An Expert Review of Spatial Repellents for Mosquito Control

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Executive Summary

Spatial repellents (SR) are a potential tool against vector borne disease, but at present most products are targeted to the consumer market. This report examines the potential role of SRs in public health through published and grey literature, and the opinions of academic and industry experts on spatial repellents. While the primary focus is *Anopheles*, there are promising data showing spatial repellent impact on *Aedes*-borne diseases and Leishmania vectors.

Literature Review and Ongoing Research

There is no current consensus on a clear definition of spatial repellents. Generally, they are defined as chemicals that, when air-borne, prevent biting by blood-seeking insects such as mosquitoes. The chemical should therefore create a space where human hosts are safe from bites and potential disease transmission. Chemicals that have been shown to have spatial repellent effects include volatile pyrethroids such as metofluthrin and transfluthrin; botanical compounds such as terpenoids; or volatiles found from human skin and skin bacteria such as 1-methylpiperazine. Historically, DDT was known to have an "excito-repellent" effect in addition to lethality when applied for indoor residual spraying. Spatial repellent actives have been incorporated into a wide range of devices including coils, heat activated vaporisers to passive emanators based on plastic, paper and hessian materials. Laboratory and semi-field trials have shown good levels of efficacy against important vector species such as *Anopheles gambiae* and *Aedes aegypti*.

Although spatial repellents aim to disrupt host seeking and feeding behaviour, many laboratory tests have concentrated on a killing effect, perhaps because of the predominance of volatile pyrethroids in the early development of spatial repellents. The World Health Organization (WHO) has produced guidelines for testing spatial repellents which recommend that movement away from a host stimulus should be the main outcome, but very few studies were found to use those methods. Semi-field testing may be more appropriate for testing spatial repellents, as the build-up of the volatile within a three-dimensional space can be better simulated. An outline protocol for testing of spatial repellents in a semi-field system is presented, based on WHO recommendations and subsequent published work.

For spatial repellents to become an accepted part of the malaria vector control arsenal, most experts agreed that data from randomised controlled trials showing an impact on disease transmission would be necessary. At present, there are data from semi-field trials showing repellency, and where pyrethroids are concerned, mortality data from laboratory trials. So far, one trial in Indonesia has shown an epidemiological effect; a 52% reduction in malaria from the use of spatial repellents. There are two further randomised controlled trials currently underway, one on malaria in Indonesia and another on *Aedes*-borne diseases in Peru that will help build on this evidence. Other studies that are currently underway include modelling work, which suggests spatial repellents could have a potentially large public impact and may be particularly useful in helping design the next generation of spatial repellents.

Economic Considerations and Commercialisation

A wide range of products are commercially available for use as spatial repellents/insecticides, primarily for the consumer market, rather than as a public health intervention with varied degrees of efficacy. There not established route to market for spatial repellent products for use as a vector borne disease intervention. The commercialisation model for spatial repellents would be very different to LLINS or IRS, because there is a vibrant repellent consumer market worldwide. A high volume "developed" market should, in theory, bring production costs down, and, therefore, support provision of cheaper spatial repellent products in developing markets. But this needs further examination and consideration.

Regulatory and Policy Issues

Spatial repellents are usually included with insecticides (where lethality is a primary objective) in most regulatory guidelines, which presents a problem where the product is not designed to kill mosquitos but prevent biting. However, there are regulatory hurdles for getting any product to market, and these did not overly concern most manufacturers. What was desired was a greater acceptance of data produced according to WHO guidelines at the national level, as these better characterise a repellent, rather than insecticidal effect. There was a desire to update the WHO guidelines, to include more up to date methods and input from industry on the outcomes that would be most useful if the data were to be presented to both the WHO PQ system and national regulatory bodies.

Target Product Profiles

To develop a target product profile for spatial repellents for public health use, a pragmatic approach was used, where an "achievable" product, with currently available spatial repellents, was considered alongside the ideal product. The interviewees gave a variety of opinions on what would be the ideal spatial repellent product. We have provided further consideration, beyond the interviewee comments. Themes pulled out from interviews included a product which was low-cost, with at least 90% protection from biting, light-weight and portable, a requirement to provide protection outdoors as well as indoors (not necessarily one product that can do both), with an effective duration of 3 to 6 months. Note, as described in more detail below, since this review began there has been an evolution in WHO strategy to now focus on a higher-level Preferred Product Characteristic for the overall product class whereas Target Product Profile is more focused on the specific product development.

Knowledge Gap Assessment

Several knowledge gaps were identified in our understanding of spatial repellents and their impact when used in vector control. Amongst the most important, was the lack of epidemiological evidence of impact. There are some data, and more data are being gathered, but a solid evidence-base is of paramount importance before spatial repellents can be advocated for use in vector control programmes. An area of debate surrounds the definition of a spatial repellent and different types of effects on the vector, which then impacts directly on what would be the most appropriate methods of evaluation. The effect of volatile pyrethroids on the problem of insecticide resistance needs to be addressed before these products can be widely advocated. In addition, their effect on non-target insects was also of concern, particularly when intended for outdoor use. Another knowledge gap exists around the practicalities of designing a spatial product, meaning replacement rate, area of effect and best placement. All of these would potentially change from setting to setting, and spatial repellents would need to remain a flexible intervention to achieve the greatest impact. Current safety data relies heavily on testing of coils, which means that the effects of smoke inhalation are included with the exposure to the active. Toxicity of emanator devices needs to be established, to help improve the acceptance of spatial repellents by some parts of the vector control community.

Feasibility and Recommendations

There was clear consensus that spatial repellents have a place in vector control, and several potential routes in which spatial repellents could be utilised are highlighted. Firstly, without any further product development, current devices may be used in fast but short-term responses to vector-borne health crises, including humanitarian relief situations or outbreak response. Spatial repellent devices with improved duration may well be suitable to protect people inside or around houses, perhaps as a replacement or even improvement on indoor residual spraying. Spatial repellents can require little in the way of behaviour change from users, so potentially may be more acceptable and easier to implement, particularly in areas aiming for malaria elimination where other interventions such as bed nets or chemoprophylaxis may become unpopular. After the review was completed an appendix on "Use Case Analysis" developed by IVCC has been added.

Other challenges that would need to be overcome to make spatial repellents effective vector control tools include economic, regulatory and implementation concerns. At present most spatial repellent devices come at a high cost. They are primarily marketed to consumers in developed areas, and include expensive materials, batteries or require electricity, all of which reduce their potential use in less developed areas where disease transmission is often highest. Ideally spatial repellents would need to demonstrate an equivalent cost per person protected to bed nets or indoor residual spraying to be considered by funders and programme managers. In addition, there are technical questions around safety and their impact on insecticide resistance that would need to be addressed before widespread roll-out could be advocated.

Several potential next steps have been identified and can be found in the conclusion, below are the key steps that would be required to take spatial repellents forward as a viable vector control tool:

- Further studies are needed to determine the epidemiological evidence to support the use of spatial repellents including specifically targeting high-risk populations and outdoor transmission. Other studies are also required to help answer questions about potential diversionary effects when spatial repellents are used widescale within a community.

- Improve the regulatory environment for these products, by revising testing guidelines in line with spatial repellent modes of action, and label requirements. This will need to involve industry, WHO Pre-Qualification and VCAG, as well as national competent authorities and regulators.
- Further work is needed to determine the effect of both insecticidal and non-insecticidal spatial repellents on the behaviour of insecticide resistant mosquitoes, as well as any effects on the development of resistance.
- Fundamental work, including modelling studies are needed to help design more effective products that can maintain doses for a range of setting and uses. In addition, social research is needed to understand how best to promote behaviour change, or design products which fit best within different communities to ensure high levels of compliance.
- Work is needed to understand the effect of different active ingredients on non-target organisms under different ecological settings.
- Research on the identification and development of novel actives should be a priority.

Objectives

The objectives of this assessment were to produce:

1. A review of the literature to identify and interpret past research on the history of spatial repellent research and their potential, with conclusions and recommendations.
2. Summary of ongoing spatial repellent research and development with conclusions and recommendations.
3. Assessment of test methods and entomological endpoints of laboratory studies.
4. Outline protocol for Phase II trials work.
5. Economic considerations for spatial repellents as a public health tool.
6. Summary of current commercialisation of spatial repellents by market segment (consumer, PCO, vector control).
7. Conceptual Target Product Profiles.
8. Outline of regulatory issues and policy status.
9. Knowledge gap assessment and solutions analysis, including review of key information, performance gaps, and potential avenues to address these gaps and provide solutions.
10. Feasibility of adoption of spatial repellents within vector control campaigns against malaria, and against *Aedes*-borne diseases.
11. Recommendations on whether, and how, to take spatial repellents forward in terms of system preference, R&D requirements and evaluation needs.

Methods

Interviews

Face-to-face and telephone interviews were conducted with bite prevention and volatile pyrethroid experts, formulation chemistry experts, vector control experts, representatives from key funding and policy bodies, nmcps, private sector, and spatial repellent manufacturers. The list of interviewees was determined by *arctec* and added to or amended in consultation with the IVCC.

A question guide was developed to allow the interviewer to keep the discussion moving and to stay focused on the topics of interest (see Appendix 1). However, individual interviews were tailored to the individual, and developed according to the answers given.

Eighteen interviews were conducted between 22nd August and 12th October 2018. The list below gives the names and affiliations of those interviewed.

- Richard Allan (MENTOR Initiative)
- Neil Lobo (Notre Dame)
- Dave Malone (Sumitomo)
- Nicole L. Achee (Notre Dame)
- Jeffry Hii (Malaria Consortium)
- Steve Lindsay (Durham)
- Sarah Moore (Ifakara)
- Dan Strickman (Bill & Melinda Gates Foundation)
- Mark Hoppe (Syngenta)
- Sebastian Horstmann (Bayer)
- Gaby Zollner (AFPMB)
- Larry Zwiebel (Vanderbilt)
- Mike Reddy (Microsoft)
- Ulrich Bernier (USDA)
- Fredros Okumu (Ifakara)
- Julia Rogers & Chris Loxley (Unilever)
- Thomas Mascari (SC Johnson)

This report also includes the authors' own opinions and expertise, based on experience working on repellents and from working with repellent manufacturers and regulators.

Literature Search

Information Sources and Search

A literature search was performed to find research on spatial repellents used to prevent vector-borne diseases. The search terms "spatial repellent" and "vector control" were used initially, with further results sought through additional terms "volatile pyrethroid", "metofluthrin", "transfluthrin", cross-referenced with "repellent". Other search terms include "confusant", "personal protection", "household protection", "push-pull" and "emanator".

The CAB Abstracts, Cochrane library, ethos (British Library e-theses service), IRIS (digital WHO Library), LILACS, Pubmed, and Web of Science databases were searched for peer-reviewed published papers. Grey literature was also searched using the same search terms in the Open Grey database.

Eligibility Criteria

This review included studies of spatial repellents and their effects under basic laboratory trials, semi field and field trials and late scale intervention trials, as well as manuscripts where novel compounds with spatial repellent effect have been identified and or evaluated. Study interventions included any spatial insect repellent regardless of active ingredient (ais traditionally used as topical repellents, but that prove suitable for use as spatial repellents will be included) or concentration used. Trials involving local populations were prioritised, however those involving travellers from developed countries or exclusively laboratory research were also considered and included in final considerations where appropriate. Studies not primarily focused on mosquitoes of the genera *Aedes, Anopheles* and *Culex* were excluded. Trials of repellent impregnated clothing were only excluded if they were unable to demonstrate spatial repellency through full coverage. All outcomes reported were recorded, but particular focus was given to any effect on disease transmission rather than vector populations. Studies were also included where the spatial repellent effect was a secondary outcome.

Study Selection

The results of literature searches were checked for duplicates and the resulting references screened for inclusion in the qualitative analyses. Studies selected were evaluated to determine their potential contribution to the following interest areas: past research, on-going research, laboratory and semi-field test methods and endpoints.

Past Spatial Repellent Research

Introduction

Malaria has been greatly reduced by the use of insecticide-treated bed nets and indoor residual spraying, however, increasing insecticide resistance threatens the efficacy of these methods and progress on disease reduction has stalled.[1] At the same time there has been an increase in *Aedes*-borne diseases including dengue and Zika. Traditional methods such as insecticide treated nets are less effective against outdoor and day-biting *Aedes*, and, therefore, there is a need for alternative vector control tools. Spatial repellents could present a novel solution to these problems.

Spatial repellents have been defined as chemicals that are volatized and prevent human-vector contact by disrupting host seeking behaviour[2, 3]. Some of the widest-used spatial repellent products are coils, usually containing an insecticide that are burnt to produce a repellent smoke. These are cheap and easy to use and can last around 8 to 9 hours. However, the smoke produced is a health concern [4] [5]. Aimed at the higher end of the market are repellent mats where a heating element is required to volatilise the active ingredient. These require electricity, which make them unsuitable currently for low income households where malaria transmission is often highest. Active ingredients can also be impregnated onto different substrates, including paper, plastic and fabric, to create passive emanators which are cheaper to produce. These can last up to a few weeks, although repellency will decline over time, and environmental factors such as temperature affect release rates.

Laboratory Studies of Volatile Pyrethroids

Volatile pyrethroids are the most studied group of spatial repellents, and include metofluthrin, allethrin, prallethrin transfluthrin and meperfluthrin. As they are insecticides, there are a number of studies that demonstrate their efficacy at knockdown and killing of mosquitoes [6-11]. These mortality rates are affected by distance from the source, and the release rate of the device, but the ability of these 'spatial repellent' devices to effectively kill mosquitoes is well established.

Other laboratory studies have used wind tunnels, arm-in-cage tests, taxis cages and Peet Grady chambers to look at the effect of volatile pyrethroids on host seeking and feeding behaviour. Results from these studies indicate that these compounds are detected by mosquitoes, stimulate flight behaviour and are even attractive in the absence of host odours [12, 13]. However, these studies all show large reductions in landing and biting in the presence of a host (Table 1).

Table 1. Laboratory studies of volatile pyrethroids showing effects on landing or biting on a host

Repellent	Species	Outcomes	Reference
Prallethrin (volatilized and ULV)	*Ae. albopictus*	No effect on flight behaviour from volatilized prallethrin. Increased flight events, the turning frequency, overall movement speed, and flight speed from ULV prallethrin.	[12]
Transfluthrin	*Aedes aegypti*	Landing counts reduced by 95% (Raid Dual Action) and 74% (Raid Shield). Probing counts reduced by 95% (Raid Dual Action) and 69% (Raid Shield). Baseline blood-feeding success reduced by 100% (Raid Dual Action) and 96% (Raid Shield).	[14]
Metofluthrin (wearable device)	*Ae. aegypti*	Significantly reduced the numbers of attracted mosquitoes.	[15]
Transfluthrin	*Ae. aegypti*	70–90% reduction in bites. Effective for up to 4 weeks.	[16]
Transfluthrin coils	*An. gambiae*	Attraction to humans was increased by the coils (laboratory studies). A reduction in feeding was observed in semi-field trials which lasted for 12 hours.	[17]
Metofluthrin emanator	*Ae. canadensis*	Landing rates were reduced by 85-100% in laboratory trials. In wind tunnels 89-91% reductions in landing rates were observed.	[18]

Laboratory Studies of Non-pyrethroid Spatial Repellents

Several non-pyrethroid compounds have been tested for their spatial repellency against mosquitoes, and include geraniol, nepetalactone, dehydrolinalool and a range of botanical extracts. Researchers have used arm-in-cage tests, static air olfactometers, triple cage olfactometers, Y-tube olfactometers and tube bioassays to try to determine potential effects of these compounds on mosquito host seeking and feeding. Results show that there are a huge range of potential non-pyrethroids that have potential as spatial repellents, with some of the best results from catnip oil, geraniol and anisaldehyde (Table 2).

Table 2. Laboratory studies of non-pyrethroids spatial repellents showing effects on landing or biting on a host

Repellent	Species	Outcomes	Reference
Geraniol **Eugenol** **Citral** **Anisaldehyde** **Citronellal**	*Ae. albopictus*	Reduction in host seeking: geraniol (100%), anisaldehyde (85.5%), citronellal (none). Interruption of blood-feeding by anisaldehyde only.	[19]
Catnip (*Nepeta cataria*) essential oil **Two isomers of nepetalactone (primary component of catnip oil)**	*Ae. aegypti*	Spatial repellency observed at 10x lower con-centrations (15.7 µg/cm2) than DEET.	[20]
Nepetalactone	*Ae. aegypti* *An. albimanus* *An. quadrimaculatus*	Weak attractant in absence of host odours. Spatial repellency better than DEET, topical repellency worse than DEET.	[21]
Catnip oil **1-methylpiperazine** **homopiperazine** **a mixture of catnip oil and homopiperazine**	*Ae. aegypti*	Reduction in host location by up to 96.7%	[22]
Dehydrolinalool **Linalool**	*Ae. aegypti*	Attraction observed in the absence of host odours. Highest spatial repellency (33.6%) observed with combination of linalool and dehydrolinalool	[23]
Lavendula stoechas ***Helichrysum italicum*** **(leaves)** ***Laurus nobilis oils***	*Ae. aegypti*	Spatial repellency demonstrated with human attractant	[24]
Parthenium hysterophorus **leaves**	*Ae. aegypti*	Spatial repellency was affected by solvent used: 80% with acetone and hexane, 60% with diethyl ether, 20% with petroleum ether and 0% with benzene	[25]

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Semi-field Trials

Semi-field evaluations usually use an experimental hut or other proxy for a building and lab reared mosquitoes to evaluate the effect on spatial repellents on mosquito entry, exit, and feeding. To test outdoor protection, a number of studies have instead used screened tunnels. The results of these studies are more varied, but most devices whether pyrethroid based or not are able to significantly reduce mosquito feeding (Table 3). The notable exception to these were patches (one containing oil of lemon eucalyptus, and a transdermal patch containing vitamin B1) and wristbands (one containing 22% citronella oil; and another with 15% geraniol, 5% lemongrass oil and 1% citronella oil) which gave no significant protection compared to controls [26]. A metofluthrin impregnated net also gave low spatial repellency results when used outdoors, but the dosing of this product was aimed at sandflies and may have been too low for mosquitoes [11].

The sub-lethal effects of pyrethroid-based spatial repellents were more evident in some of these trials, with mortality assessed at greater distances than in laboratory studies. This does raise the potential of these to affect the development of insecticide resistance [27, 28].

Table 3. Semi-field studies of spatial repellents showing effects on mosquito entry, exit, landing or biting on a host.

Repellent	Species	Outcomes	Reference
Metofluthrin coils **DDT-treated fabric**	*Ae. aegypti*	58% (coils) and 70% (fabric) deterrence	[3]
Transfluthrin	*Ae. aegypti*	Semi-field: reduction in mosquito entry of 88% (Raid Shield) and 66% (Dual Action)	[14]
OFF! Mosquito Lamp (metofluthrin)	*Ae. aegypti*	100% mortality indoors and >80% knockdown and 90% mortality within 6 m outdoors	[29]
Emanators: OFF! Clip-On (metofluthrin) and Terminix (cinnamon oil; eugenol; geranium oil; peppermint; Lemongrass oil) **Wristbands: with citronella oil; or Geraniol, lemongrass oil and citronella oil** **Patches: with oil of lemon eucalyptus or vitamin B1**	*Ae. albopictus* *Cx. pipiens*	No significant protection from patches or wristbands Reduction in biting of over 88-96% by *Ae. albopictus*, and 92-97% by *Cx. pipiens*.	[26]
Metofluthrin-impregnated net	*Ae. aegypti* *An. dirus*	No spatial effect observed for *Ae. aegypti*, and a short lived repellency against *An. dirus*.	[11]
Metofluthrin and esbiothrin coils	*An. gambiae*	Repellency was 93% (metofluthrin) and 85% (esbiothrin). Both coils were operating at below 95% insecticidal effect.	[30]
Transfluthrin coils	*An. gambiae*	Reduced feeding by 65-86%. The effect on feeding lasted for 12 hours	[17]

Repellent	Species	Outcomes	Reference
Pyrethroid-based mosquito coils	*An. gambiae* *Cx. quinquefasciatus*	Coils significantly reduced the number of indoor resting mosquitoes. Induced exophily was 92-96% for *Cx. quinquefasciatus* and 60-64% for *An. gambiae*. Feeding was reduced by 91-100% in *Cx. quinquefasciatus* and 59-100% in *An. gambiae*.	[13]
Metofluthrin emanators	*Ae. aegypti*	The metofluthrin emanator reduced biting to zero within the treated room, and also reduced biting in neighbouring rooms. No repellency or induced exophily was observed.	[28]
Metofluthrin emanators	*Ae. aegypti*	Rapid knockdown meant biting was reduced almost to zero. No increased exophily was observed.	[31]
Metofluthrin emanators	*Ae. aegypti*	Landing rates were reduced to 0-2.5% within 10 minutes. Distance from the emanator and the size of the room strongly affected the knock-down and landing.	[27]
Metofluthrin emanators	*Ae. aegypti*	At 3m from the emanator, a 40 minute exposure was required to observe significant mortality. No effects on fecundity were observed.	[32]
Linalool, geraniol and citronella candles and diffusers	*Aedes* spp. *Culex* spp.	Repellencies of 22% (citronella), 58% (linalool) and 75% (geraniol) observed 6m from diffusers	[33]
Linalool	*An. gambiae*	No effects on feeding inhibition or repellency. However, mosquitoes exposed to linalool were 3 times more likely to die after 24 hours compared to the negative control.	[34]

Field Testing of Entomological Efficacy

Researchers have used human landing catches and trapping to try to evaluate the efficacy of spatial repellents in the field. By using wild mosquito populations, there is better evaluation of potential effect on long-range host seeking and behaviour than might be achieved under semi-field or laboratory conditions.

Given the good results from laboratory and semi-field studies, the good results of spatial repellents in the field is not surprising (Table 4). Two of the most promising products have been metofluthrin emanators (OFF! clip-ons or lamps) and allethrin emanators (ThermaCELL), which have achieved over 70% protection in multiple studies [26, 35-38]. As illustrated in this table there is a range of different measured outcomes, landing rates, biting rates, traps counts etc. This issue needs to be highlighted in defining and comparing the effectiveness of different products.

Table 4. Field testing of spatial repellents showing effects on mosquito repellency, landing or biting.

Repellent	Species	Outcomes	Reference
Off! Clip-on Mosquito Repellent device (metofluthrin)	*Ae. albopictus* *Ae. taeniorhynchus*	Over 70% protection for over 3 hours, even when left open for 1 week.	[38]
OFF! Clip-On (metofluthrin) **Mosquito Cognito (linalool)** **No-Pest Strip (dichlorvos)** **ThermaCELL (d-cis/trans allethrin)**	*An. quadrimaculatus* *Cx. erraticus* *Psorophora columbiae*	Traps treated with metofluthrin, linalool and d-cis/trans allethrin products were associated with significant reductions in mosquito catches.	[36]
ThermaCELL (allethrin) **OFF! Clip On (metofluthrin)** **Lentek Bite Shield (geraniol)** **Bug Button (natural oils)**	*Ae. albopictus*	Significantly reduced catches from ThermaCell (76%) and OFF! Clip On (64%), but not Lentek (43%) or Bug button (17%) on traps treated with devices.	[37]
ThermaCELL (allethrin) **OFF! Clip On (metofluthrin)** **Lentek Bite Shield (geraniol)** **Bug Button (natural oils)**	Field populations of mosquitoes in Israel	All three products gave over 90% protection within 1m, over 77% protection within 2.5m and over 55% protection within 3.33m in human landing catches.	[26]
ThermaCELL Mosquito Repellent (TMR, cis-trans allethrin)	Phlebotomine sand flies *(Phlebotomus papatasi)* Mosquitoes *(Ochlerotatus caspius)*	Reduction in biting rates of 92% (sandflies) and 93% (mosquitoes), for up to 6 hours.	[35]
Metofluthrin emanator	*Ochlerotatus* spp. *Ae. vexans*	In the field 91-97% reductions were observed.	[18]
d-allethrin, d-transallethrin coils	*Cx. quinquefasciatus*	Mosquito reduction in houses was 70-75%	[39]
Transfluthrin coils	*An. arabiensis* *An. funestus*	Landings reduced by 80%, although no effect was seen on indoor mosquito density. Incomplete coverage (combination of repellent and blank coils), resulted in diversion of feeding from repellent users to non-repellent users.	[40]
Metofluthrin-impregnated plastic strips	*An. gambiae*	Intervention houses had a significantly lower mosquito density despite large openings.	[41]
Metofluthrin-impregnated plastic strips	*Cx. quinquefasciatus*	Two strips repelled >60% of for 11 weeks, whereas four strips repelled >60% for over 15 weeks.	[42]
Metofluthrin-impregnated plastic strips	*Ae. aegypti* *Cx. quinquefasciatus*	A single strip was effective for 6 weeks.	[43]
Metofluthrin-impregnated plastic strips	*Ae. aegypti*	8 weeks of efficacy, however average room temperature and the total area of openings into the rooms affected overall efficacy.	[44]

Push-Pull Strategies

Spatial repellents can be used within push-pull systems to push mosquitoes from an area with human hosts, towards baited traps. This may potentially reduce any potential diversion of biting to unprotected areas. The results of various push-pull trials are given in Table 5.

Although results of one study saw little difference between push-only, pull-only and push-pull households where around 50% reductions were observed in mosquitoes entry, modelling of the results concluded that a 20-fold reduction in transmission could be possible with the combination of both push and pull strategies [45]. A similar study also used microencapsulated delta-undecalactone impregnated netting to screen the eaves of houses in Kenya, and concluded that screening the eaves was effective by itself and the addition of repellent had limited value [46].

Spatial repellents may work by affecting host seeking behaviour, and it is possible that once exposed to the repellent, mosquitoes are then less likely to be attracted to baited traps. This was tested using DDT, transfluthrin and metofluthrin repellents in combination with BG Sentinel traps, and no impact was observed [47].

The push-pull systems tested have not necessarily demonstrated an additional effect from the combination of push-pull strategies, but the reduction in mosquito entry from the use of spatial repellents is clear, and further refinement of the systems may lead to the development of an effective system.

Table 5. Performance of spatial repellents within push-pull systems.

System	Outcomes	Reference
Trap baited with a five-compound attractants combined with net impregnated with delta-undecalactone repellent placed in the eaves of houses	Push-only households saw a 52.8% reduction in mosquito entry. Pull-only households saw a 43.4% reduction in mosquito entry. Push-pull households saw a 51.6% reduction in mosquito entry.	[45]
Attractant baited traps inside the experimental huts, and repellents (PMD, catnip oil and delta-undecalactone) placed at external corners of the hut.	Push alone saw 45-81% reductions in mosquito entry. Push-pull saw reductions in mosquito entry of up to 95%	[48]
Outdoor baited traps were combined with passive transfluthrin emanators indoors	Entry of *An. albimannus* was reduced by 54%, however the push-pull system was not more successful than a push-system alone.	[49]
Catnip oil was used in combination with BG sentinel traps	Human landing catches decreased by 50% in laboratory tests. But this protection was not seen outdoors.	[50]

Acceptability Studies

One study tested 10% metofluthrin in polyethylene emanators in two villages (Ou Chra and Pu Cha) in Cambodia, in the Mondulkiri province. A baseline survey of the households was done where behavioural data were collected for occupants (n=448). Participants noted biting mostly occurred in the evening and indoor and in the outdoor area surrounding the house. One month following the instalment of spatial repellents, a follow up survey was done where spatial repellents were well received, as 96.6% were willing to continue using the product, and willing to pay US$0.3 per unit [51].

Likewise, earlier focus group assessments of the acceptability of "push-pull" *Aedes aegypti* control strategies in Peru and Thailand revealed that participants use household-level strategies for insect control that reveal familiarity with the concept of spatial repellent and contact irritant actions of chemicals and that placing traps in the peridomestic environment to remove repelled mosquitoes was acceptable[52]. Epidemiological Studies

One randomized, double-blinded placebo-controlled study was conducted to assess the effect of spatial repellent with malaria risk in Indonesia. Clusters were given a placebo or transfluthrin coils. Weekly blood smear screening and human landing catches were done for 6 months. Households with transfluthrin coils had 52% protective effect on malaria compared to controls. Similarly, human landing catches were reduced was 32% lower compared to controls [53]. A separate household randomized, controlled trial tested the efficacy of 0.03% transfluthrin coils alone and in combination with LLINs in Western Yunnan Province, China. The trial had four arms where they received: 0.03% transfluthrin coil alone, LLINs alone, a combination of both or nothing (control). A total of 2,052 households were recruited and *Plasmodium falciparum* and *Plasmodium vivax* were tested by RDTs. Coils alone provided 77% protection (95% CI: 50%-89%), LLINs provided 91% protection (95% CI: 72%-97%) and the combination of coils and LLINs provided 94% protection (95% CI: 77%-99%) against *Plasmodium falciparum* compared with the control arm, although there was no statistically significant difference between these reductions in *P. falciparum* between the treatment arms [54].

Other studies have investigated the effect of the use of spatial repellents on disease incidence. A cross-sectional study investigated the effect of mosquito coils on self-reported health issues in Ghana. Questionnaires were administered to 480 households. Respondents who only used mosquito coils were grouped as the test cohort, and respondents who did not apply any mosquito repellent methods were grouped as the control. The cohort that used mosquito coils self-reported a malaria incidence of 86.3% and the control reported 72.4%. Furthermore, the cohort that used coils reported a high incidence rate (52.6%) of cough symptoms compared to controls [55]. However, studies that rely on self-reporting often rely on participant's memory, which may not be accurate

Safety and Toxicology of Spatial Repellents

Most data on the safety of spatial repellents comes from animal testing of coils containing volatile pyrethroids (Table 6). The effects of coils not only come from whichever active ingredient they contain, but also from the particulate matter in the smoke itself. One study compared a transfluthrin and a blank coil and found the worst damage, acute upper respiratory tract irritation occurred in both groups. A risk-benefit analysis was conducted on the effectiveness of mosquito coils and the toxic emissions that may emanate from the coils. The effectiveness was calculated by testing the knockdown/mortality in experimental chambers and the toxicity was evaluated by analysing particulate emission. The resulting hazard index for the compounds in the coils (CO, VOCs, SO2, NO2, PM2.5 and PM10) was low, suggesting a low health risk [55]. Additionally, a clinical examination of 156 adults and 110 children exposed to a neem oil kerosene lamp did not reveal any adverse effects after 1 year of exposure [56]. Residue on walls and ceiling may also present a health hazard, particularly to pets or children, and closed rooms have been shown to have 10 times higher residue build up [57].

Table 6. Studies on the safety of spatial repellents

Exposure	Product	Study Animal	Outcomes	Reference
Nose-only exposure for 6h/day, 5 day/week for 13 weeks	Transfluthrin and blank coils	Rats	Clinical signs of acute upper respiratory tract sensory irritation to smoke both with and without transfluthrin	[5]
Inhalation for 8h/day in prenatal, postnatal and perinatal periods	Allethrin coils	Rat pups	Significant oxidative stress was observed from all exposures. Affects to the hippocampus were accompanied decreased learning and memory performance.	[58]
Exposure over 2, 4, 8, 12 and 16 weeks	Transfluthrin and d-allethrin coils	Male rats	Effects were observed to increase with exposure, including lung damage, liver damage, and sperm abnormality	[4]
Single application	1% neem oil burned in a kerosene lamp	Rabbits Guinea pigs	No skin irritation or other adverse effects	[56]

Release Rates

Release rates are central to the efficacy of spatial repellent devices, and modelling of these release rates is a useful way of exploring their interaction with temperature and air velocity. Bal *et al.* developed a model of a metofluthrin-based device, in order to determine initial loading concentrations, and the relationship between surface area and duration of effect [59]. Controlled release systems for pesticides has been a major focus of research for years[60]. Similarly there has been work, including *in silico* modelling on the development of "controlled release devices" for transfluthrin and metofluthrin[61].

Insecticide Resistance

Spatial repellents induce deterrence, irritancy and excito-repellency, reduced blood feeding and mortality. However, the long-term effects of spatial repellents in mosquito populations are unknown, especially in relation to resistance. *Aedes aegypti* mosquitoes were exposed to transfluthrin vapours (1.35g/m3) and separated according to their response. After nine generations, mosquitoes that were initially repelled (in F0 generation) continued to be repelled, however, selective breeding of non-responders did produce mosquitoes that were insensitive to transfluthrin after four generations. This same study showed that the SR insensitivity could be reversed to full sensitivity (compared to controls) within one back-cross generation. The insensitive strain also had a decreased susceptibility to toxicity and a higher frequency of the V10161kdr mutation [62]. In one study, *Ae. aegypti* were exposed to 10% metofluthrin at 3 meters in a room at 0, 5, 10, 20, 30 and 40 minute intervals. Females exposed at 60 minutes had a 50% mortality rate after a 24-hour recovery, however, exposure did not affect fecundity to mosquitoes that survived. Males had a significant mortality rate at 40 minutes and there was no difference between exposed and unexposed mosquitoes in relation to the viable eggs they produced [32].

Spatial repellents will present a gradient of concentration to the mosquito, and therefore there is a danger of sub-lethal exposure to volatile pyrethroids. It is not yet known whether mosquitoes that are already resistant might respond differently to spatial repellents and whether the use of these products might lead to increased problems with resistance.

A laboratory study by the LSTM commissioned by IVCC looked at contact bioassays on lethality of transfluthrin, concluding:

In summary, the suggestion that volatile pyrethroids like transfluthrin and metofluthrin are not vulnerable to the mechanisms commonly expressed by pyrethroid resistant strains of mosquitoes, Anopheles and Aedes, are not supported by our results, which instead suggest that strains highly resistant to contact pyrethroids are likely to be highly resistant to volatile pyrethroids. Metabolic resistance mediated by P450s appears a key element of this correlation, as also evidence by the results from the metabolism assays and enriched transgenic lines presented in the other report from work performed at LSTM[63].

In a study of the impact of pyrethroid resistance in *Aedes aegypti*, behavioral performance was assessed in 15, 30, and 60 min exposures in a high throughput vapor phase spatial repellency assay to three contact repellent standards: N,N-diethyl-3-methylbenzamide (DEET), ethyl 3-[acetyl(butyl) amino] propanoate (IR3535), and 2-undecanone, as well as pyrethrum extract, transfluthrin, and metofluthrin in susceptible (Orlando) and a pyrethroid-resistant Puerto Rico strain of Aedes aegypti. Additionally, electroantennographic studies were used to investigate the antennal sensitivities to these compounds in both strains. Resistance was found to all tested insect repellents in the Puerto Rico strain of Ae. aegypti. Resistance ratios at the different time points were about 2 for DEET, 3 for 2-undecanone, and 12 for IR3535. Resistance was also observed to pyrethrum extract (~9-fold), transfluthrin (~5-fold), and metofluthrin (~48-fold) in repellent behavioral response. Electrophysiological analysis found decreased antennal sensitivity to all repellents tested, consistent with their behavioral effects. The authors concluded that the reduced sensitivity to these repellents may represent a fitness cost arising from the kdr mutation present in Puerto Rico Aedes aegypti[64].

Studies by Sebastian Horstmann and Rainer Sonneck showed that the level of pyrethroid metabolic resistance depends on the structure of the molecule and that structurally different compounds such as transfluthrin may still be effective because detoxifying enzymes are unable to bind to these uncommon structures[65].

In a further study they determined that transfluthrin showed the highest efficacy potential against most of the tested species of *Aedes, Culex* and *Anopheles* mosquitoes with metabolic resistance to carbamates, DDT and pyrethroids, with and without target-site resistance. Only *Anopheles gambiae* Tiassale resisted transfluthrin at a high rate, and further studies should be conducted to come to a conclusion regarding the impact of the resistance mechanisms in that species to transfluthrin. Transfluthin was not only active through tarsal contact but also through active ingredient that evaporated from the treated tile. The tetrafluorobenzyl pyrethroid structure of transfluthrin obviously provided advantages in the biological efficacy on susceptible and resistant mosquitoes versus pyrethroids lacking that tetrafluorobenzyl ring[66].

Field studies of spatial repellent with pyrethroid-resistant Anopheles do not indicate decreased effectiveness. There have been several studies of transfluthrin-treated materials in Tanzania among both *An. arabiensis* and *An. funestus* populations resistant to multiple public health insecticides including pyrethroids, carbamates and organochlorides.[67] Likewise studies in Malawi using metofluthrin did not show any decreased efficacy against pyrethroid resistant *An arabiensis* and *An funestus*[68].

Ongoing Spatial Repellent Research and Development

Introduction

Spatial repellents research is a relatively small area of research, and there are a range of ongoing projects studying the potential of spatial repellents in public health. Some recent promising results, including the 52% protective effect found in a trial of spatial repellents in Sumba, Indonesia [53] may be responsible for renewing or maintaining interest in spatial repellents amongst funders and researchers. Interviews with industry also indicated that there was a large appetite for the development of further spatial repellent products. Some companies had active projects and others had development projects in the pipeline.

Ongoing projects identified included two modelling projects, two randomised controlled trials, three semi-field trials, and one field feasibility study.

Modelling Projects

A recent PhD thesis submitted to the Swiss Tropical Public Health Institute used the low technology spatial repellent device (transfluthrin impregnated hessian strips) described by Ogoma *et al.* [69, 70] as the basis for modelling the potential public impact of spatial repellents. The results still require peer-review, but the early outcomes suggest that spatial repellents could have a potentially significant effect. Transfluthrin-treated eave ribbons act mainly by killing or disarming mosquitoes, suggesting transfluthrin-treated eave ribbons do not increase risk for non-users, making their combination with traps less necessary[71].

Another modelling team incorporated data from trials of transfluthrin-treated hessian strips into a mathematical model to predict its public health impact across a range of scenarios. Different target product profiles were examined, which show the extra epidemiological benefits of spatial repellents that induce mosquito mortality[72] .

Work is also ongoing looking at the effect of spatial repellent induced diversion of mosquitoes to untreated houses, and also the potential of using modelling to help better screen candidate repellent actives, and also potentially bridge between entomological outcomes to epidemiological ones [73]. Modelling work is also directed at the movement of mosquitoes in response to spatial repellents, and the use of these interventions within push-pull systems [74]. More modelling work is planned around push-pull designs including epidemiological outcomes, cost-effectiveness, optimal distances between push and pull components, and impacts in a range of settings.

Randomised Controlled Trials

A cluster-randomized, double-blinded, placebo-controlled trial was conducted to estimate the protective efficacy (PE) of a spatial repellent (SR) against malaria infection in Sumba, Indonesia. Following radical cure in 1,341 children aged >/= 6 months to </= 5 years in 24 clusters, households were given transfluthrin or placebo passive emanators (devices designed to release vaporized chemical). Monthly blood screening and biweekly human-landing mosquito catches were performed during a 10-month baseline (June 2015-March 2016) and a 24-month intervention period (April 2016-April 2018). Screening detected 164 first-time infections and an accumulative total of 459 infections in 667 subjects in placebo-control households, and 134 first-time and

253 accumulative total infections among 665 subjects in active intervention households. The 24-cluster protective effect of 27.7% and 31.3%, for time to first-event and overall (total new) infections, respectively, was not statistically significant. Purportedly, this was due in part to zero to low incidence in some clusters, undermining the ability to detect a protective effect. 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 one-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% PE). Primary entomological analysis of impact was inconclusive. Although this study suggests SRs prevent malaria, additional evidence is required to demonstrate the product class provides an operationally feasible and effective means of reducing malaria transmission[75].

A similar study is currently recruiting in a semi-urban area of Iquitos Peru with the same active. This trial is looking at *Aedes* borne viruses including dengue, chikungunya and Zika. The primary analyses (PE/seroconversion; PE/PCR; *Aedes aegypti* abundance and parity) are now completed and those outcomes will be presented to WHO VCAG in June 2020. Secondary, tertiary and *ad hoc* analyses are planned over the proceeding months. There are plans to submit the primary manuscript (and preprint) to align with the VCAG formal report when it is posted in July or August 2020.

Semi-field Research

There is a variety of semi-field research currently underway. Transfluthrin, on a passive plastic emanator, has been tested in Thailand in tunnels and outdoors. Initial results suggest over 70% protection from biting in a semi-enclosed environment, but this halves when the emanator is moved outdoors[76].

There is also a lot of work on spatial repellents as the 'push' factor within push-pull systems. Others are also looking into new delivery methods, particularly low-cost and low technology solutions such as impregnated hessian fabric and also wearable spatial repellents such as shoes and sandals.

Other Trials

In the humanitarian sector, spatial repellents are of interest because of their potential faster rollout than interventions like IRS that can take a few weeks to set up. Spatial repellents may also be important in situations where the population is living in temporary shelters – including tarpaulins stretched over sticks – where IRS or LLINs are impractical. There are two large trials of transfluthrin passive spatial repellents for emergency contexts. The first targets sandflies where the NGO MENTOR Initiative and SC Johnson are partnering on a large Grand Challenge – Canada [77] innovation grant, to evaluate feasibility, acceptability and effectiveness of spatial repellents when used on mass in Urban and Camp settings in NE Syria, for sandfly / leishmaniasis control. They are working with a university partner in Turkey and finalising protocols. Piloting starts this summer to finalise entomological monitoring and other study methods and begin the full study in Urban and camp clusters (IRS + case management, spatial repellents + case management, case management alone) in Feb 2021 through to June 2022. Second is a Unitaid-supported project led by University of Notre Dame that includes an arm to use the same SC Johnson transfluthrin passive emanators implemented by Catholic Relief Services for Displaced populations in Mali and Uganda[78].

Laboratory Test Methods and End Points

WHO Test Guidelines

Various methods have been used to test the efficacy of spatial repellents against mosquitoes. Laboratory experiments test the efficacy and the longevity of protection in controlled environments. The World Health Organization (WHO) guidelines for efficacy testing of spatial repellents [79] state that the movement away from a chemical stimulus, and the interference of host seeking behaviour (attraction-inhibition), and feeding behaviour, should be measured with laboratory studies. The dose response (ED50 and ED95) should be established for movement away from a chemical stimulus and for host attraction inhibition and the efficacy and duration of protection of formulated products. The WHO recommends determining movement away from a chemical stimulus using a cylinder bioassay where two cylinders (control and treatment) are both connected to a middle clear cylinder where 20 mosquitoes are placed and mosquito movement is observed after 10 minutes. A minimum of 9 replicates of 5 dilutions of an active ingredient to cover a wide range of responses (including concentrations that will give <50% and >50% response) should be tested.

To test the host attraction-inhibition, a Y-tube olfactometer is recommended, where a dual-choice olfactometer with a control and treatment arm is used. Mosquitoes are placed at the end of the tube and mosquito movement is observed to either arm of the bioassay (treatment or control), and human odour is used as an attractant. It is recommended to use 10 mosquitoes per replicate, and six replicates are recommended per active ingredient. Furthermore, serial dilutions are recommended per active ingredient. The exposure time is species-specific and determined during the negative control initial attraction response. The mean percentage attraction and ED50 and ED90 are determined.

A free-flight room test is used to determine the protective efficacy (PE) of spatial repellents. Fifty mosquitoes are released in one room (30 m3), with a volunteer sat in the adjacent room conducting a human landing catch. Efficacy should be assessed until PE falls below 50%. The landing and feeding inhibition is then calculated, and only a dose that achieved 99.9% protection should then be tested in semi-field trials [79].

The WHO guidelines are currently the best benchmark to guide testing of spatial repellents, as they have excluded mortality and knockdown outcomes that may only apply to volatile pyrethroids. However, the guidelines are consensus of a number of experts, many of whom have developed testing methods further, and there remains a need to develop and justify more robust test methods for spatial repellents.

Test Methods in Published Literature

There were a variety of laboratory methods used to test spatial repellents in the literature, and a summary is given in Tables 7 and 8. Few assessed the movement away from a chemical stimulus, instead relying on knockdown and mortality measurements. A common set up saw mosquitoes placed in square cages where they were then simply exposed to the compound.

In one study, a Peet Grady bioassay chamber was used to determine the KT50, KT95 and 24 hour mortality, however, the behavioural response to the spatial repellent was not assessed [10]. Only one study was found that used a similar cylinder test bioassay to the one described by the WHO guidelines [20], however, as it was published before the guidelines, it unsurprisingly deviates from these methods in some places.

Three laboratory studies were found that assessed host-attraction inhibition, however, only one study [22] used a Y-tube olfactometer as described in the guidelines. The others used wind tunnel set ups [14, 15]. All studies were able to demonstrate high levels of repellency for the spatial repellents tested, but the equivalence of the methods is not known.

No published studies were found that tested the protective efficacy of a product using a free-flight room.

Conclusions

The WHO guidelines were published in 2013, but even amongst the few publications since that time, uptake of the methods has been very limited. The variation in testing methods makes comparison of published results between researchers difficult.

Many researchers used knockdown and mortality outcomes, perhaps because of regulatory requirements that still require these measures for a spatial repellent to pass. However, the movement away from these measures towards more relevant outcomes for spatial repellents such as movement away from a chemical stimulus, or host attraction inhibition is one of the strengths of the current WHO guidelines. Current regulatory requirements that still demand knockdown and mortality data will need to change to firstly allow equivalent space in the market for non-insecticidal spatial repellents, and second to allow the development of better test methods including bite prevention end-points.

Table 7. Methods and outcomes used to test movement away from a chemical stimulus.

Study	Bioassay Method	Number & Species	Exposure Time (minutes)	Number of Replicates	Active Ingredient & Concentration	Outcomes Measured
WHO Guidelines [66]	Cylinder test	20	10	9	Minimum of 5 concentrations per active ingredient	Knockdown in each cylinder Mortality after 24 hours Spatial activity index.
Chin *et al.* 2017 [9]	Glass chamber	20 *Ae. aegypti*	20	3	0.01% metofluthrin 0.20% d-allethrin 0.15% d-trans allethrin 0.04% prallethrin	Knockdown
Avicor *et al.* 2015 [6]	Glass chamber	25 *An. gambiae*	60	4	0.01% metofluthrin 0.25% and 0.30% d-allethrin 0.15% d-trans allethrin	Knockdown
El-garj *et al.* 2015 [10]	Peet Grady chamber (WHOPES)	25 *Ae. aegypti*	60	3	0.2% and 0.3% d-allethrin 0.1% and 0.15% d-trans allethrin	KT_{50}, KT_{90} Mortality
Peterson and Coats 2011 [20]	Cylinder test	25 *Ae. aegypti*	15	5	0.1% and 1% catnip oil; 0.1% and 1% Z,E isomer; 0.1% and 1% E,Z isomer	Repellency
Bibbs *et al.* 2018 [7]	Fumigant bioassay	20 *Ae. aegypti, Ae. albopictus, Cx. quinquefasciatus, An. quadrimaculatus*	120, 240, and 24 hours	Not stated	5%, 1%, 0.50%, 0.10%, 0.05%, 0.01% prallethrin, flumethrin, transfluthrin, meperfluthrin, and metofluthrin	LC_{50} and LC_{90}

Table 8. Methods and outcomes used to test host attraction inhibition.

Study	Bioassay Method	Active Ingredient & Concentration	Attractant	Number & Species	Exposure Time (minutes)	Number of Replicates	Outcome
WHO Guidelines [79]	Y-tube olfactometer	n/a	Host odour	10	Species specific	6	ED50 and ED95
McPhatter *et al.* 2017 [14]	Wind tunnel olfactometer	0.4% and 1% transfluthrin	Human breath	20 *Ae. aegypti*	10	5	Landing & probing Blood feeding reduction
Rodriguez *et al.* 2017 [15]	Wind tunnel olfactometer / taxis cage	31.2% metofluthrin	Human volunteer	50-125 *Ae. aegypti*	15	4	Attraction rate
Obermayr *et al.* 2012 [22]	Y-tube olfactometer	2.5% and 5% catnip oil, thyme oil, 1-methylpiper-azine, homopiper-azine; and 2.5% catnip oil and homopiperazine	Human forefinger	15-21 *Ae. aegypti*	5	10	Repellency

Outline Protocol for Semi-field Trials of Spatial Repellents

Background

Semi-field trials are intended to extend the results of laboratory efficacy studies, allowing for the testing of formulated products against free-flying populations of target species under conditions that simulate real world use. The methods described here are based on the current WHO guidelines for testing spatial repellents [79], with modifications suggested by more recent published work [14, 34, 80, 81].

Objectives

The following objectives should be addressed by semi-field trials:

1. Determination of the protective efficacy within the field of effect
2. Determination of the duration of protective efficacy provided

The following objectives may also be addressed by semi-field trials:

1. Evaluation of feeding inhibition
2. Determination of optimum dosage(s)
3. Determination of protective efficacy over distance from a spatial repellent device
4. Evaluation of excito-repellency (or exit rate after exposure)
5. Determination of reduction in mosquito entry

Trial Design

Spatial repellents should be tested in a fully randomised design to measure feeding inhibition or, at a minimum, human contact rate using human landing catches within enclosed arenas where laboratory reared mosquitoes are released. Treatments and volunteers should be randomised using a Latin square design (as far as this is possible given the type of intervention being tested). All replicates and different treatments should be tested independently, and if tested simultaneously the arenas should be sufficiently separated to avoid any interaction between treatments.

Ideally, the test should be repeated with three mosquito species that cover a range of biting behaviours (anthropophily, endophagy, diel cycle). Depending on the species chosen, it may be necessary to carry out testing in different ecological settings (e.g. semi-urban, agricultural, forest).

Outcomes

The outcome of feeding tests is feeding rate and for human landing catches is the landing rate. These are compared between treatments to calculate the protective efficacy in terms of biting or landing inhibition.

Sample Size

A sample size calculation must be performed to ensure sufficient replicates are performed to achieve the specific aims of the trial.

Interventions

The spatial repellent(s) should be tested alongside negative and positive controls. Care should be taken to ensure the spatial repellent is tested at an appropriate interval after set-up to allow sufficient time for the active to reach its effective dose. These data should be available from laboratory studies, possibly with the addition of modelling data.

Products should be stored between evaluations according to the label claims under environmental conditions similar to those used during evaluation. Longer-lasting products can be stressed or aged experimentally in environmental chambers to facilitate logistics.

Randomisation and Blinding

If possible, those carrying out human landing catches should be unaware of which treatment or control they are testing. Therefore, ideally negative controls should be a placebo or blank product, rather than a no treatment condition. Actives may have a distinctive odour or other identification that make blinding impossible, in which case the analysis must be coded and performed by a statistician unaware of the treatment allocation.

As described above treatments should be rotated between test arenas according to a Latin-square design. Therefore, sufficient time should be allowed between tests to allow the arenas to be ventilated and cleaned to ensure no contamination persists from previous testing. Rotation of treatments is relatively easily achieved with 'point-source' treatments such as coils, diffusers and emanators. Some treatments such as treated wall surfaces are less amenable to this. In some cases, the treatments can be applied to removable boards that are fixed to the walls during treatment and can be rotated between arenas. However, if this is not possible, then landing catches must be run prior to testing to demonstrate that control outcome data is not variable between the arenas.

Participants

Participants taking part in human landing catches should be heathy adults who have given written informed consent or employees approved to conduct testing through institutional safety and occupational health reviews. They should be fully trained in the use of all aspirator equipment before the start of the trial. Participants should be asked to avoid the use of scented personal care products before and during each test period. If volunteers are recruited from a disease-endemic area, they should be screened before and after the study for any relevant mosquito borne diseases and provided with treatment in line with national guidelines if required.

Human Landing Catches

Following set-up of the treatment, a single trained volunteer should be seated in the test space with an aspirator and collection cups. The volunteer should have a limb exposed. For each replicate, 100 mosquitoes should be released from the release point. Mosquitoes landing on the exposed limb of the volunteer during the test period should then be caught using the aspirator and placed into labelled collection cups. The test period can be divided into suitable intervals, such as hourly intervals, and the collected mosquitoes should be placed in separate holding cups for each interval. At the end of the test period, the remaining mosquitoes should also be collected, and again kept in separate collection cups.

To evaluate feeding inhibition, the volunteer will sit or lie in the test arena and allow mosquitoes to feed. Engorged and resting mosquitoes are then carefully collected and placed in collection cups. Again, these collections can be repeated at suitable intervals. At the end of the test period, the remaining mosquitoes should also be collected.

Testing should be carried out a time appropriate to the peak biting of the species being tested.

If landing on the negative control is < 50%, or biting is < 25%, the data should be discarded and another replicate performed.

All mosquitoes collected should be held for 24 hours at optimum temperature and humidity conditions, with access to sugar solution for observation of mortality. If insecticidal activity is indicated in laboratory studies, knock-down must also be monitored at 1 hour after collection.

Indoor Testing

To evaluate a spatial repellent intended for indoor use, experimental huts or tents should be used that as far as possible mimic local building materials and house design. It is helpful, however, to use huts with cement floors, and a surrounding water-filled moat to prevent entry of ants, to minimise loss of dead, resting or blood-fed mosquitoes. Doors, windows and other entry points should be screened to prevent mosquito entry or exit. Each hut should be of a standardised design, described in the report. Care should be taken to ensure the size of the huts is taken into considerable when deciding on the deployment of the treatments (number, time interval between set-up and the start of collections).

Huts should be checked for contamination by an appropriate control test before evaluation of each new product. Temperature and humidity should be recorded throughout the test. Instrumentation should be mounted in each compartment in the same location to allow consistent comparisons of measurements. Mosquitoes should be released from designated release points within the hut.

To evaluate excito-repellency, exit traps should be fitted to windows, eaves or other exit points.

Outdoor Testing

Semi-field trials should be carried out in large enclosures that allow free mosquito flight (at least 10 x 10 x 2 m, or 200m3). These should be screened with mesh that allows temperature, humidity and airflow to mimic external conditions, but prevents mosquitoes from escaping. The position of the volunteer and spatial repellent should be fixed in the centre of the enclosure, but the release points may be varied according to prevailing wind direction.

To determine the protection as different distances from the repellent device the location of the device and volunteer should be varied. In these cases, the distance between the volunteer and the mosquito release point should remain the same.

To evaluate reduction in mosquito entry to a hut, the experimental huts should be placed inside these screening enclosures, and mosquitoes released outside the hut.

Test Insects

Testing should be conducted with well-characterized mosquito species reared in a colony that is pathogen free. Only female mosquitoes should be used; they should be unfed, nulliparous and of uniform age, preferably 3-8 days post-emergence (or as appropriate for the species and strain to observe host-seeking behaviour).

Data Analysis

Percentage protective efficacy (PE) is calculated as:

$$\text{Protective efficacy (\%)} = \frac{\text{Mosquitoes on Negative Control} - \text{Mosquitoes on Treatment}}{\text{Mosquitoes on Negative Control}} \times 100$$

Total mosquito numbers can be used if the number of replicates is equal (i.e. the full Latin square randomisation was completed). If some replicates are missing, then averages per replicate should be used.

To determine the duration of protective efficacy, the PE should be calculated for a range of time points following activation of the spatial repellent. To determine the optimum dosage, the PE should be calculated for each of the dosages tested. To determine the protective efficacy over distance, the PE should be calculated for each of the distances tested.

To evaluate feeding inhibition, the numbers of bloodfed mosquitoes only should be used in the calculation above.

Ethical Considerations

Human landing catches will require the use of human volunteers, and studies should be carried out in compliance with Good Clinical Practice when possible. All study protocols should be approved by the relevant research ethics or biosafety committees in the country or institution in which the study is taking place. Volunteers should give fully informed consent before taking part and, their confidentiality maintained as far as possible. Participants' well-being must be assured and their autonomy respected. Particular consideration should be given to the potential adverse effects of any treatments on volunteers.

Economic Considerations for Spatial Repellents as a Public Health Tool

Introduction

Although there are significant sums of money in pesticides and the chemical vector control market (the vector control market was worth an estimated US$15 billion in 2017), the proportion dedicated to public health is a very small fraction of this. For example, vector control insecticides may account for only 2% of the pesticide market [82]. Therefore, vector control tools aimed at the public health market must make a profit that justifies their continued production.

Research and Development Costs

Note the following statements on research and development costs are contributions from several of the persons interviewed.

Funding for research and development is challenging as there are limited funders interested in novel vector control tools. In the last decade, the focus of funding bodies has moved to malaria eradication and innovative product development. Therefore, whilst the general outlook for funding research on spatial repellents has improved, there are still fewer opportunities than for established tools. Spatial repellents are a potential tool against Aedes borne diseases, which is one of the fastest growing public health threats today. Therefore, shifting the focus of spatial repellent research from malaria to *Aedes*-borne pathogens may be a route to additional funding streams.

Public health tools for malaria control generally need to get authorisation through the WHO and VCAG. For new product classes this requires demonstration of efficacy in terms of disease reduction, which is expensive and can be both difficult and risky. This creates a disincentive for companies who are first to register a product type.

Product authorisation through the WHO can be expensive in both time and money, and this cost will be reflected in the eventual market price. At worst case, manufacturers may not see any commercial gain in the development of new tools. However, other companies are not just willing, but very keen to develop further into this market.

Technology Costs

Current spatial repellent products include some that rely on a fan to disperse the active ingredient (AI) or an electricity powered heat pad to vaporise the AI. These products, therefore, require batteries or a reliable electricity supply in order to be effective, which presents a significant cost barrier to low-income households. Passive emanators are available that require no such power, and low technology solutions have been tested successfully in Tanzania [69]. Spatial repellent tools for public health are likely to be drawn from these passive devices, unless innovative solutions can be made, such as the solar-powered dispensers tested by Andrés *et al.* [80]. Solar power may be a serious consideration for spatial repellent devices moving forward.

Market Considerations

Companies need to see market potential for a product before they invest heavily in research and development. However, spatial repellents are not supported by any WHO position statement, and they are, therefore, not used by any regional or national malaria control programmes or bought by any donors. This represents a major barrier to their further development and eventual use in public health. The costs and risks of product development mean that spatial repellent products often end up on the consumer market even though they may not provide significant protection for the community beyond perhaps some personal protection for the user when companies focus on recovering development costs. Having a number of sub-standard products on the market can lead to a loss of trust in the market from a consumer point of view. Even when products are effective, there is scope for further development, particularly in trying to design a product for public health use. Nevertheless, convincing companies to take this step when they have an existing product can be difficult.

There is an established consumer market for spatial repellents in higher-income areas, which includes towns and cities where *Aedes*-borne diseases are a significant public health problem. Therefore, it is possible that higher cost products may be acceptable in these settings. The challenge remains, however, to ensure the available products are both efficacious and used appropriately. The lack of reach of current spatial repellent products to low income populations is an access problem that at least one company is very aware of and is trying to address. The potential challenge seen by these companies is not necessarily in product development, but in changing user behaviour. The market potential is large enough that spatial repellents are a priority for many of those in industry, although their approach to growth in the area varies between companies. In 2109 Unitaid provided a $33.7m grant to the University of Notre Dame for “Innovative repellents for disease-carrying mosquitoes”[83] The project examines a transfluthrin passive emanator in several different contexts, against both dengue in malaria, in semi-urban and village settings as well as displaced person temporary shelters.

Recommendations

Innovative approaches to funding may need to be sought in order to both invest in the required research and development and to ensure the products reach all households where they are needed.

Industry has driven much of the research and development for spatial repellents, and so it is recommended that work including development of test methods and product development are done in close collaboration with industry.

Conclusion

Several interviewees identified cost as a barrier to spatial repellents becoming a vector control tool in a public health setting. Products currently available were not seen as being cheap enough for regular use by low-income households.

At present the vector control community is looking for a tool that is easy to use, cheap, and long lasting. Current spatial repellent products, while relatively easy to use, have a short duration of effect and are not thought to be cheap enough. The cheapest spatial repellents are coils, which last only hours and come with concerns over inhalation safety. However, work by Ogoma and colleagues has demonstrated the efficacy of a very low-technology solution that could be adapted to screening houses or other areas [70, 84]. How this technology might be scaled up and commercialized remains unclear.

Many interviewees stressed the need for spatial repellents to be comparable in costs to established vector control tools such as long-lasting insecticidal nets (LLINs) or indoor residual spraying (IRS). However, given the lack of vector control tools to protect at risk populations outdoors and displaced populations, comparing costs to IRS and LLINs is not always logical.

Commercialisation of Spatial Repellents

Introduction

There is a significant range of spatial repellents on the market, most geared to the consumer market in more developed regions. This analysis uses interview responses from academic and industry experts to examine the types of products and the effect of commercialisation.

Existing Spatial Repellent Products

The majority of products available for use as spatial repellents act through the passive or active emission of a repellent/insecticidal chemical into the air. Passive emission products do not rely on heat, electricity or any energy in-put to release the active ingredient/s into the air, and include metofluthrin-impregnated paper or plastic, essential oils on vermiculite, and DDT in the form of IRS which has been reported to have more of a repellent effect than a toxic effect in some vector species. Active emission products work similarly, except they require energy such as an air current, heat or aerosols [85]. Existing products include catalytic heaters with allethrin on a paper strip, mosquito lamp candle-heated strips; solar powered fans that emit linalool, mosquito coils impregnated with spatial repellents are very popular worldwide and can have a variety of active ingredients [86]. Kerosene lamps with active ingredients either added to the fuel or kept above the flame are also used, although not available in many countries. Products such as electric reservoirs that can provide up to 30 days of emission are also available. Other devices that are worth noting are radiofrequency and sonic products that are believed to interfere with the sensory system of mosquitoes by emitting a frequency that disrupts their flight and prevents them from coming into close proximity with people. Literature does not support the efficacy of these products although there are many products currently available on the market. Other possible repellents include magnetic or electric fields that disrupt mosquito behaviour or prevent entry to a space. Products using this technology are yet to be commercialized. If significant research supports these physical barrier products, it will provide a solution to those who do not want to be in close proximity to chemicals. In developing these products, people do not need to be exposed in order to test the efficacy of the products.

Commercialisation of Spatial Repellents

As more efficacious spatial repellent products become widely available there is potential for them to be implemented into global vector control programmes [87]. This section provides a summary of the products available, but product efficacy has not been considered here.

Some products contain DEET, IR3535 and Picaridin [88]. The formulations vary but are often characterised by high concentrations of the active ingredient. The concentration of DEET in commercially-available products on the market can vary from 5-100%, whereas IR3535's concentration ranges from 5-20% [88]. Repellents containing transfluthrin or metofluthrin are heavily consumer driven and are geared towards indoor use. Sumitomo Chemical Company, for example, has developed a metofluthrin (SumiOne®) based product that lasts for roughly 6 to 8 weeks and has knockdown effects on mosquitoes [18]. For other companies contacted, spatial repellent development may form a part of their general insect control aims, but as yet are not major priorities compared to conventional insecticidal product development. However, we are aware of other companies who are pursuing the development of spatial repellents, but they were not interviewed here.

Spatial repellents designed for home-use, must of course be acceptable by the home-owner. Consumer acceptability of a global product can be a challenge and may present barriers to market/ impact. Interviews conducted in Cotonou, a malaria endemic region of Benin, revealed that people who are given products such as ITNs for free, link the distribution with government initiatives and do not trust the incentives of organisations including NGOs that give out free products [86]. Local residents in that region preferred to buy products from their local distributors; products such as coils, insecticide sprays such as Baygon®, burning and burying local plants (Azadirachta indica; Hyptis suaveolens and Citrus sinensis). In doing so, communities felt more involved with their protection when they made a conscious choice to buy a product [86]. Products that had a "nice smell" were preferred over "strong-smelling products that interfered with the smell of the house" [89]. The repellents that were available were deemed to be expensive and take up a significant portion of a households' annual budget. Topical formulations of repellent were available but were unfavourable because of their smell and they were deemed to be unsafe for use on the skin because of their chemical nature [86]. How the product is marketed, has a significant effect on how it is received by local communities. Spatial repellents offer a relatively cheap and nonintrusive tool that can be distributed locally [86].

A common problem that can arise with the commercialisation of spatial repellents is that consumer products are not subjected to the same rigorous efficacy testing that public health products are. While this current review does not quantify the value of the consumer spatial repellent sector, it is certainly very large, particularly in Asia. The 2019 IVCC Market Access Landscape for the Indo-Pacific notes that the region accounts for about 55% of the global market share for mosquito repellents[90].

The primary aim of consumer products is to make money, so the effectiveness of these products is important, but not always the most important factor. Regulation of spatial repellents is not standardised across national borders, which means huge variation in product quality. It is suggested that before new products are introduced onto the market, the existing ones must first undergo efficacy testing according to standardised protocols, such as those provided by the WHO. It is recommended that a better understanding of what is marketable to people in disease-endemic regions is in order to further develop spatial repellent products. The goals of public health and consumer products can conflict, when the cost of further product development must be weighed against a company's need to make profit in the short term.

Target Product Profile

This conceptual Target Product Profile (TPP) was primarily built using opinions from academics and industry experts. A common theme from the interviews was a distinction between firstly what was acceptable and attainable immediately, and then what would be ultimately desirable possibly after further research and development work. Therefore, the TPP has been split into the "Acceptable" and "Ideal" spatial repellent products (Table 9).

Target

The aim of the spatial repellent product should be to reduce the transmission of any mosquito borne disease. They, therefore, need to be effective against both *Anopheles* and *Aedes* mosquitoes, and ideally against other disease vectors such as *Culex* mosquitoes, sandflies, or blackflies. This will require devices that can be adaptable to the range of biting behaviours that covers. There is also a desire to protect against nuisance biting as this will increase acceptability and compliance with end-users. The current low effectiveness of some spatial repellent devices was mentioned by multiple interviewees, and the consensus was that 90-100% reduction in biting would be required within the range of the device. However, data on how much reduction in biting would be required to see an epidemiological effect is not yet available, and these figures are mostly based on a guess about what users might want rather than what would effectively protect from disease transmission. This is a very important statement and indicates one of the most fundamental questions that needs to be answered about spatial repellents to assess as a viable malaria control tool. The Indonesia trial indicated good epidemiological outcome with a 32% lower HLC and the China study showed a 82-92% reduction in indoor mosquito catches and gave very good protection against malaria. There may be data available that could be added to indicate a range of possibilities as some question if setting the bar at 90-100% is too high.

Setting

The settings and populations for whom spatial repellents would be most effective was a topic for which there were as many opinions as interviewees. Some points were commonly raised, however, including the requirement for spatial repellents to work well both indoors and outdoors. Indoor efficacy is readily achievable with current tools, and an alternative to IRS may be possible, however, outside of dwellings, the problem becomes more difficult to solve, as the release rate and extent of coverage required outside is something that would be challenging to determine even using modelling tools, as factors such as wind speed and human movement make the environment highly variable. Importantly, spatial repellents are likely to be best used alongside, rather than instead, of other vector control tools, so it will be important that the spatial repellents are complimentary and work well in combination (perhaps in push-pull systems). Other logistical issues need to be considered also, for example, a burning coil should not be placed next to flammable impregnated bet nets, screens or curtains. Additionally, the potential unknown sub-lethal effects of pyrethroids such as transfluthrin and metofluthrin were of concern with the continued use of pyrethroid nets in high resistance settings.

Powered devices require an electrical supply, which may be a barrier to implementation particularly in low-income settings. However, solar panels have been trialled previously to power mosquito traps [91] and a similar strategy could prove valuable with spatial repellent devices.

It is key that spatial repellents can be implemented in both low and middle income households, and rural areas in particular. Settings that might be most amenable to spatial repellents use included humanitarian crises where the traditional tools may be limited (e.g. nowhere to hang bed nets); mobile workers (as spatial repellents are potentially lighter to carry then bed nets); and low transmission settings where passive devices may be more acceptable than those which require high behaviour change. Spatial repellents could potentially be used anywhere, and modelling, particularly for outdoor use may help refine product better for different scenarios.

Delivery

The delivery of the spatial repellent should be informed by the use case, and key considerations identified were duration of efficacy (and therefore frequency of replacement); cost; power; and area of effect. It was also felt important that public health focused devices were packaged similarly to commercial products so that people would want to use them.

Passive devices have the advantage of not requiring batteries or electricity to power fans or heating elements. This also makes them lower cost and maintenance free until the time they require replacement.

An attractive design and fragrance is desirable, and one interviewer thought that spatial repellents do not necessarily need to advertise that they are insect control product. This company has investigated a number of household products that might be impregnated with spatial repellent actives to create a bite free space within the home and have for example looked into wall hangings and even calendars. Another feature that may increase use and replacement habits is some kind of signal (perhaps colour change) to show when the device was working and/or needed replacing.

Mode of Action

Current spatial repellent devices were criticised for their duration of effect, and correspondingly high replacement rate and costs. It was felt that ideally a single device should be able to protect for a transmission season, so potentially 6 months. Lower durations of 3 months might be acceptable in some situations where this was comparable to IRS performance. Otherwise a sustainable, and acceptable, way of replacement would need to be developed. This aspect has an important interaction with behaviour change, so a product that lasted all season and required no behaviour change was ideal. However, in some scenarios a spray that needed daily application might prove more effective than a device that requires replacement every two weeks as this might be more easily forgotten. Therefore, there is likely to be a trade-off between efficacy and rate of replacement.

In terms of active ingredients, currently only the volatile pyrethroids such as transfluthrin and metofluthrin are considered to have sufficient evidence of efficacy to be used in an intervention. However, alternatives may be feasible in the future including volatile terpenoids or other botanicals. An active that not only discouraged entry to a particular area, but through sub-lethal exposure was able to reduce biting on unprotected people is also potentially possible with the current tools, although the precise scale of the effect is not yet known.

The range of effect is also key, and devices need to be engineered to give a certain release rate in the field that can maintain an efficacious air concentration. The size of effect required will depend on the intended use, and further research may be required to determine factors such as how far and fast people move during peak biting periods.

Safety

The potential risk from spatial repellents that are burnt such as coils is a concern, as not only the active ingredient will build up inside the room being protected, but also potentially dangerous particulate matter. Emanatory devices that avoid the need to burn any substrate are therefore to be preferred. Even these devices will need to demonstrate safety in terms of surface residues that might be contacted by children or pets. The safety of the active ingredient itself is also of prime importance, given the potential exposure of at-risk groups (infants, children, pregnant women, elderly, hospital patients) when used as a public health intervention.

Evidence

Evidence of efficacy must be obtained from robust randomised trials, of which there are very few at present. Well-designed trials are underway, but in the interim, alternatives might be considered, particularly where safety has been well established. Trials with entomological end-points must suffice for many emerging vector-borne diseases such as many *Aedes*-borne viruses with unpredictable outbreaks. Modelling to bridge from entomological effects to predicted public health outcomes can be informative for development and delivery decision making in these situations.

Cost

The cost of spatial repellents was a high priority for most interviewees. In order to make them available for large scale distribution for malaria control, the cost of production and delivery of spatial repellents devices ideally needs to be comparable to existing interventions such as LLINs and IRS. These are expressed in terms of costs per person protected, which without epidemiological data is not possible to estimate yet for spatial repellents. The recent work by Syafruddin et al in Indoneisa may help to provide a starting point for this question and is certainly something to consider for future trials. But the huge range of devices available, means that costs can vary and low-cost solutions are not out of the question. In addition, there may be some settings such as humanitarian crises where a higher cost might be tolerated as conventional tools are difficult to implement. Note, that for arbovirus control, comparison to LLIN and IRS may not be applicable.

Logistics

The potential of spatial repellents to be small and lightweight in comparison to both LLINs and IRS, makes then attractive in terms of ease of transport and delivery. However, this relies on each unit being as effective as possible, so the number of units required to protect a household is minimised, and the interval of replacement is maximised.

Table 9. Conceptual target product profile, as determined by interviewees, for a spatial repellent to be used as a public health intervention. We have provided further consideration, beyond the interviewee comments.

Please note that since the beginning of this review there has been an evolution in the WHO concepts of Target Product Profiles and Preferred Product Characteristics. As currently defined[92]:

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).

Target Product Profiles (TPP) are a planning tool 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 a minimal and preferred performance characteristic. The minimal target could be considered a potential go/no-go decision point in the product development gateway process. The preferred characteristic target should reflect what is required to rapidly and effectively achieve global health impact.

Given these current definitions some of the consensus statements below may fall better into the category of PPC rather than TPP.

<table>
<tr><th></th><th>Acceptable</th><th>Ideal</th></tr>
<tr><td rowspan="2">Target</td><td>80-90% reduction in biting by Anopheles or Aedes mosquitoes.</td><td>Close to 100% reduction in biting by all mosquitoes.</td></tr>
<tr><td colspan="2">Further considerations: ideally, a product would target all indoor or outdoor biting mosquitoes, including Culex and other vectors and nuisance biting insects. It may also have an effect on other species such as sandflies, bed bugs, etc. A product (or combinatory aproduct) with broad effectiveness against a range of insects perceived to be the most troublesome is more likely to appeal to the end-user, improving uptake.</td></tr>
<tr><td rowspan="2">Setting</td><td>Humanitarian crises, mobile workers, low transmission settings. Spatial repellents should also be effective indoors, and in semi-open structures, and readily accessible in low-income and rural settings.</td><td>Humanitarian crises, mobile workers, low transmission settings. Spatial repellents should be effective outdoors as well as indoors, and should be compatible with existing tools including LLINs.</td></tr>
<tr><td colspan="2">Further consideration: a spatial repellent product would ideally be effective in as many different household settings within different types of communities, as well as the settings mentioned above by the interviewees.</td></tr>
<tr><td rowspan="2">Delivery</td><td>Passive device without requirement for batteries or electricity.</td><td>Passive device without requirement for batteries or electricity.</td></tr>
<tr><td colspan="2">Further considerations: there are many relevant communities that have access to electricity either via the grid or a generator. However, solar power is becoming more popular in rural settings and could provide a way of powering spatial repellent devices.</td></tr>
<tr><td rowspan="2">Active, Duration and Range of Effect</td><td>Insecticidal active ingredients that are currently available.

Devices should remain effective for 1 month.

Range of effect should be up to 2 m from the device.</td><td>An active ingredient (insecticidal or non-insecticidal) which is effective against susceptible and pyrethroid resistant mosquitoes.

Devices should remain effective for a transmission season (6 months to 1 year).

Range of effect over 2m from the device, with lasting sub-lethal effects that dampen biting behaviour outside this range.</td></tr>
<tr><td colspan="2">Further consideration: whilst range is important to consider, a product designed to be used within a household, would ideally prevent household entry.

Further consideration: Shorter duration devices (24-hour effect) may have a place where changing user habits is possible, and the reinforcement of effect may make these types of devices more acceptable to some communities.</td></tr>
</table>

	Acceptable	Ideal
Safety	Low human toxicity, particularly when used indoors Risks to non-target species in line with accepted standards for PHPs at the time of registration submission. Appropriate disposal routes and recycling for waste products	No human toxicity, particularly when used indoors Risks to non-target species in line with accepted standards for PHPs at the time of registration submission. Appropriate disposal routes and recycling for waste products
	Further consideration: ideally a spatial repellent product would have low toxicity and minimal environmental effects (e.g. on non-target organisms). The active ingredient must hold a registration with a major regulatory authority (EPA, EU, Japan) or WHO approval.	
Evidence	Entomological efficacy and safety data may be used to support use in public health settings.	Safety and efficacy data from randomised trials.
	Further consideration: although RCTs may not be necessary for all spatial repellent products, some smaller scale, robust, entomological data would be necessary to assess efficacy.	
Cost	Low-cost as possible to allow large-scale distribution.	Equivalent cost-effectiveness to LLINs or IRS.
	Further consideration: cost considerations are use-case specific. Ideally a spatial repellent would be cheaper than LLINs or IRS. In arbovirus outbreak settings or to protect displaced persons comparison to unacceptable tools such as LLINs is not logical. Some substantial modelling would be needed to fully understand the economics of what would be suitable for a particular product, in a particular setting.	
Logistics (and disposal)	Spatial repellents should be small and lightweight. Plastic waste should be kept to a minimum.	Spatial repellents should be small and lightweight. Plastic waste should be kept to a minimum. Release rates should be stable for the conditions of use.
	Further consideration: device constructed of biodegradable material, or with low environmental impact, would be ideal. Ideally the product would require little maintenance and infrequent replacement of actives.	

Regulatory Issues and Policy Status

Regulation of Spatial Repellents

To sell a spatial repellent to consumers, companies must register the product with a national regulatory authority. The type and level of evidence of efficacy that is required varies between countries, which can complicate the picture. This problem is recognised, and organisations including UNITAID, APLMA (Asia Pacific Leaders Malaria Alliance), I2I (Innovation 2 Impact) and IVCC (Innovative Vector Control Consortium) have worked to address this [93].

In general, national regulatory agencies require evidence of efficacy and safety. The malaria control community and leaders at the World Health Organization have yet to accept spatial repellents as viable tools for malaria control. However, the U.S. EPA has registered several spatial repellent products for both indoor and outdoor use [94, 95]. These products were registered based on entomological efficacy, primarily for nuisance mosquito control, and these end-points are not easily translated into epidemiological end-points.

Spatial Repellents in Vector Control Policy

At present the WHO does not have a position statement on the use of spatial repellents in vector control, although it does recommend topical repellents for personal protection [96]. Therefore, the use of spatial repellents in public health will need to follow the New Intervention Pathway through VCAG (Vector Control Advisory Group) and must demonstrate epidemiologic impact for malaria control public health value [97]. This means evidence of impact on disease outcomes, as would be generated from randomised controlled trials. A systematic review of multiple trials is preferred in order to generate a recommendation for a new intervention type, although the current guidelines do not suggest this would be necessary to register a single product.

Whilst working to establish a critical path of development for spatial repellents, the WHO core working group identified three hurdles to that process [98]. These are the generation of epidemiological evidence of efficacy; identification and validation of entomological end points corresponding to a public health impact; and finally to get a consensus amongst the scientific community on the need to shift the focus of screening protocols away from mortality outcomes.

Key Challenges

One of the key challenges in registering a spatial repellent comes from the type of evidence required by regulatory agencies. As most spatial repellents currently on the market are pyrethroid-based active ingredients, there is a tendency to view them as insecticides, and to require knockdown and mortality evidence of efficacy. However, new spatial repellent actives will not necessarily have any insecticidal impact and, therefore, the requirement of a killing effect could prevent these products getting to market.

The cost of testing can be prohibitive as different countries may require testing to be carried out in country or through different methods. However, larger and more experienced companies can usually find a way to navigate this uneven regulatory landscape.

The costs of registration will inevitably be reflected in the price of the product when it eventually gets to market. Therefore, a long and expensive testing process will result in a more expensive product, which will be less attractive to both consumers and funding agencies.

Data from randomised controlled trials is costly both in terms of time and money, meaning there are actually few companies that would have the funding to support a spatial repellents aimed at the public health market. In addition, the current data requirements for spatial repellents can change due to changes in personnel at VCAG, adding another potential delay to authorisation.

WHO PQT-VC is moving towards requiring that studies on vector control products be carried out by GLP compliant test facilities. Facilities offering studies on spatial repellents are currently in the process of completing the necessary requirements to become GLP certified.

Recommendations

Spatial repellent compounds are often intended for use indoors in close proximity to people, and, therefore, their safety, including inhalation toxicity, is required for registration. Products in the past have used animal data, but human data should now be required. This in turn will also require the development of better safety labelling, and potentially also the development of different products for use indoors and outdoors.

The requirement for epidemiological data on efficacy by VCAG in order to recommend a malaria vector control tool provoked a wide variety of opinions amongst those interviewed. Some believed there was space for other data such as laboratory, semi-field or modelling studies to be taken into account, particularly in situations that do not always lend themselves well to randomised controlled trials such as humanitarian crises. Another suggestion was to create a simplified fast track system, particularly for products such as existing volatile pyrethroid-based spatial repellents where safety is already established.

One recommendation was to facilitate national regulators to using the WHO guidelines for spatial repellent testing. This would have the dual benefit of reducing testing duplication, and potentially preventing sub-standard products from making it to market. This will also help remove the requirement for knockdown and kill for spatial repellents, by making them a category in their own right. Although it was noted that as a new product class epidemiological endpoints may still be required to prove efficacy.

The WHO guidelines themselves were thought to require updating by the majority of interviewees. The areas that were identified as particularly needing attention were: field study protocols, and efficacy against Aedes-borne diseases. When they are reviewed input from industry should be key, as manufacturers have unique knowledge of the regulatory hurdles these products must go through and the types of product claims the testing must support.

Summary

The WHO PQ process (and the WHOPES authorisation process before that) was seen as a challenge to spatial repellent development by more than one interviewee, mainly due to the time required to gather the evidence demanded, which can stretch to years. The requirement for strong evidence is understandable and necessary, but it is clear that potentially impactful products are not being developed or improved due to this delay in selling the products. One expert estimated that the current regulatory practice slows the process from 3 years to 5-10 years. Balancing the need to encourage manufacturers to develop innovative products, with the desire to prevent the entry of ineffective product on to the market is delicate.

Knowledge Gap Assessment

Introduction

Spatial repellents are not new interventions, and the concept of burning a particular herb or compound with the aim of driving biting insects from a space is a long documented traditional practice [99]. More recently, volatile pyrethroids such as transfluthrin and metofluthrin have allowed the development of spatial repellent devices that are comparatively safe and effective as described above. Spatial repellents are an active area of interest for a number of academic and industry research groups around the world, but there remain a number of gaps in knowledge that need to be answered before spatial repellents can be more widely advocated for public health vector control.

The knowledge gaps were identified by interviewing experts in the field of spatial repellents and vector control from academic, industry and operational backgrounds. The main themes were identified and cross-referenced with published data where possible.

Modes of Action

Despite the progress that has been made concerning spatial repellents as a vector control tool, several integral areas have been identified due to their paucity of research and understanding. A key area that has been highlighted is the actual definition of a spatial repellent. Spatial repellents were originally defined as compounds or agents that can produce repellency at a distance [100]. This definition has since been refined as a compound dispensed into the atmosphere of a 3-dimensional space that inhibits the ability of mosquitoes to locate a host [101]. The confusion surrounding the definition largely surrounds the chemicals that are regarded as true spatial repellent active ingredients such as linalool and dehydrolinalool, as compared to volatile pyrethroids. While volatile pyrethroids are also regarded as spatial repellents, due to their insecticidal effects, there is debate on whether they truly belong in this category. The behavioural response of mosquitoes to these compounds differs, with non-insecticides eliciting a reduction in flight activity and ability to detect host odours [22, 23]. Whereas insecticide exposure resulted in accelerated flight activity [17, 102], and potentially at high doses increased attraction to the host [23].

Much of the work carried out on spatial repellents so far has concentrated on coils. However, smoke from coils not only contains the active ingredient, but also other gases and particulate matter, which may all have an influence on mosquito behaviour. The potential health impact of coils mean that future products should move away from this type of technology and the effect of the active alone is of greater interest. As more active are developed and tested, they are each likely to have slightly difference modes of action, and each will need to be assessed in terms of their effect on host location and feeding activity.

Sub-lethal Effects

Spatial repellents do not provide a physical barrier to the mosquito in the way bed nets do, which makes them much more flexible as an intervention tool as they can be used by people working outdoors and efficacy is not affected by damage to the barrier. However, the concentration of the spatial repellent in the air will affect the efficacy of the repellent and is paramount to product effectiveness. There is a lot of work to be done on how difference devices can maintain an efficacious dose particularly outside. Computer modelling is a relatively underused area for spatial repellents but has potential to give invaluable data on the build-up and loss of spatial repellents from a three-dimensional space.

As mentioned before, volatile pyrethroids are often evaluated in terms of mosquito mortality, however sub-lethal concentrations of metofluthrin (from a coil) were able to reduce mosquito entry to experimental huts by 58% [3]. This demonstrates the disjunct between mortality and behavioural outcomes, and the importance of studying sub-lethal effects on mosquitoes. Studies in *Aedes aegypti* indicate that spatial repellents can reduce fecundity and interrupt oviposition behaviour[103].

Another concern is the diversion of biting from protected areas to people in non-protected areas. In a cross-over study in Tanzania, houses with partial coverage with transfluthrin coils showed a significant increase in blood-fed *An. arabiensis* compared to completely covered houses [40]. Later work in a semi-field systems indicated that both users and non-users can be protected by transfluthrin-treated eave ribbons[104]. However, other spatial repellent actives that have been shown to decrease host seeking behaviour may have given very different results, and further testing in this area will be important in identifying which actives should be recommended for widespread use.

Deployment and Logistics

The volatile nature of spatial repellents makes them favourable in comparison to compounds such as DEET which is a topical repellent and requires direct contact to have an effect. The efficacy is also dependent on the conditions the product is applied in and requires reapplication to remain potent. The efficacy of the product can also be affected by perspiration, which reduces the duration of protection, this is unfavourable as most endemic regions are found in the tropics [86]. In contrast, spatial repellents are volatile compounds that protect an area. The area that is covered is dependent on several factors including the active ingredient in the repellent, release rate, temperature, humidity, airflow and how it is administered.

Before a spatial repellent intervention can be deployed in the field it will be necessary to understand better where best to locate devices, and how often they should be replaced. In particular, the time interval at which devices should be refilled was discussed by many of those interviewed. While some preferred a device that could last a season, which would be comparable to a bed net, others saw a place for a daily spray device that might see greater acceptance by users. Modelling of spatial repellents is still very much in its infancy, but this is probably the most useful tool to address these type of questions. Also note the development of innovative products incorporating transfluthrin-treated hessian strips include sandals[105] and chairs[67].

Safety

Despite widespread scepticism amongst the experts interviewed on the safety of spatial repellents, there a huge number of these products on the market in developed countries with strict safety regulations. Most data come from animal testing of volatile pyrethroids in burning coils and the findings of some of the published studies are summarised in Table 6. The effects of coils not only come from whichever active ingredient they contain, but also from the particulate matter in the smoke itself. One study compared a transfluthrin and a blank coil and actually found the worst damage, acute upper respiratory tract irritation occurred in both groups.

Better data is required on the safety of each potential spatial repellent active on its own, and the poor safety of coils should not be used to prevent the development of new devices that avoid the inhalation of particulates from burning.

Environmental Effects

Any future spatial repellent product should have no adverse effects on the people that use them or the environment. With regard to spatial repellents, the effect of volatile pyrethroids was of high concern to several of those interviewed. The sub-lethal effect on target mosquito populations has already been mentioned above but placing more insecticides in the environment may also result in effects on non-target organisms. Indoor use of spatial repellents may potentially limit this risk. However, outdoor use was advocated by many, particularly in forest and other rural environments, and this raises the potential for exposure of a huge range of insects, amphibians and other vulnerable species to insecticides. Future studies, particularly of outdoor use of spatial repellents will need to take this concern into account and determine the potential impact if any on non-targets.

Spatial repellent devices are mostly aimed at the consumer market and, therefore, are packaged and designed to be as attractive and appealing as possible. This often means some form of plastic shell or casing around the device, or the active being impregnated directly into the plastic. This then raises the problem of plastic waste, particularly if these devices are distributed to low-income settings where recycling facilities are limited. Biodegradable formulations would therefore be more acceptable. Research and development of these products will need to take the whole supply chain into account to ensure a sustainable future for spatial repellents.

Conclusions

For spatial repellents to be widely available on the market, there are several hurdles that must first be overcome. Many of these hurdles are associated with the paucity of scientific knowledge and defining social and regulatory parameters. For spatial repellents to be widely received there must be epidemiological data that supports the claims that spatial repellents are effective in disease endemic areas [98]. Although there are existing data that have made an association between spatial repellents and reduced disease transmission, these publications do not yet make the connection between the epidemiological and entomological components. Phase III community trials that would provide data on the vector population and the incidence of infection are underway, and their results will be pivotal for the direction of research over the next few years [106-108].

Other key gaps include understanding the impact of repelling vectors on people located in untreated locations and defining any potential limitations of spatial repellents in insecticide resistant and susceptible mosquito populations. Standardised protocols will need to be developed to evaluate vector behaviour post-exposure to spatial repellents and to be able to identify any long-term effects that spatial repellents have on vectors. Finally, the identification of modes of action, mainly genetic or neurobiological mechanisms on how repellents effect the vectors which will give insight into the properties of future spatial repellents.

Feasibility of Adoption of Spatial Repellents within Vector Control Campaigns

Introduction

Vector control campaigns for malaria currently rely on the use of insecticide treated nets (LLINs) and indoor residual spraying (IRS). ¬*Aedes* mosquitoes, in contrast are usually targeted in the larval stage through a variety of methods. There is scepticism among some policy makers to the wide scale use of larval control in malaria as *Anopheles* larval habitats are thought to be too wide-spread and difficult to locate. Similarly, the use of bed nets and traditional IRS is often not recommended for *Aedes* control as they usually feed in the daytime when people are not under their nets, often bite outdoors and rest in areas where they may not come in contact with traditional IRS. Note however the newer strategy of "Targeted IRS" that may hold promise for *Aedes* control[109]. In contrast spatial repellents have the potential to protect against biting by both genera, and in fact should work against all mosquitoes, and potentially any insect vector including sand flies, blackflies, tsetse flies, and triatomine bugs.

Outdoor Settings

The difficulty of maintaining an effective concentration of the active ingredient outdoors raised questions as to whether spatial repellents are suitable interventions against outdoor biting mosquitoes [110]. However, several interviewees were supportive of the use of spatial repellents to protect high risk groups. These groups include mobile populations, outdoor workers (including rubber plantations workers, farmers, and forestry workers), and those living in refugee camps.

Several studies have investigated the use of clip-on emanator devices for use outdoors [8, 26, 38]. However, these devices are limited by range [8, 111], longevity [30, 38] and their inability to provide complete protection [40]. There may be a role even so for such spatial repellent devices in elimination settings where an extra layer of protection could be useful, and other interventions such as chemoprophylaxis become less attractive due to the low risk of transmission.

Indoor settings

Eave screening and house modification have been topical research areas in vector control. These methods aim to reduce human contact with endophagic mosquitoes, which include the important vector species; An. gambiae s. s. Giles, Cx. quinquefasciatus and Ae. aegypti [112]. Many houses across rural parts of Africa have open eaves [113], and screening them has therefore been found to reduce mosquito entry in multiple studies [46, 112, 113]. Although limited research on the effect of house screening on malaria prevalence exists, results from a study on Bioko Island which tested ~23,000 children for P. falciparum, found the prevalence of those living in screened houses was 11% lower than those in unscreened houses [113]. It is possible that spatial repellents could play an important role in eave screening. A field study in western Kenya found net fibre eave screens treated with micro-capsulated delta-undecalactone (dUDL), reduced mosquito house entry by 50%. Using a transmission model, they predicted that the addition of a push-pull system using repellent treated eave screening with an odour-baited trap over a wide area, alongside current interventions could reduce the malaria entomological inoculation rate by 20 fold [45]. An earlier field study found eave screening to be very effective alone, and the addition of spatial repellent to make little difference [46]. However, as with bed nets damaged screens are likely to be more effective when treated with a repellent or insecticidal compound. In addition, in areas where full house screening is challenging due to the large number of entry points the addition of a spatial repellent would also act as a semio-chemical barrier [45]. Improved houses, with metal roofs and cement walls may also have an impact on reducing indoor-resting vector survival rates and subsequent malaria transmission [114] It is unclear if spatial repellents would make the indoor environment less supportive for indoor-resting vectors.

Spatial repellents designed for indoor use need to be safe, as the active will much more easily build up within the confined space. Mosquito coils have been associated with the risk of acute respiratory infections [115], and negative effects of irritancy and toxicity to eyes and the respiratory system, are also reported from the traditional burning of plant materials containing botanical insecticides [116]. When discussing the feasibility of incorporating spatial repellents into current vector control measures, push-pull strategies are a good starting point. This is demonstrated in a study which examined an 'accidental' push-pull strategy which was created when An. arabiensis was repelled by ITNs and attracted to cattle outside the home [117]. Using spatial repellents to drive highly anthropophilic anopheline and Aedes mosquitoes away from domiciles could potentially change their behaviours back to zoophily over time.

An effective spatial repellent developed for use indoors, could potentially substitute IRS, provided it is as easy for the consumer as IRS, to ensure there is good compliance. IRS is difficult in some situations especially urban/higher income and therefore spatial repellents could be more appropriate than IRS in such settings. Rapid operational rollout of spatial repellents may also be much more feasible than IRS – relevant for arboviral diseases needing rapid response for epidemic prevention. However, the general consensus amongst experts is that spatial repellent devices would rarely be a stand-alone intervention and would generally be used to supplement other vector control methods.

Push-Pull Systems

The use of push-pull strategies are common in agriculture [118] and a recurring theme in the use of spatial repellents for vector control. Push-pull systems attempt to avoid the problem of diversion by trapping diverted mosquitoes with an alternative attractant. The use of CO_2 and odour-baited traps as a pull in conjunction with spatial repellents as a push, has been found to successfully reduce house entry by Ae. aegypti in semi-field settings [50, 119]. Similarly, the use of attractant odour baits as a pull, in conjunction with dispersed repellent (dUDL) using the 'Mosquito magnet™', resulted in a 95.5% reduction of anopheline mosquito house entry in a semi-field trial [48].

Could Spatial Repellents Reduce Malaria and *Aedes*-borne Diseases?

Most field research on spatial repellents focuses on the use of volatile pyrethroids such as metofluthrin or transfluthrin. Although there is extensive evidence supporting spatial repellents reduce mosquito biting and feeding, few studies exist on the degree of protection these spatial repellents actually provide from disease. A field study in Indonesia comparing the use of the spatial repellent metofluthrin in mosquito coils to a placebo control, measured malaria infections by blood smear, alongside mosquito landing over six months. Results indicated 52% increase in malaria protection in the households using spatial repellent mosquito coils compared to the placebo households. The human landing catch rate was also found to be 32% lower in homes with spatial repellent coils. Although the results were not significant after accounting for the effects of clustering, this study does provide justification for a larger trial to detect such effects [53]. A subsequent RCT trial by Syafruddin et al detailed above was able to demonstrate an impact of a transfluthrin passive emanator on malaria incidence[75].

Evidence also suggests that transfluthrin emanator devices significantly reduce Ae. aegypti host-seeking in both laboratory and semi-field settings. In a wind tunnel experiment, both products reduced host-seeking, with a reduction in landing of 95% and 75% respectively. When placed outside military style tents in a field setting the devices reduced mosquito entry by 88% and 66%, respectively [14].

There is potential for spatial repellent use inside and outside of the domicile, however their effectiveness against malaria and arboviruses would depend on the mosquito species present and their behaviours. Aedes are known to be highly endophagic, whereas Anopheles can also be found to bite outside in regions such as across S. America and S.E Asia. Therefore, there may be differences in the effectiveness of spatial repellent devices depending on whether they are targeted for outdoor or indoor biting mosquitoes.

Potential Barriers to Adoption

A common theme raised when discussing spatial repellents for use in vector control is acceptance; because IRS have been in use since the late 1940s [120], and pyrethroid bed nets since the 1970s [121], they have shaped the landscape of disease control and there is inherent bias towards them [98]. