Vector control is an essential component of malaria prevention and control. WHO promotes universal coverage of effective vector control for all at-risk populations. WHO recommends specific vector control interventions primarily based on evidence of their protective efficacy against infection and/or disease in humans (i.e., their epidemiological efficacy).

The WHO Global Malaria Programme is responsible for developing policy recommendations for malaria vector control,1 while considering the broader context of malaria control or elimination programmes. A policy recommendation is a position statement or recommendation issued by WHO. The most recent WHO recommendation takes precedence over any previously issued recommendations.

This information note was developed to outline the key principles of the revised evaluation process for vector control products and to clarify which malaria vector control interventions currently have a WHO policy recommendation. It also defines the applicability of these policy recommendations to vector control products that: a) have previously been evaluated and received a recommendation under the WHO Pesticide Evaluation Scheme (WHOPES); b) are currently under evaluation by WHOPES; or c) will be submitted for evaluation by WHO through the revised process.

**TERMS EXPLAINED**

**Biochemical mode of action**

A biochemical mode of action describes the manner in which pesticides interfere with the biochemistry of animals and plants.
Entomological effect
Entomological effect refers to a product’s effect on a disease vector in terms of killing, deterring, and reducing fertility or susceptibility to infection. Products with different biochemical modes of action may have similar entomological effects on target insects; for example, indoor residual spraying (IRS) formulations with pyrethroids and carbamates differ in their biochemical modes of action, yet are considered to have a similar impact on the target insect in areas of insecticide susceptibility.

Non-inferiority
A vector product under evaluation shows non-inferiority when it demonstrates an equal or better entomological effect and/or protective efficacy against infection and/or disease in humans in reference to a comparator product in a similar epidemiological setting.2

Product class
A product class in vector control is a group of products that share a common entomological effect by which it reduces pathogen transmission and thus reduces infection and/or disease in humans. For products in a class not currently recommended by WHO, efficacy trials with a ‘first in class’ product must generate epidemiological evidence of protective efficacy against infection and/or disease. The evidence is then reviewed by the Vector Control Advisory Group (VCAG) to validate the public health value of the product class. This validation forms the basis of a WHO policy recommendation for the new product class. A product class may contain one or more target product profiles (TPPs) depending on the intended effect of the product(s) and claim(s).

First in class
First in class refers to the first product with a novel entomological effect (e.g., reducing human–vector contact, or decreasing vector survivorship, biting rates or susceptibility to infection or transmission), the public health value of which is ascertained by VCAG based on the demonstration of its entomological and epidemiological efficacy against vectors and human infections and/or disease, respectively. Once the public health value of a ‘first in class’ product is ascertained, a new product class is established.

Product claim
A product claim is information contained in the product’s label and advertisement materials. For vector control products, this includes the product’s chemical content; target arthropod vector; entomological effect in controlling target vectors or protecting against infection and/or disease; duration of effect; and role in mitigating insecticide resistance.

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.

Target product profile
A target product profile (TPP) is a detailed technical description that defines the preferred characteristics of a product and guides the development process to demonstrate its performance. A product class may contain one or more TPPs depending on the intended effect of the product(s) and claim(s).
OVERVIEW OF THE REVISED EVALUATION PROCESS

From January 2017, a WHO Pre-submission Coordination Committee (PCC) will review product developers’ submissions to WHO for the evaluation of vector control products. The PCC will decide which of two possible evaluation pathways the submission will follow, based on whether or not there is an applicable WHO policy recommendation.

If the PCC categorizes a product as belonging to a class with a product claim (or claims) for which a WHO policy recommendation has been issued, the submission will be assessed by the WHO Prequalification Team (PQT). For these interventions, entomological indicators will need to be measured in order to confirm that the product under assessment is non-inferior to the ‘first in class’ product or another suitable comparator. Work to further define the data requirements and methods for assessing non-inferiority is ongoing. Once all requirements for prequalification have been met, the product will be considered WHO prequalified and will be listed as such.

If the PCC categorizes a product as belonging to a class and/or having a product claim (or claims) for which there is no applicable WHO policy recommendation, the submission will be referred to the Vector Control Advisory Group (VCAG). These products will be assessed for their potential public health value. In addition to entomological data, this process will require epidemiological data on the product’s protective efficacy against infection and/or disease. If there is insufficient evidence, VCAG will advise the product developer on the data required and on appropriate trial designs with which to generate the evidence needed to ascertain the product’s public health value. As data are acquired, VCAG will review the public health value of the product in an iterative manner and provide regular progress updates to the Malaria Policy Advisory Committee (MPAC). MPAC will provide a recommendation to WHO based on the available evidence for the product class or claim.

