Global **Malaria** Programme

Insecticide-treated nets 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 threat of drug and insecticide resistance. It encourages innovation and the development of new tools and strategies to maintain progress in malaria control and advance towards elimination. To accelerate implementation of the GTS, in 2018, the World Health Organization's (WHO) Global Malaria Programme (GMP) reviewed its policy-making process to ensure that it is transparent, consistent, efficient and predictable. One of the outcomes of the review was the adoption of "preferred product characteristics" (PPCs) as a key tool to incentivize and guide the development of urgently needed health products. The use of PPCs is aligned with an organization-wide effort to improve communication about public health needs and to 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 policy recommendations and prequalification listings.

Within GMP, the Vector Control & Insecticide Resistance Unit is developing a series of PPCs to encourage further innovation in vector control. The PPC published here describes the characteristics of new types of insecticide-treated nets (ITNs) 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, particularly to pyrethroids. Such resistance threatens the effectiveness of the current standard of malaria vector control in many countries, namely pyrethroid-only long-lasting insecticidal nets (LLINs).

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. PPCs accommodate a number of target product profiles (TPPs).

Target product profiles (TPPs) are planning tools used by manufacturers to guide the development of specific products. TPPs generally provide much more detailed information than PPCs, such as intended use, target populations, and safety and efficacy-related characteristics. They include both minimally acceptable and preferred performance characteristics. The minimum performance characteristics should be considered a "go/no-go" decision point in the product development process. The preferred product characteristics should reflect the ideal characteristics required to rapidly and effectively achieve a global health impact.

INSECTICIDE-TREATED NETS FOR MALARIA TRANSMISSION CONTROL IN AREAS WITH INSECTICIDE-RESISTANT MOSQUITO POPULATIONS

Background and purpose

ITNs are one of two malaria vector control interventions recommended for large-scale deployment by WHO, the other being indoor residual spraying. The current policy recommendation for ITNs is based on evidence of public health value that was generated through cluster randomized trials conducted between 1988 and 2013 (*1*). Most of these studies have shown that ITNs provide personal protection to people sleeping under the net, as well as protection to other community members who are not sleeping under a net. The latter has been termed a "community effect".

All ITNs covered by a WHO policy recommendation are treated with a pyrethroid insecticide (*2*). The evolution and spread of resistance to pyrethroids in mosquito populations has, however, been recognized as a significant threat to the continued effectiveness of ITNs. Development of new vector control interventions, including ITN products designed to be effective against mosquito populations resistant to insecticides (primarily pyrethroids), has been identified as a key public health need in order to provide options for insecticide resistance management and to contribute to meeting the milestones of the GTS *(3)*. In this context, "effectiveness" means that new ITNs should reduce or prevent malaria infection and/or disease in humans in settings with well-characterized insecticide-resistant mosquito vector populations.

In view of the challenges of maintaining the ITN coverage of at-risk populations over time *(4)*, new ITNs should have equal or greater durability and effectiveness compared to pyrethroid-only LLINs and also be acceptable to users. It is recognized, however, that the use of active ingredients other than pyrethroids may affect wash-fastness, excito-repellency and killing. The extent to which these characteristics affect the efficacy of ITNs in reducing or preventing malaria infection and/or disease in humans is being studied *(5,6)*. The field studies published to date indicate that new types of ITNs have differential performance and lose their competitive advantage well before the end of their physical lifespan *(7,8)*.

This PPC was developed to outline the current public health need for new types of ITNs and the preferred characteristics of products to address that need. To a certain extent, these characteristics reflect those of ITNs already being used against malaria, given the close similarities in the intervention approach. Based on WHO's horizon-scanning activities (https://www.who.int/research-observatory/monitoring/processes/health_interventions/en/), it is anticipated that product developers have developed/will develop TPPs to provide ITNs that are effective against pyrethroid-resistant *Anopheles* mosquito populations and that, at least in the short to medium term, products with such TPPs will fall into the second or third provisional ITN class endorsed by WHO's Malaria Policy Advisory Group in May 2020 *(9)*, which are listed below.

1. **ITNs designed to kill host-seeking insecticide-susceptible mosquito populations that have demonstrated public health value[1] compared to untreated nets and whose entomological effects consist of killing and**

1 An intervention is considered to be of public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans.

reducing the blood-feeding of insecticide-susceptible mosquito vectors: Existing prequalified pyrethroid-only nets. Policy recommendation in place.

