analysis which included insecticide-treated curtains and ITNs together, and includes two studies solely evaluating insecticide-treated curtains and one study evaluating both ITNs and insecticide-treated curtains. There was no obvious heterogeneity (that would lead to a subgroup analysis to examine if the effects were different) and the results from studies evaluating insecticide-treated curtains were consistent with the results of those evaluating ITNs. The Guidelines Development Group drew on the analysis to make recommendations related to ITNs only.

Implementation considerations

- Universal coverage should be achieved and maintained in endemic settings

Monitoring and evaluation

- Improved post-distribution monitoring of nets is needed: durability, usage, coverage

Research priorities

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

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: Studies were conducted in Burkina Faso *(1)*; Cambodia *(2)*; *Côte d'Ivoire (3)*; Ghana *(4)*; Kenya *(5-7)*; Myanmar *(8)*; Sierra Leone *(9)*; Pakistan *(10)*; and United Republic of Tanzania *(11)*.

Source: Original review: Pryce J, Richardson M, Lengeler C. Insecticide-treated nets for preventing malaria. Cochrane Database Syst Rev. 2018;2:CD000363. doi:10.1002/14651858.CD000363.pub3, supplemented with new literature search and compilation of GRADE tables.

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)
	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 (12). 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: Studies were conducted in Cameroon *(13)*; Colombia *(14)*; Ecuador *(14)*; Gambia *(15–17)*; Madagascar *(18)*; Nicaragua *(19)*; Peru *(14)*; Thailand *(20,21)*; and Venezuela *(22)*.

Source: Original review: Pryce J, Richardson M, Lengeler C. Insecticide-treated nets for preventing malaria. Cochrane Database Syst Rev. 2018;2:CD000363. doi:10.1002/14651858.CD000363.pub3, supplemented with new literature search and compilation of GRADE tables.

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty 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 (12). 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 have potentially influenced the likelihood of reporting a fever, this was not deemed likely to have seriously affected 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.

A4.2a. What is the effect of indoor residual spraying alone?

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

Strength of recommendation

For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
STRONG				

Overall certainty 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 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 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 in endemic settings.
- The primary vector should be endophilic.
- Implementation of the intervention should take place prior to the onset of the peak transmission season.

Monitoring and evaluation

- Residual activity of the insecticide(s)

Research priorities

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

In malarial areas, is indoor residual spraying effective?

Population: People at risk of malaria
Intervention: Indoor residual spraying
Comparison: No indoor residual spraying
Setting: Studies were conducted in India *(23)*; Pakistan *(24)*; and United Republic of Tanzania *(25)*.
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)	Certainty of evidence (GRADE)
	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] *(24)*
[b] *(25)*
[c] *(23)*
[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] The India study reported on this outcome as well *(23)*. 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 the Tanzania study *(25)*.
[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] The India study reported on this outcome as well *(23)*. 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 the Tanzania study *(25)*.

A4.2b. What is the effect of IRS compared to ITNs?

Recommendation

IRS and ITNs are both recommended as malaria prevention and control interventions in most epidemiological and ecological scenarios.

Rationale for the recommendation

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

Strength of recommendation

For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
STRONG				

Overall certainty of evidence for all critical outcomes

High	Moderate	Low	Very Low
		LOW	

Balance of desirable and undesirable effects

Desirable	Undesirable
• IRS may decrease the incidence of malaria compared to ITNs. There may be little or no difference in parasite prevalence between IRS and ITNs.	• No undesirable effects identified in systematic review. • May play an as yet undetermined role in 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 leave unsightly residue on sprayed surfaces.

Remarks

The evidence review followed the original 2003 analysis, which included insecticide-treated curtains and ITNs together, and includes two studies solely evaluating insecticide-treated curtains and one study evaluating both ITNs and insecticide-treated curtains. There was no obvious heterogeneity (that would lead to a subgroup analysis to examine if the effects were different) and the results from studies evaluating insecticide-treated curtains were consistent with the results of those evaluating ITNs. The Guidelines Development Group drew on the analysis to make recommendations related to ITNs only.