Once the product’s public health value has been ascertained by VCAG and endorsed by MPAC, WHO will formulate the requisite policy recommendation and operational guidance, and the product will be deemed “first in class” (having a unique product claim). After a policy recommendation has been issued, subsequent products in this class will be eligible to be considered for WHO prequalification. Once all requirements for prequalification have been met, the product will be considered WHO prequalified and will be listed as such.

During the transition to the revised WHO evaluation process, all products with a WHOPES recommendation (interim or full) will be given a time-limited WHO prequalification and will be listed accordingly. To ensure clarity on each product’s status during transition, the time-limited listing will specify the product’s suitability with respect to the eligibility criteria, the claims for which it has been assessed, whether additional data are required for further product evaluation, and the timeframe for the product developer to provide these data. If data requirements are not met within the specified timeframe, the product will be delisted.

WHO will publish further details on the revised evaluation process in a separate document. This information note on WHO malaria vector control policy recommendations will be updated as needed, as further experience of the revised WHO process for evaluation of vector control products is gained.
WHO POLICY RECOMMENDATIONS FOR MALARIA VECTOR CONTROL

The specific vector control interventions recommended by WHO are categorized as either core or supplementary interventions. Below is an overview of the applicability of current policy recommendations to different interventions and products.

CORE INTERVENTIONS

Core interventions for malaria vector control are those interventions that are recommended for populations at risk of malaria in most epidemiological and ecological scenarios. The present WHO recommended core interventions are:

- insecticide-treated nets (ITNs), which in most settings are long-lasting insecticidal nets (LLINs);4
- indoor residual spraying (IRS) with a WHO recommended insecticide.

Universal coverage with effective vector control is defined as having at least 80% of the population at risk of malaria with access to at least one of these measures.

Insecticide-treated nets

The current WHO policy recommendation for ITNs/LLINs applies only to those mosquito nets that have a WHOPES recommendation and that contain only an insecticide of the pyrethroid class (called “pyrethroid-only LLINs”) (1). This policy recommendation does not apply to LLINs that contain another class of insecticide, either alone or in addition to a pyrethroid insecticide, nor does it apply to LLINs with a pyrethroid plus a synergist.7 For LLINs that have no policy recommendation, WHO will determine the data requirements for assessing their public health value based on technical advice from VCAG.

Due to the complexity of how LLINs provide personal and community-level protection, entomological outcomes are currently not considered to be reliable indicators of epidemiological impact, especially in areas of pyrethroid resistance. Due to the uncertainties associated with assessing public health value based on entomological endpoints, WHO currently requires epidemiological data for the assessment of LLINs with mixtures of active ingredients, synergists or non-pyrethroid insecticides only. Therefore, any LLIN products that are not pyrethroid-only LLINs will not be eligible for PQT assessment until a policy recommendation has been formulated on the basis of epidemiological data that demonstrate their public health value. The correlation between entomological and epidemiological outcomes will be further studied as part of ongoing epidemiological trials in order to determine whether entomological endpoints are reliable surrogates for epidemiological outcomes. If such a relationship can be demonstrated, WHO will review its current data requirements for the evaluation of LLINs.

In 2015, WHO reviewed data on the effectiveness of LLINs that contain a pyrethroid and the synergist piperonyl butoxide (PBO) (called “PBO nets”) in order to determine their public health value. Based on this review, WHO recommended pilot exploratory implementation of PBO nets accompanied by robust evaluation that includes the generation of epidemiological data (2). In June 2017, WHO will review new data from a study designed to address this request, based largely on the epidemiological impact of these nets.
Indoor residual spraying

The current WHO policy recommendation for IRS pertains to the spraying of an insecticide formulation that has a WHOPES recommendation. These formulations contain only one insecticide belonging to one of four classes: pyrethroids, carbamates, organophosphates (OP) or organochlorines (3). This recommendation will be extended to IRS products containing other insecticide classes with similar entomological effect if they are shown to be non-inferior to existing IRS formulations in terms of their entomological indicators. This extension of the current WHO policy recommendation is based on the fact that IRS aims to kill mosquitoes resting on indoor walls or ceilings; therefore, an equal or better killing effect is assumed to translate into similar protection against infection and/or disease. However, epidemiological studies to confirm this assumption are encouraged, and WHO is in the process of preparing guidance on the design of such studies.

Products with an entomological effect that differs from that of existing IRS formulations (e.g., non-neurotoxic compounds or insect growth regulator (IGR)) will be considered a new class of IRS and, therefore, epidemiological data for the assessment of their potential public health value will be required. WHO will determine the data requirements for assessing the public health value of a new class of IRS based on technical advice from VCAG.