2. **ITNs designed to kill host-seeking insecticide-resistant mosquitoes and for which a first-in-class product has demonstrated public health value compared to the epidemiological impact of pyrethroid-only nets:** This class is provisionally thought to include both insecticide treatments with active ingredients other than pyrethroid-based formulations and nets with synergists. It includes pyrethroid-PBO nets that are currently covered under an interim WHO policy recommendation, pending results of trials to demonstrate public health benefits in at least two study sites. The class would be expanded to include pyrethroid + chlorfenapyr nets once their public health value has been demonstrated by means of at least two geographically separate epidemiological trials. The class would then be expanded to also include other products with the same entomological effect but with different chemical modes of action to pyrethroid-only nets without the need for further epidemiological trials.

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

It should be noted that implementation of the above classes requires the revision of ITN testing guidelines to facilitate a comprehensive evaluation of nets other than pyrethroid-only products, as well as the identification and closure of existing data gaps for new types of nets currently prequalified. Work in this area is being undertaken by the WHO Prequalification Team for Vector Control Products (https://extranet.who.int/pqweb/vector-control-products). Given these developments, this PPC document will be dynamic and will be updated as new data indicate the need to make changes to the parameters and characteristics and/or to the identified public health need itself.

Parameter	Preferred product characteristic
Indication	
	• Uses any mechanism expected to reduce vectorial capacity so as to provide community protection to individuals not covered by ITNs. • Prevention of biting on individuals under a net is considered an added advantage. • Reduces or prevents infection and/or disease caused by malaria in humans. • Suitable for use by all age groups, including women of child-bearing age, pregnant and lactating women, and children under 5 years of age.
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). Resistance mechanisms to be overcome include: target-site (Kdr, AChE, RDL) and metabolic (monooxygenases, esterases, glutathione *S*-transferases). The current priority is ITNs that effectively control pyrethroid-resistant mosquito populations. • Other arthropod vectors and the diseases they transmit and/or nuisance-biting arthropods are considered an added advantage.
Epidemiological efficacy	
	• Protective efficacy to reduce or prevent malaria infection and/or disease in humans in areas where the primary vector(s) is/are insecticide resistant (particular focus lies on areas of pyrethroid resistance). Efficacy should be equivalent to that of pyrethroid-only LLINs in areas of pyrethroid susceptibility. **Note:** Data from individual and cluster randomized controlled trials on pyrethroid-only nets demonstrate, overall, the saving of 5.6 lives (95% CI, 3.6 to 7.6) each year for every 1000 children protected. ITNs have also been shown to reduce the incidence of uncomplicated episodes of *Plasmodium falciparum* malaria by almost half (rate ratio, 0.55; 95% CI, 0.48 to 0.64; five trials, 35 551 participants, high-certainty evidence) and probably to reduce the incidence of episodes of uncomplicated *P. vivax* malaria.

Parameter	Preferred product characteristic
Entomological efficacy	
Knockdown/ mortality	• Treatment(s) with no or low excito-repellency and/or slower killing than pyrethroids should demonstrate high kill and/or sterilization of insecticide-resistant mosquito vector(s). The killing effect is required to occur during the extrinsic incubation period of the malaria parasite (i.e., < 10–14 days). • Rapid knockdown of *Anopheles* mosquitoes would be preferable in order to provide personal protection from being bitten, particularly when the nets start to deteriorate due to normal wear and tear, e.g., holes in the material. **Note:** Specific performance standards for these ITNs cannot be proposed until WHO has assessed data on epidemiological efficacy that support the public health value of ITNs treated with active ingredients other than pyrethroids and associated evaluations of entomological efficacy.
Sterilization/ fecundity reduction	• For interventions deploying an insecticide that reduces the fecundity of mosquitoes, it is thought that a high level (>90%) of sterilization of the host-seeking mosquito and/or a significant reduction in egg laying/hatching or larval development by the treatment(s) on the ITN is required. **Note:** Specific performance standards cannot be proposed for ITNs with active ingredients that reduce mosquito fecundity until WHO has assessed data on epidemiological efficacy that support the public health value of ITNs treated with active ingredients other than pyrethroids and associated evaluations of entomological efficacy.
Mode(s) of action	
	• Acts preferably on one or more target sites that differ from each other and from that of pyrethroids. **Note:** WHO will utilize the classification used by the Insecticide Resistance Action Committee specifically designed to clarify different modes of action (https://irac-online.org/modes-of-action/).
Access and affordability	
	• The intervention needs to be affordable so that its cost does not constitute