Supplemental Information. Overarching Preferred Product Characteristics (PPC) for Spatial Repellents (Based on WHO PPC template)

Achee et al, Spatial repellents: The current roadmap to global recommendation of spatial repellents for public health use

Overview

Spatial repellents have the potential to be an important component of vector-borne disease control from both indoor and outdoor biting arthropod vectors, to include mosquitoes, sand flies, and triatomines. ***The term 'spatial repellency' is used here to refer to a range of insect behaviors induced by airborne chemicals that result in a reduction in human–vector contact and therefore personal protection. The behaviors can include movement away from a chemical stimulus, interference with host detection (attraction inhibition) and feeding response***.[1] Any single or combination of these behaviors can collectively reduce biting and feeding of mosquitoes on humans. Such a reduction in human-biting rate of anthropophilic arthropod vectors is likely to lower vectorial capacity of those vectors and potentially affect fecundity due to challenges in successful blood-feeding which will in turn influence the basic reproductive rate of pathogens that they transmit.

Added value of Spatial Repellents in Vector-borne Disease Control

In combination with existing WHO-recommended vector control interventions, spatial repellents may add protective benefit in reducing vector-borne disease.[2] This is most highlighted in settings where traditional long-lasting insecticidal nets (LLINs) or indoor residual spraying (IRS) may not be sufficiently protective against anthropophilic arthropod vectors due to varying circumstances: 1) early-evening blood feeding;[3] 2) when LLINs and/or IRS are not in use or used intermittently;[4] 3) be unavailable, or are impractical and/or infeasible such as during humanitarian emergency relief operations;[5] and/or 4) where vectors do not or limit resting time indoors on insecticide-treated surfaces.[6] Control or elimination of vector-borne diseases in these circumstances will require innovative approaches; as example spatial repellents providing a highly beneficial protective role against transmission.[7]

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[1] World Health Organization. (2013). Guidelines for efficacy testing of spatial repellents.

[2] World Health Organization, 2017. Global Vector Control Response 2017–2030. *WHO.* World Health Organization.

[3] Pates H, Curtis C, 2005. Mosquito Behavior and Vector Control. Annu Rev Entomol 50: 53-70. Durnez L, Coosemans M, 2013. Residual Transmission of Malaria: An Old Issue for New Approaches. Anonymous Anopheles Mosquitoes - New Insights into Malaria Vectors. London, UK: IntechOpen.

[4] Harvey SA, Lam Y, Martin NA, Olórtegui MP, 2017. Multiple Entries and Exits and Other Complex Human Patterns of Insecticide-Treated Net Use: a Possible Contributor to Residual Malaria Transmission? *Malar J 16:* 265. Monroe A, Asamoah O, Lam Y, Koenker H, Psychas P, Lynch M, Ricotta E, Hornston S, Berman A, Harvey SA, 2015. Outdoor-Sleeping and Other Night-Time Activities in Northern Ghana: Implications for Residual Transmission and Malaria Prevention. *Malar J 14:* 35.

[5] World Health Organization, 2013. Malaria Control in Humanitarian Emergencies – An Inter-Agency Field Handbook. Second Edition. WHO. Geneva, Switzerland: World Health Organization.

[6] Pates H, Curtis C, 2005. Mosquito Behavior and Vector Control. Annu Rev Entomol 50: 53-70. Durnez L, Coosemans M, 2013. Residual Transmission of Malaria: An Old Issue for New Approaches. Anonymous Anopheles Mosquitoes - New Insights into Malaria Vectors. London, UK: IntechOpen.

[7] Achee NL, et al, 2012. Spatial Repellents: from Discovery and Development to Evidence-Based Validation. Malar J 11: 164. Hemingway J, Shretta R, Wells TNC, Bell D, Djimdé AA, Achee N, Qi G, 2016. Tools and Strategies for Malaria Control and Elimination: What Do We Need to Achieve a Grand Convergence in Malaria? PLoS Biol 14: e1002380.

Terminology

Preferred Product Characteristics (PPC) are designed to communicate unmet public health needs identified by WHO, stimulate innovation and investment in the identified area, and communicate the desired performance and operational characteristics of health products developed to address this need. The target audience are 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).

Aims:

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

Parameter	Preferred Product Characteristic
Indication	
	● Repel and/or deter adult arthropod vectors when/after exposure to volatile chemicals during host-seeking or other salient behaviors. ● Provide a space free of arthropod disease vectors and nuisance pests. ● Reduce or prevent human infection and/or disease caused by anthropophilic arthropod vectors.
Target Human Population	
	● All age groups and populations in vector-borne disease endemic countries, including women of child-bearing age, pregnant and lactating women.
Access and Affordability	
	● Meets demand for minimal coverage required for impact. ● Priced competitively, cost below or similar to that of current WHO recommended adult vector control interventions against the target disease [i.e., LLINs and/or IRS for malaria; ULV-spray for *Aedes*-borne viruses etc.]. ● Suitable for procurement through global donor mechanisms, and complementary private/commercial markets.
Safety and Regulatory	
Regulatory	● Registration with a Stringent Regulatory Authority (for example EPA, CPAC other regional schemes), and be registered in the country of origin. ● Meets safety, efficacy and quality standards of WHO [PQ-VCT].
Risk Assessment	● Risk in use/exposure within acceptable margin of human safety defined by the WHO generic risk assessment for spatial repellents.* **Note: established when/if a global health policy is recommended*.
Environmental safety, including disposal	● Does not pose increased environmental safety risks than that of currently used WHO recommended chemical vector control interventions.

Non-target species	• Within accepted standards of risks to non-target species at time of registration submission. • Insect-specific target site that precludes off-target toxicity and allows for high efficiency at low dose.
Parameter	**Preferred Product Characteristic**
Entomological Efficacy	
Deterrence / Abundance	• Reduced vector entry into treated spaces, reducing human-vector contact.
Irritancy / Abundance	• Increased vector exit from treated spaces, reducing human-vector contact.
Blood-feeding / Anti-biting	• Reduced blood-feeding in treated spaces, reducing pathogen transmission.
Knockdown / Mortality	• No acute chemical toxicity, mitigating resistance selection pressure.* **Note: Debate regarding inclusion of rapid knockdown at close source if primary behavior-modifying effects are not elicited.*
Parity / Fecundity	• Interruption in egg development [and/or hatching], reducing vector population.
Diversion / Deferred Biting	• No greater biting on human hosts at untreated spaces adjacent to treated spaces than levels without product.* **Note: Increased biting on non-human animal hosts may be acceptable.*
Epidemiological Efficacy	
Incidence / Disease	• Significant protective effect compared to placebo/control, or contemporaneous standard of care [LLINs, IRS, ACTs, ULV, no intervention etc.].* **Notes:* *1. Malaria prevalence study in China evaluating mosquito coils w/ 0.03% transfluthrin demonstrated 77% reduction in Plasmodium falciparum cases[8] and coils containing 0.00975% metofluthrin provided 52% protective efficacy against new (incident) malaria infections in Indonesia.[9]* *2. A large-scale cRCT in Indonesia indicated a protective effect of 27.7% and 31.3%, for time to first-event and overall (total new) infections, respectively, neither statistically significant. Subgroup analysis of 19 clusters where at least one infection occurred during baseline showed 33.3% (p-value = 0.083) and 40.9% (p-value = 0.0236, statistically significant at the 1-sided 5% significance level) protective effect to first-infection and overall infections, respectively. Among 12 moderate- to high-risk clusters, a statistically significant decrease in infection by intervention was detected (60% protective efficacy).[10]* *3. A large-scale cRCT in Peru indicated a significant protective effect of 34.1% against ABV infection (1-sided 95% CI lower limit, 6·9%; 1-sided p-value=0·0236, z=1·98). Aedes aegypti abundance and blood-fed rates were significantly reduced by 28·6% (95% CI 24·1%, ∞); z=-9·11) and 12·4% (95% CI 4·2%, ∞); z=-2·43), respectively. The trial provides the first conclusive statistical evidence from a pre-planned cRCT with a pre-defined effect size on the primary endpoint that was appropriately powered to prospectively quantify and statistically test for a difference in the impact of a spatial repellent to reduce the risk of ABV transmission.[11]*

[8] Hill N, Zhou HN, Wang P, Guo X, Carneiro I, Moore SJ, 2014. A Household Randomized, Controlled Trial of the Efficacy of 0.03% Transfluthrin Coils Alone and in Combination with Long-Lasting Insecticidal Nets on the Incidence of *Plasmodium falciparum* and *Plasmodium vivax* Malaria in Western Yunnan Province, China. *Malar J 13:* 208.

[9] Syafruddin D, et al, 2014. Impact of a Spatial Repellent on Malaria Incidence in Two Villages in Sumba, Indonesia. *Am J Trop Med Hyg 91:* 1079-1087.

[10] Syafruddin, Din, et al, 2020. Efficacy of a spatial repellent for control of malaria in Indonesia: a cluster-randomized controlled trial. *Am J Trop Med Hyg* 103.1: 344.

[11] Morrison, Amy C., et al. 2022. Efficacy of a spatial repellent for control of *Aedes*-borne virus transmission: A cluster-randomized trial in Iquitos, Peru. *Proceedings of the National Academy of Sciences* 119.26: e2118283119.

Parameter	Preferred Product Characteristic
Claims	
Physical durability	● Meets WHO specifications for durability. ● Sufficient quality to provide protection from infection and/or disease for least 6mo.* **Note: Span of peak seasonal transmission for most VBD, emergency outbreaks, and/or current deployment patterns of IRS in holoendemic malaria settings.*
Target species	● Effective against at least one key vector species of disease importance in each global region: malaria (*Anopheles spp.*); *Aedes*-borne viruses (*Aedes spp.);* Chagas (*Triatoma spp., Rhodnius spp., Panstrongylus spp.*), and/or Leishmaniasis (*Phlebotomus spp., Lutzomyia spp*.). ● Effective against species/strains: 1) resistant to insecticides in current use* (pyrethroids, organophosphates, carbamates, neonicotinoids and/or DDT); 2) that exhibit host-seeking/biting behavior for which current control strategies are not appropriate or sufficient (day-biting, early-evening, and/or outside biting).
Mode(s) of action	● Novel mode of action acting on an unrelated target site than currently used chemical actives [pyrethroids, organophosphates, carbamates, neonicotinoids and/or DDT] to mitigate selective pressure from acute chemical toxicity.* **Note: While insecticide resistance management is an unmet public health need for which new AIs and/or new MoAs are warranted, and are a component of SR R&D, current volatile PYRs in spatial repellent formulations have demonstrated to be viable public health tools (see epidemiological efficacy above) until such new AIs can be formulated and evaluated in non-inferiority studies.*
Shelf life & storage	● Meets WHO specifications for stability. ● Minimum 24 months at 37°C and 75% humidity without impacting stability or efficacy of the product.
End User Suitability	
User acceptability	● Suitable for routine use, does not disrupt normal human activity patterns. ● No excessive dermal irritation or other adverse effects so as to not discourage users from undergoing routine lifestyle habits in treated space [sleeping, cooking, washing etc.]. ● Tamper proof and easy to maintain/use.
Distribution	● Meets demand for minimal coverage required for impact. ● Distribution through existing delivery channels, namely mass campaigns, and continuous distribution channels including CHWs, schools, and/or retail [commercial market].
Supervision	● Minimal to no training for deployment or application.