Vector control products targeting outdoor malaria transmission

Preferred product characteristics

World Health Organization

OVERVIEW

The *Global technical strategy for malaria 2016–2030* (GTS) *(1)* seeks 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, technologies and strategies (collectively referred to as "interventions") to maintain progress in malaria control and to advance towards elimination. To accelerate implementation of the GTS, the World Health Organization's (WHO) Global Malaria Programme has reviewed 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 about 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 and Insecticide Resistance Unit is developing a series of PPCs to encourage further innovation in malaria vector control *(2-5)*. The 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 work to identify, monitor and mitigate threats to malaria control. A draft PPC is developed in consultation with subject matter experts in an ad hoc manner, then reviewed by the Vector Control Advisory Group, updated based on input from Vector Control Advisory Group members and posted online for public consultation. 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. Feedback from the consultation is incorporated where feasible into a near final draft, which is again reviewed by the Vector Control Advisory Group before being finalized. Given the 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.

TERMINOLOGY

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, including researchers, regulatory agencies, procurement agencies, and funders of research and development. PPCs are usually developed before a mature pipeline of products is available and should reflect the ideal characteristics of interventions required to rapidly and effectively achieve public health impact.

Target product profiles (TPPs) in the context of public health are used to set research and development targets for manufacturers and researchers to guide the development of specific products. TPPs provide more detailed information than PPCs and 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.

Outdoor malaria transmission is defined in the context of this PPC as malaria transmission that results from mosquitoes biting humans outside residential buildings or structures used to keep livestock. This includes peri-domestic spaces and open temporary shelters where indoor residual spraying (IRS) and insecticide-treated nets (ITNs) are not practical (e.g. farm huts and temporary shelters for migrant workers and displaced populations). It is opposed to transmission that results from mosquitoes biting human hosts inside a residential building, which is the most common location where ITNs and IRS are deployed and where these interventions primarily impact host-seeking mosquitoes.

BACKGROUND AND PURPOSE

Malaria vector control relies heavily on the distribution of ITNs and IRS, both of which target indoor biting and/or indoor resting vectors. High coverage of these interventions over the last decade has significantly contributed to reducing the burden of malaria. In turn, the wide-scale use of these interventions has also exerted considerable selection pressure on anopheline mosquitoes, leading to insecticide resistance, particularly to pyrethroids. In addition, malaria vectors are showing changes in behaviour in response to these indoor interventions. Changes in the time of biting and the proportion of indoor biting/resting vectors have been observed (e.g. *(6,7)*). In some settings, there have also been changes in mosquito species composition resulting from the effective control of those species that generally feed/rest indoors (e.g. *(8-10)*). Mosquito species that were historically secondary vectors due to their predominantly outdoor biting/resting behaviour have taken on the role of primary vectors. At least in some settings, outdoor biting now contributes considerably to "residual malaria transmission" *(11,12)*, which is defined as the persistence of malaria transmission following the implementation in time and space of a widely effective malaria control programme *(13)*. Innovation and development of optimized vector control interventions will be required to effectively deal with outdoor biting/resting vector populations in order to sustain current levels of control and further enhance impact *(14)*.

This PPC was developed to indicate that WHO has identified vector control products targeting outdoor malaria transmission as an unmet public health need and to outline the preferred characteristics of such interventions. While keeping the scope of the PPC as broad as possible, it is primarily tailored to encourage new insecticidal/repellent products. Endectocides/ectocides, as well as genetically modified mosquitoes, both of which could be considered to fall into the category of interventions targeting/contributing to the reduction of outdoor malaria transmission, are already covered by a separate PPC *(4)* or warrant the development of one.

A number of interventions with the potential to control mosquitoes outdoors, such as outdoor-deployed attractive targeted sugar baits and spatial repellents, have already been developed and are being evaluated for their epidemiological impact. The TPPs for these interventions were used as a basis to inform the content of this PPC, which is meant to encourage and guide further innovation in this area. A separate PPC for outdoor personal protection interventions may be developed in the future, once a review of topical and spatial repellents, and treated clothing *(14)* has been updated to reflect the current evidence base and to specifically investigate the potential impact of topical repellents at the individual level. It is anticipated that stakeholders in vector control will draw on the information provided here to develop additional TPPs for interventions to be deployed to control outdoor malaria transmission.

Parameter	Preferred product characteristic
Indication	
	• Reduction of malaria transmission outside residential buildings and/or structures housing livestock is provided at the population rather than individual level. • Reduction of malaria transmission through a mechanism that interferes with outdoor anopheline mosquito feeding and/or host seeking, noting that for some products this may also induce lethality, disarm and possibly reduce fecundity
Potential use cases	
	• As a supplementary or standalone intervention deployed at the community level in settings where malaria transmission continues, despite high coverage of ITNs or IRS, due to outdoor biting behaviour of key vector(s) and/or in areas where a portion of the human population works or conducts leisure activities outdoors during anopheline biting times • As a supplementary or standalone intervention deployed at the community level in settings where deployment of IRS or ITNs at high coverage faces challenges, such as in farm huts, temporary shelters for migrant workers and tented refugee camps
Target population – humans at risk	
	• Populations at risk of malaria
Target population – disease vectors	
	• *Anopheles* malaria vectors with documented outdoor infectious bites (as measured by assessing sporozoite rates), including populations resistant to insecticides in current use. • Control of other arthropod vectors and/or nuisance-biting arthropods is considered an added advantage.
Epidemiological efficacy	
	• Protective efficacy to reduce or prevent malaria infection and/or disease in humans, demonstrated using similar assessments and epidemiological end-points as those used for evaluating the efficacy of current WHO-recommended indoor interventions, unless other evaluation methods or end-points are well justified. Evaluation in settings where outdoor biting plays a substantial role in residual transmission is recommended
Entomological efficacy	
	• Protective efficacy to reduce or prevent anopheline mosquito biting outdoors through repellency and/or killing effects

