Indoor residual surface treatments for malaria transmission control in areas with insecticide-resistant mosquito populations

Preferred product characteristics

World Health Organization

OVERVIEW

The *Global technical strategy for malaria 2016–2030* (GTS) aims to harness and expand research to accelerate progress towards the elimination of malaria and to counteract the emerging threats of drug and insecticide resistance *(1)*. It encourages innovation and the development of new tools, technologies and strategies (collectively referred to as "interventions") to maintain progress in malaria control and to further advance towards elimination. To accelerate implementation of the GTS, the World Health Organization's (WHO) Global Malaria Programme conducted a review of its guidelines and guidance development processes to ensure transparency, consistency, efficiency and predictability. One of the outcomes of the review was the adoption of "preferred product characteristics" (PPCs) to incentivize and guide the development of urgently needed health products. The use of PPCs is aligned with an organization-wide effort to improve WHO's communication on identified public health needs and to encourage and facilitate innovation to meet those needs.

WHO PPCs aim to:

- communicate unmet public health needs;
- stimulate the development of relevant new products to meet those needs; and
- facilitate the timely, effective assessment of new products, and the formulation of WHO recommendations and prequalification listings.

Within the Global Malaria Programme, the Vector Control & Insecticide Resistance Unit is developing a series of PPCs to encourage further innovation in vector control. The development process starts with the drafting of a PPC designed to address unmet public health priorities. These priorities are identified through WHO's horizon scanning process and through WHO's work on identifying, monitoring and mitigating threats to malaria control. A draft PPC is then reviewed by the Vector Control Advisory Group (VCAG), updated based on the group's inputs and posted online for public consultation. Feedback from the consultation is incorporated where feasible into a near final draft, which is again reviewed by VCAG before being finalized. As part of routine WHO procedures all VCAG members provide conflict of interest statements (COI) that are assessed by WHO. No COIs were obtained as part of the public consultation. Given ongoing and anticipated developments in malaria vector control, PPC documents are dynamic and will be updated as new information indicates the need to make changes to the parameters and characteristics and/or to the identified public health need itself.

The PPC published here describes the characteristics of new products for indoor residual surface treatment (IRST), including indoor residual spraying (IRS), designed to control malaria transmission in areas with insecticide-resistant mosquito populations. The document was developed to address the public health need caused by the evolution and spread of insecticide resistance in anopheline mosquitoes. Insecticide resistance is one of the identified threats to the effectiveness of the current interventions for malaria vector control, including IRS and other insecticide use patterns related to it *(1)*.

TERMINOLOGY

Preferred product characteristics (PPCs) are designed to communicate unmet public health needs identified by WHO, stimulate innovation and investment in the identified areas, and communicate the desired performance and operational characteristics of health products to address those needs. The target audience consists of product developers, regulatory agencies, procurement agencies, and funders of research and development and public health priorities. PPCs accommodate a number of target product profiles (TPPs) and should reflect the ideal characteristics required to rapidly and effectively achieve global health impact.

Target product profiles (TPPs) are generally planning tools used by manufacturers to guide the development of specific products. TPPs provide much more detailed information than PPCs and include both the minimum acceptable and preferred performance characteristics. The minimum performance characteristics should be considered a "go/no-go" decision point in the product development process.

INDOOR RESIDUAL SURFACE TREATMENTS FOR MALARIA TRANSMISSION CONTROL IN AREAS WITH INSECTICIDE-RESISTANT MOSQUITO POPULATIONS

Background and purpose

The WHO categorization of existing and potential new vector control interventions is evolving from using the term "indoor residual spraying" (IRS) for the intervention class to using the term "indoor residual surface treatment" (IRST). The latter term captures the current use pattern of IRS for malaria vector control and conceptually allows for the inclusion of other delivery approaches, such as insecticidal paints or wall linings, or for the partial or selective treatment of walls. While no insecticidal paint or wall lining products have been prequalified by WHO to date, and partial wall treatment has not been comprehensively evaluated in terms of its epidemiological impact compared to full spraying/covering of all walls (and ceiling), evolution of the current WHO recommendation for IRS to a broader one for IRST is envisaged, provided that new evidence presented to WHO supports such broadening of the intervention class.

IRS for malaria vector control is currently covered by a strong recommendation based on low-certainty evidence *(2)*. It is one of two malaria vector control interventions recommended for large-scale deployment, the other being insecticide-treated nets (ITNs). WHO's recommendation for IRS is largely based on historical and programme data; a systematic review of the evidence on the disease-control impact of this intervention was unable to quantify the effect size of this intervention in different transmission settings and encouraged further trials to strengthen the evidence base *(3)*. Now that additional evidence in this area has been generated (e.g. *(4)*), a new systematic review covering IRST, as well as partial and outdoor residual surface application of insecticides has been commissioned by WHO with a view to: i) informing a revisit and potential broadening of the existing WHO recommendation for IRS to IRST, ii) informing the potential formulation of new recommendations covering outdoor residual surface treatments, and iii) outlining evidence gaps in this area.

