Endectocide and ectocide products for malaria transmission control

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 *(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 endectocide and ectocide products deployed with the aim of controlling malaria transmission. These products may be existing drugs that are repurposed for malaria control or new ones specifically developed for this purpose. In this context, endectocides are defined as drugs that kill both endoparasites, such as parasitic worms, and ectoparasites (including mosquitoes) that feed on treated hosts. To date, ivermectin has been the most studied example of an endectocide in the context of malaria vector control *(2)*; it was used as a prototype in the development of an earlier WHO PPC on endectocides *(3)*. There are a number of other potential options in this area that warrant closer investigation with respect to the essential and desired criteria for an effective transmission-reducing or transmission-blocking agent *(4,5)*. Some of the potential drugs, such as nitisinone, for which activity against tsetse flies and mosquitoes has been demonstrated in the laboratory in the presence of tyrosine *(6)*, do not kill endoparasites, but may provide mosquito control. These types of products will be referred to as ectocides throughout this document.

This and other PPC documents *(7,8)* have been developed to address the public health need for additional malaria vector control interventions to close current gaps, such as the lack of tools to control outdoor biting, and to provide options to manage the evolution and spread of resistance to insecticides currently used and deployed. This document is a revision and expansion of the PPC on endectocides published by WHO in June 2017 *(3)*. The update was conducted according to WHO's latest processes for PPC development to incorporate lessons learned since 2017, reflect on the latest research in the field, and ensure alignment in structure and content with other PPCs for malaria vector control, where such alignment is justified.

TERMINOLOGY

Area under the curve (AUC) is a term used in the field of pharmacokinetics to describe the region under a plotted line in a graph of drug concentrations in blood plasma over time. Typically, the area is calculated starting from the time the drug is administered to the time when the concentration in plasma is insignificant. The area under the curve represents the total exposure of the body to an active substance and helps to evaluate and compare bioavailability profiles between drugs. The time at which the highest concentration of the active substance is found in the blood is called **Tmax**, and the maximum and minimum concentrations of the active substance found in the blood stream are called **Cmax** and **Cmin**, respectively.

Ectoparasite: A parasite that lives and/or feeds on the outer surface of its host. Examples are fleas, mites, ticks and, in the present case, female *Anopheles* mosquitoes.

Endectocide: A drug that is effective against both endoparasites and ectoparasites

Endoparasites: A parasite that lives in the internal organs or tissues of its host. There are intercellular and intracellular forms of endoparasites. Intercellular parasites are those that inhabit the spaces of the body of the host, for example parasitic worms. Intracellular parasites are endoparasites that live within the cell of the host such as the protozoan *Plasmodium*.

Ectocide: A drug without established activity against endoparasites that is effective at killing haematophagous ectoparasites once they have ingested one or more blood meals from a treated host

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). The preferred product characteristics 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, such as intended use, target populations, and safety and efficacy-related characteristics. They include both minimum acceptable and preferred performance characteristics. The minimum performance characteristics should be considered a "go/no-go" decision point in the product development process.

ENDECTOCIDE AND ECTOCIDE PRODUCTS FOR MALARIA TRANSMISSION CONTROL

Background and purpose

The recognition that a drug originally shown to kill endo- and ectoparasites may provide a useful addition to the existing set of malaria vector control interventions is based on decades of research demonstrating effects on anopheline mosquitoes once they have fed on treated hosts. In vivo studies have shown that ivermectin kills *Anopheles* mosquitoes that ingest sufficient doses in a blood meal and also causes numerous sublethal effects *(9–13)*. These results have been confirmed in clinical studies using membrane *(14)* and direct-feeding *(15)* methodologies. Modelling based on estimates of survival impact documented in these studies indicates that mass drug administration (MDA) with ivermectin has the potential to reduce malaria transmission *(16,17)*. In vivo laboratory work has also shown impact on fitness and fertility, the potential to inhibit sporogony, effects on locomotor functions and an increase in time between blood feeds. Work on potential alternatives to ivermectin is at an earlier stage, but has generated some promising findings so far *(4–6)*.

This PPC was updated to acknowledge WHO's continued identification that endectocides for malaria vector control are an as yet unmet public health need, to update the preferred characteristics of such an intervention class where required, and to expand it to ectocides. Since the publication of the first WHO PPC on endectocides in 2017, the evaluation process for new vector control interventions has evolved, and a provisional intervention class to accommodate endectocides and ectocides has been created *(18)*. It is anticipated that product developers and researchers will draw on this information to develop a range of TPPs for products in this potential intervention class.