Parameter	Preferred product characteristic
Access and affordability	
	• The intervention needs to be affordable so that its cost does not constitute a barrier to access, including in low- to middle-income countries. • The cost-effectiveness of the intervention should be no less than that of the current standard of vector control in a specific setting. Indicative cost-effectiveness figures for ITNs, IRS and larviciding interventions are provided elsewhere *(15)*.
Feasibility	
Procurement	• Should be suitable for procurement through global donor mechanisms and by national programmes
Distribution/ application	• Easy to deploy by operators, peripheral health or aid workers or by members of the community • Suitability for distribution with other public health tools
Supervision	• Minimal training required to ensure safe delivery, storage and installation of the intervention to guarantee efficient use
Regulatory	
Safety – human health	• The product should ideally be suitable for use near all age groups, including women of childbearing age, pregnant and lactating women, and children under 5 years of age. • The end-use product should not pose an unacceptable risk to operators, bystanders and users, as assessed by a regulatory agency or the WHO Prequalification Team for Vector Control Products. • Appropriate safety/toxicological information needs to be provided to enable WHO to develop a hazard assessment for the active ingredient(s) and a risk assessment for the final product. When available, WHO may use a hazard assessment by a stringent regulatory authority to inform its own assessment. • New active ingredient(s) should preferably be registered by a stringent regulatory authority
Safety – environmental effects, including disposal	• The application of the product, whether containing non-volatile or volatile ingredients, according to label instructions should not adversely impact the environment where deployed, as assessed by a regulatory agency or WHO. • Biodegradable products and containers/packaging would be preferred. • Pesticide-contaminated product containers and/or packaging should not be reusable to avoid potential human or environmental risks.
Drug–drug interactions	• Risks to non-target species, such as bees and butterflies, should be in accordance with required environmental and ecotoxicology standards at the time of submission for registration.
Interactions with existing vector control interventions	• The product should not negate the effects of co-deployed vector control interventions.

Parameter	Preferred product characteristic
Product quality	
Shelf life and storage	• The product must be stable, allowing for safe transport and long-term storage. • The product in its packaging should remain fully effective after storage for up to 36 months under field conditions (i.e. > 30°C, 75% humidity).
End user suitability	
Community acceptability	• Users should not be deterred from employing the intervention because of packaging design, application method, formulation (odour) and/or aesthetics. • Easy to adopt and use/maintain/replace by the target population, including minimal challenges associated with ensuring high compliance.

METHODS AND ACKNOWLEDGEMENTS

The PPC for Vector control products targeting outdoor malaria transmission was developed in accordance with the WHO target product profiles, preferred product characteristics, and target regimen profiles: standard procedures (unpublished document, available on request from the WHO Research for Health Department, 2022) and based on associated procedures applied for development of other PPCs in the area of malaria vector control. A first draft of the document was developed by staff of the Global Malaria Programme's Vector Control Unit, namely Jan Kolaczinski and Jennifer Stevenson. The initial draft drew on content from a TPP for attractive targeted sugar baits provided by Mathias Mondy (Innovative Vector Control Consortium, United Kingdom of Great Britain and Northern Ireland) and on a set of TPP and PPC documents for spatial repellents resulting from a NIH/NIAID workshop in 2020 provided by Nichole Ache (University of Notre Dame, United States of America). The resulting draft PPC was shared on two occasions with the WHO Vector Control Advisory Group (VCAG), with comments being provided by Heather Ferguson (University of Glasgow, Glasgow, United Kingdom) Audrey Lenhart (US Centers for Disease Control and Prevention, United States), Mamadou Coulibaly (University of Sciences, Techniques and Technologies of Bamako, Mali), Steven Bradbury (Iowa State University, United States), Neal Alexander (Centro Internacional de Entrenamiento e Investigaciones Médicas, Colombia), Bobby Reiner (University of Washington, United States), Camilla Beech (Cambea Consulting, United Kingdom), Tom Smith (Swiss Tropical and Public Health Institute, Switzerland) and John Bradley (London School of Hygiene and Tropical Medicine, United Kingdom). Input was sought from collaborating WHO units, namely RPQ/PQT/VCP and NTD/VVE. Alongside this, the PPC was formally disseminated for public consultation via the WHO GMP website and listerv for the duration from 8 December 2022 to 13 January 2023. Public inputs were received from Sarah Moore (Ifakara Health Institute, United Republic of Tanzania), Mike Macdonald (Independent Consultant, United States), Christophe Boëte (Institut des Sciences de l'Évolution, France) and Geoff Turner (Imperial College London, United Kingdom). Throughout the process, inputs were assessed for potential conflict of interest of the contributing individual in the context of her/his affiliation. No relevant conflicts of interest were identified with regards to the inputs provided into this guidance document. This final version of the document was cleared by WHO's Quality, Norms and Standards Department and the Research Department. WHO gratefully acknowledges all of the contributions made during the development of this PPC document.

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