Implementation considerations

- Decisions on selection of insecticide to be used for IRS 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 of IRS on insecticide-resistant populations
- Generate high-quality evidence on the impact of insecticide rotations as an insecticide resistance management tool
- Impact of IRS in different mosquito behaviour/settings (outdoor transmission)

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: Studies were conducted in India *(23)*; and United Republic of Tanzania *(24)*.

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)	Certainty 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] *(24)*

[b] *(23)*

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.

A4.3. Is the combined deployment of IRS and ITNs more effective in reducing malaria transmission than the deployment of ITNs alone?

Recommendations

Malaria 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.

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 certainty 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 may increase effectiveness against malaria.	• None identified in systematic review. • The 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 ("combination") is potentially useful as an insecticide resistance management approach in areas of 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
- Status of vector resistance to the proposed IRS active ingredient
- In resource-constrained situations, it is unlikely to be financially feasible to deploy both core interventions together.

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.

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 + insecticide-treated nets

Comparison: Insecticide-treated nets

Setting: Studies were conducted in Benin *(26)*; Eritrea *(27)*; Gambia *(28)*; and United Republic of Tanzania *(29)*.

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)	Certainty of evidence (GRADE)
	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) *(29)* with traps (320 CDC light traps per month) and in Corbel (2012) *(26)* 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) *(28)*.

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

A4.4. 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 certainty 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 deployed for malaria control in several countries, including Somalia and Sudan; however, certainty of the evidence of epidemiological effects is low or very low.

Remarks

Should larviciding vs no larviciding be deployed for controlling malaria?

Population: People 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 Gambia *(30)*; Kenya *(31)*; Sri Lanka *(32)*; and United Republic of Tanzania *(33)*.

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)	Certainty of evidence (GRADE)
	Risk with no larviciding	Risk with larviciding			
Habitats exceeding 1km² 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 <1km² 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 (I2 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) (31). 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 *(32)*. In GRADE assessment, the point estimate of 0.07 is considered moderate certainty of evidence.

A4.5. 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 certainty 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 Guidelines Development Group recognizes that there are specific settings in which the intervention is currently implemented, and in these specific settings programme staff consider it to be effective. In some of the settings where larvivorous fish are being deployed, programmatic evidence exists; however, this was not determined appropriate for inclusion in the systematic review due to unsuitable study design or other concerns. The Guidelines Development Group acknowledges that there may be data at country/programme level that it is not aware of.

Remarks

Implementation considerations

- There is evidence that this intervention would require mosquito aquatic habitats to be 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 sampling) should be conducted in areas where programmes include larvivorous fish in order to generate an evidence base

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 conducted in Comoros *(34)*; Ethiopia *(35)*; India *(36–38)*; Indonesia *(39)*; Kenya *(40,41)*; Sri Lanka *(42,43)*; Sudan *(44)*; Republic of Korea *(45,46)*; and Tajikistan *(47,48)*.

Source: Walshe DP, Garner P, Abdel-Hameed Adeel AA, Pyke GH, Burkot T. Larvivorous fish for preventing malaria transmission. Cochrane Database Syst Rev. 2017;12:CD008090. doi:10.1002/14651858.CD008090.pub3, 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)	Certainty 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 (*36,38,40,45–48*). For (*48*), 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 (*36,38*), ponds in Kenya (*40*), and rice fields in Republic of Korea

(*45,46*) and Tajikistan (*47,48*). The longest follow-up was in India and still showed benefit at 12 months (*36*). In one study from India (*38*), the duration of effect seemed to be influenced by the number of fish introduced. For (*48*), 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 (*36, 38, 40, 45–48*).

[6] Downgraded by 1 for inconsistency: Effects were variable. Large effects were observed in water canals in Sudan (*44*), but only until 9 months post-intervention. Effects on immature vector populations in Central Java were dependent on vector species (*39*). 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) (*41*).

[7] No serious indirectness: These three studies introduced larvivorous fish into ponds in Kenya (*41*), ponds in Sudan (*44*) and rice fields in Central Java (*39*). 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 (*42*). 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) (*43*).

[9] No serious indirectness: Two studies introduced larvivorous fish into river bed pools below dams in Sri Lanka (*42,43*). 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 (*35*). 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 (*34,37*).

[12] No serious indirectness: These two studies introduced larvivorous fish into household water sources in Comoros (*34*) and India (*37*). The longest follow-up was in Grande Comore Island (*34*) and still showed benefit at 1 year post-intervention.

A4.6. 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 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 certainty 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 its deployment.

Remarks

Implementation considerations

- Specialist technical equipment required

Research priorities

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

No GRADE table produced, as no suitable studies identified

Should insecticide space spraying versus no insecticide space spraying be deployed for preventing malaria transmission?						
Population: People at risk of malaria						
Intervention: Insecticide space spraying						
Comparison: No insecticide space spraying						
Setting: Studies were conducted in El Salvador *(49)*; Haiti *(50)*; India *(51)*; and Malaysia *(52)*.						
Source: Pryce J, Choi L, Malone D. Insecticide space spraying for preventing malaria transmission (Protocol). Cochrane Databae Syst Rev. 2017;6:CD012689. doi:10.1002/14651858.CD012689						
Outcome	**Illustrative comparative risks (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of evidence (GRADE)**	**Importance of the outcome to decision-making**
	Assumed risk	**Corresponding risk**				

A4.7a Do topical repellents reduce malaria?

Recommendation

Deployment 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..

Strength of recommendation

For Intervention		No Recommendation	Against Intervention	
Strong	Conditional		Conditional	Strong
			CONDITIONAL	

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

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

Population: People at risk of malaria

Intervention: Topical repellent

Comparison: No repellent

Setting: Studies were conducted in Bolivia *(53)*; Cambodia *(54)*; Lao People's Democratic Republic *(55)*; Pakistan *(56)*; Thailand *(57)*; and United Republic of Tanzania *(58)*.

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)	Certainty 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: One study used alternate allocation and reported a baseline imbalance (*58*); random sequence generation and allocation concealment were not described for two studies (*54,56*); one study did not have a placebo so the intervention was not blinded (*54*).

[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: One used alternate allocation and reported a baseline imbalance (*53*); random sequence generation and allocation concealment were not described for two studies (*54,57*).
[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 for two studies (*54,56*). One study was not placebo-controlled and the intervention was not blinded (*54*).
[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 for two studies (*54,57*).

A4.7b Does insecticide treated clothing reduce malaria?

Recommendation

Deployment of insecticide-treated clothing for malaria prevention is not currently recommended as a public health intervention. Such 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 certainty 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 certainty 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

Does insecticide-treated clothing provide protection against malaria?

Population: People at risk of malaria

Intervention: Insecticide-treated clothing

Comparison: Placebo or no treatment

Setting: Studies were conducted in Colombia *(59)*; and Pakistan *(60)*.

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)	Certainty of evidence (GRADE)
	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: one study did not describe how randomization and allocation concealment were assured (59); one study did not describe the method used for allocation concealment (*60*).

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

A4.7c Do spatial/airborne repellents reduce malaria?

Recommendation

No recommendation on the deployment 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 certainty 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. It is therefore unknown whether spatial/airborne repellents protect against malaria parasitaemia.

Remarks

Research priorities

- Investigation 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

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: Studies were conducted in China *(61)*; and Indonesia *(62)*.

Source: Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ. Mosquito repellents for malaria prevention (Protocol). CochraneDatabase Syst Rev. 2015;4:CD011595. doi:10.1002/14651858.CD011595.

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty 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: one study was not blinded (*61*).

[2] Downgraded by 1 for imprecision: one study 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 (*61*).