Parameter	Preferred product characteristic
Indication	
	• Drug concentration in the hosts' blood that is lethal to feeding mosquitoes or that causes other effects on the mosquito vector that lead to reduced malaria transmission • Reduction in transmission is provided at the population level, rather than at the individual level.
Potential use cases	
	• Mass drug administration (MDA) as standalone therapy • MDA deployed alongside other drug-based malaria interventions o Inclusion with seasonal malaria chemoprevention (SMC) regimens
Target population – human	
	• Populations at moderate to high risk of malaria (with subgroups depending on specific use cases) • The product should ideally be suitable for use by all age groups, including women of child-bearing age, pregnant and lactating women, and children under 5 years of age. • Most transmission occurs in children over the age of 5; this may be a preferred target population. Covering 6 months–15 years of age would, however, cover > 75% of the population contributing to transmission and may generate better impact *(19)*.

Parameter	Preferred product characteristic
Target population – disease vector	
	• *Anopheles* malaria vectors, including populations resistant to insecticides in current use • Control of other arthropod disease vectors, nuisance-biting arthropods and/or intestinal parasites is considered an added advantage.
Epidemiological efficacy	
	• Transmission reduction efficacy leading to at least 20% reduction in the incidence of clinical malaria at the population level
Entomological efficacy	
	• Ideally a single dose of a new (end)ectocide should provide efficacy in terms of increasing mosquito mortality by a hazard ratio that is equal to or greater than 4 throughout the 30-day post-treatment period. This means that a mosquito that has taken a human blood meal containing an endectocide/ectocide within a period of 30 days of the human having ingested the drug has a four times greater daily probability of dying compared to a mosquito that has not been exposed. • Rapid knockdown (≤ 1 hour) of *Anopheles* after ingestion of a blood meal from a treated host would be preferable, as would other sublethal effects such as reduced fitness, fertility and locomotor function, as well as longer intervals between feeding episodes and sporontocidal effects.
Dosage, schedule & formulation	
	• The repeatedly administered human dose (mcg/kg/day) that most closely achieves the desired area under the curve (AUC), or ideally, Cmin at day 30 needed for the efficacy target • Timed to ensure sustained high population coverage during the malaria transmission season • Oral tablet(s) or injection given once a month to provide at least 30 days of effective coverage is considered acceptable. Ideally, administration would consist of a single treatment (rather than doses delivered on the same or consecutive days) and would require re-treatment of the target population less frequently than once a month. • Single-dose administration of a slow-release formulation to sustain the mosquitocidal effect over the transmission season (efficacy for longer than three months) may be preferred, as it could facilitate programmatic delivery. Risk–benefit analysis will be required to evaluate longer residual efficacy against potential risk factors, such as the impact of a longer half-life drug on toxicity or development of vector or parasite resistance. • A paediatric formulation appropriate for use in children 5–15 kg is seen as an advantage, particularly when an oral formulation is used.
Access and affordability	
	• The intervention needs to be affordable; costs should not constitute a barrier to access, including in low- to middle-income countries. • The cost-effectiveness of the intervention should be similar to or better than that of the current standard of vector control in a specific setting.

Parameter	Preferred product characteristic
Feasibility	
Procurement	• Should be suitable for procurement through global donor mechanisms and by national programmes • Depending on the use case, the procurement of the product should allow for it to be tied to that of antimalarials for co-administration.
Distribution/ application	• Should be suitable for distribution through existing delivery channels, namely through the current WHO recommendations for MDA, including minimum requirements for dose determination in limited resource settings
Supervision	• Little to no additional training required for health care providers would be preferable.
Regulatory	
Safety – human health	• The end use product should not result in severe adverse events with a frequency of > 1:20 000. • The end use product should not cause lysis of endogenous parasites such as *Loa loa*. • The drug's deployment should be accompanied by a well-established and straightforward protocol (affordable in limited resource settings) for reporting, managing and responding to adverse events.
Safety – environmental effects, including disposal	• Use, disposal or degradation of the product should not pose an undue environmental hazard.
Drug–drug interactions	• No significant pharmacological and/or toxicological interaction(s) with antimalarials, antiretrovirals, TB drugs, anthelminthic and common over-the-counter drugs
Interactions with existing vector control interventions	• The endectocide/ectocide intervention should have no antagonistic effect on co-deployed existing vector control interventions. The mode of action should differ from that of public health insecticides used in the targeted communities. The endectocide/ectocide should not be affected by common field insecticide resistance mechanisms (e.g. cytochrome P450 overexpression).
Product quality	
Shelf life and storage	• For tablet formulations, the packaged product should remain stable for at least 36 months at 37 °C and 75% humidity. For packaged injectable formulations, the product should remain stable for at least 36 months under refrigerated conditions (from 2°C to 8 °C). • For tablet formulations, the packaged product should remain fully effective for up to 24 months of storage under field conditions; for packaged injectable formulations, the product should remain stable for at least three months under field conditions (i.e. > 30 °C, 75% humidity).
Packaging and presentation	• The product must be stable for safe transport and storage under the temperature and humidity conditions for the time periods described above.
End user suitability	
Community acceptability	• Preferably the product should be acceptable in all age groups including children 5–15 kg, women of reproductive age without a pregnancy test, and pregnant and lactating women.

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