Five chemical classes of insecticides are currently covered by the WHO recommendation for IRS, namely carbamates, neonicotinoids, organophosphates, pyrethroids and, as an option of last resort, the organochlorine DDT. DDT should only be used in full compliance with the Stockholm Convention on Persistent Pollutants *(2)*. WHO-prequalified IRS products are available for the above-mentioned insecticide classes, except for DDT.

In line with the evolution of WHO terminology, two provisional IRST classes have been developed for malaria vector control: one for fast-acting and the other for slow-acting insecticidal products. Based on current WHO test procedures for IRS, fast-acting has been defined as mosquito mortality ≥ 80% after a 24-hour holding period, following 30 minutes' exposure on a treated substrate in cone bioassays *(5)*. For slow-acting products, at least 80% mosquito mortality, corrected for control mortality, would need to be achieved in the period up to 10 days after insecticide exposure to ensure that, under field conditions, uninfected mosquitoes that pick up malaria parasites during blood-feeding die before they become infectious. In this context, it should be noted that cone bioassays may not necessarily be predictive of the effect of insecticides on free-flying mosquitoes. It may therefore be necessary to review and revise the grouping of products into fast- or slow-acting categories based on data from these assays once an ongoing comprehensive review of WHO testing guidelines has been completed.

Regarding epidemiological impact, the public health value of fast-acting IRS has been confirmed and a WHO recommendation is in place *(2)*. This recommendation will be extended to other application methods under the broadened class of IRST, provided that products such as paints or wall linings are shown to be non-inferior to IRS in terms of entomological end-points. To date, the public health value of slow-acting IRS/IRST has not been confirmed, nor is a WHO recommendation in place.

This PPC document was developed to stimulate further innovation in the area of IRST by articulating that WHO has identified a public health need for new interventions to treat indoor surfaces in order to provide additional options for the control of indoor biting/resting malaria vectors with a particular focus on providing alternatives for insecticide resistance management. If partial or selective wall treatments were proven to be equally effective as conventional full surface IRS, it could also yield considerable cost savings. The identified public health need has arisen due to the evolution and spread of resistance in mosquito vectors to insecticides in most of the insecticide classes currently used for IRS. Insecticide resistance now poses a significant threat to the continued effectiveness of insecticide-based interventions for malaria vector control *(6)*. It is thus essential to develop new vector control interventions, including IRST products, designed to be effective against mosquito populations resistant to insecticides. Such interventions would provide options for insecticide resistance management and contribute to meeting the GTS milestones and goals *(1)*.

The PPCs outlined below reflect aspects of IRST that are thought to be key to the effectiveness of this approach. To a large extent, these are based on existing experience with IRS because the intervention approach of applying a substance to the indoor walls of a permanent structure remains the same. Whether the substance is delivered by spray or by other means is not relevant in this context.

Parameter	Preferred product characteristic
Indication	
	• Reduces or prevents malaria infection and/or disease caused by *Plasmodium* parasites in humans • Uses any mechanism to reduce vectorial capacity so as to provide community protection to individuals o Prevention of biting (human–vector contact) in addition to effects that reduce mosquito longevity or fertility is considered an added advantage.
Target population – human	
	• Populations at risk of malaria
Target population – disease vector	

	• *Anopheles* mosquitoes, including strains resistant to insecticides in current use (pyrethroids, organophosphates, carbamates, neonicotinoids and organochlorines)
	  o Resistance mechanisms to be overcome in *Anopheles* include target-site (Kdr, AChE, RDL, nAChR) and metabolic (monooxygenases, esterases, glutathione *S*-transferases) mechanisms.
	  o The priority at the time of PPC publication is for products that effectively control pyrethroid- and/or organophosphate-resistant mosquito populations, but this is expected to evolve with the increasing deployment of neonicotinoids and other insecticides presently undergoing WHO evaluation.
	• Control of other arthropod vectors and/or nuisance-biting arthropods is considered an added advantage.

Epidemiological efficacy	
	• Protective efficacy to reduce and/or prevent malaria infection and/or disease in humans in areas where the primary vector(s) is/are resistant to insecticides o A systematic review on IRS updated in 2019 was unable to quantify the effect size for this intervention due to a lack of data and due to