SUPPLEMENTARY INTERVENTIONS

In specific settings and circumstances, the core interventions of ITNs/LLINs and IRS can be supplemented using larval source management (LSM), including habitat modification, habitat manipulation, larviciding, and biological control.

The current WHO policy recommendation for LSM applies to larvicides with an insecticide formulation that has a WHOPES recommendation and to larvicidal devices. Approved larvicide formulations contain either an OP, an IGR, a benzoylurea, a spinosyn or a juvenile hormone mimic, or contain one or two bacterial larvicide compounds (4). This recommendation does not currently apply to formulations that contain a different insecticide class or more than one insecticide class. Such products will not be eligible for WHO prequalification until a policy recommendation has been formulated on the basis of sufficient data demonstrating their public health value. WHO will determine the data requirements for assessing their public health value based on technical advice from VCAG.

It is recognized that some intervention types for which there is a WHO policy recommendation may not necessarily have an associated vector control product that requires evaluation by WHO (e.g., larval habitat modification or manipulation).

Currently, neither space spraying nor aerial spraying has a WHO policy recommendation for use in malaria vector control.

PERSONAL PROTECTION MEASURES

For personal protection with topical repellents, WHO currently recommends three active ingredients8 for personal use only. Skin-applied repellents that provide personal protection are eligible for prequalification.
Other personal protection measures, such as spatial repellents or use of protective clothing, are currently not covered by a WHO policy recommendation for malaria prevention.

**OTHER INTERVENTIONS**

New vector control products submitted to WHO that do not align with an existing policy recommendation (as defined above) will be assessed for their public health value and a policy recommendation developed for those product classes. WHO will determine the data requirements for assessing their public health value based on technical advice from VCAG.

**Endnotes**

1. With the support of the Vector Control Technical Expert Group and/or the Malaria Policy Advisory Committee

2. This relies on a measurement of effect whereby the difference should be only a small amount, called delta. Delta is pre-specified based on the desired epidemiological (or entomological) effect. Specifying a smaller delta for a non-inferiority trial can test whether a new product’s performance is similar to that of a comparator product (i.e., effect is <delta), but demonstrating statistical significance may require larger sample sizes. WHO is currently developing detailed guidance on the data requirements and methods for assessing non-inferiority.

3. ITNs are mosquito nets that repel, disable or kill mosquitoes that come into contact with the insecticide on the netting material. The two categories of insecticide-treated nets are conventionally treated nets and long-lasting insecticidal nets.

4. LLINs are factory-treated mosquito nets made of a material that has insecticide incorporated into or bound around its fibres. Nets must retain their effective biological activity for at least 20 WHO standard washes under laboratory conditions and 3 years of recommended use under field conditions.

5. IRS is an operational procedure and strategy for malaria vector control that involves spraying interior surfaces of dwellings with a residual insecticide in order to kill or repel endophilic mosquitoes.

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

7. A synergist is a compound that enhances the toxicity of some insecticides to insects, but itself has limited toxicity.

8. These ingredients are DEET (diethyltoluamide), IR 3535 (3-[N-butyl-N-acetyl]aminopropionic acid ethyl-ester) and KBR3023 (also called Icaridin or Picaridin).
Figure 1. Overview of intervention types and product classes for malaria vector control products, including a) applicability of WHO policy recommendations and b) related assessment pathways under the revised WHO evaluation process.

**Interventions**
- **Insecticide-treated nets**
  - Pyrethroid-only nets: Covered by existing policy, Eligible for PQT assessment
  - Pyrethroid plus synergist nets: Covered by existing policy, Eligible for PQT assessment, To be reviewed by ERG in June 2017
  - Non-pyrethroid insecticide nets: Not covered by existing policy, To be assessed by VCAG
  - Nets containing IGR or sterilizing agent/s: Not covered by existing policy, To be assessed by VCAG
  - Slow-acting insecticide formulations: Not covered by existing policy, To be assessed by VCAG
- **Indoor residual sprays**
  - OP, organochlorine, carbamate or pyrethroid formulations: Covered by existing policy, Eligible for PQT assessment
- **Larvicides**
  - OP, IGR, benzoylurea, spinosyn, juvenile hormone mimic, or containing one or two bacterial compounds, & larvicidal devices: Covered by existing policy, Eligible for PQT assessment
  - Larvicide not meeting above classification: Not covered by existing policy, To be assessed by VCAG
- **Products providing personal protection**
  - Topical repellents for personal protection: Covered by existing policy, Eligible for PQT assessment
  - Product designed for personal protection not meeting above classification: Not covered by existing policy, To be assessed by VCAG

REFERENCES