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

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Annex 5. Principal malaria vectors and key ecology and behaviours, by WHO region

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
WHO African Region							
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	
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?
Forest, Guinea savanna, Sudan savanna, Sahel	*An. coluzzii*	Favours more permanent larval habitats than *An. gambiae s.s.* e.g. agricultural irrigation schemes and margins of small artificial lakes					Formerly described as molecular form 'M' of *An. gambiae s.s.*
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
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 s.s.*	Predominantly indoors	Member of Funestus Subgroup

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
Forest and savanna	*An. nili*	Streams among debris and floating vegetation, swamps	Predominantly anthropophilic	Largely outdoors	00:00 to 01:00	Predominantly outdoors	
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	
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	
WHO Region of the Americas							
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)	
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	
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	
Above 600m	*An. braziliensis*						
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

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
	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			
Lowland species, associated with wetlands, secondary forests and human intervention	*An. marajoara*	Sunlit and clear or muddy water, incl. gold diggings	Zoophilic and anthropophilic	Indoors and outdoors	Evening peak	Exclusively exophilic(?)	Member of Albitarsis Complex
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	
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	
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)

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
WHO Eastern Mediterranean Region							
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 s.s.*	More exophagic than *An. gambiae s.s.*	Early evening and early morning	Predominantly outdoors	Very variable behaviours
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
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	
Mountain fringe Iran	*An. d'thali*						
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	
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
Foothills	*An. maculipennis s.s.*						
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

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
Alluvial plains	*An. pharoensis*	Clear, stagnant, shallow water with thick vegetation. Shade essential. Drains, irrigation channels, seepages, pools, borrow pits, especially rice fields	Zoophilic and anthropophilic	Predominantly outdoors (animal shelters)	Peak biting in first 3h after sunset. 2nd peak just before dawn	Predominantly outdoors	Principal vector in Delta and Nile valley of Egypt
Savanna, plains and valleys of Iraq and Afghanistan	*An. pulcherrimus*	Warm, sunny, stagnant habitats with abundant submerged vegetation, rice fields	Zoophilic and anthropophilic				
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
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	
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	
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

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
WHO European Region							
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
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
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				
Savanna, plains in Georgia	*An. melanoon*	Fresh water, incl. rice fields (N Italy) and marshes and swamps (Spain)	Predominantly zoophilic				
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
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
Western Europe	*An. subalpinus*	Fresh or slightly saline water, swamps or ponds, rivers, rice fields	Predominantly zoophilic	Predominantly outdoors			

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
WHO Regions of South-East Asia and Western Pacific							
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
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
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
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
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)

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
Forest and forest fringe, plantations; mountain fringe	*An. cracens*		Anthropophilic and zoophilic (monkeys)	Outdoors	20:00–21:00		
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
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
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		
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

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
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
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
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
Mountain fringe	*An. harrisoni*						
Forest and forest fringe, plantations	*An. introlatus*						
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

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
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
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
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		
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
Mountain fringe	*An. maculatus s.l.*	Clean water often exposed to direct sunlight, 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	Predominantly zoophilic	Indoors and outdoors	18:00–21:00		Member of Maculatus Subgroup
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

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
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
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	
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
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

Ecological zone	Vector species	Aquatic habitats	Biting behaviour			Resting behaviour	Remarks
			Anthropophily / Zoophily	Exophagy / Endophagy	Peak biting time(s)	Exophily / Endophily	
Savanna, plains and valleys; Urban (Goa)	*An. subpictus*	sp. B coastal, brackish water. spp. A,C,D 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
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	
Coastal (Indo-Malay region)	*An. sundaicus*	Sunlit habitats containing pooled stagnant water, algae and non-invasive vegetation; 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	Predominantly anthropophilic	Indoors and outdoors	20:00–03:00	Indoors and outdoors	Sundaicus Complex. 4 species
Savanna, plains and valleys, incl. rice fields DPRK and Rep. of Korea	*An. yatsushiroensis*						

Note: Blanks indicate where no information was found

Sources for Annex 5

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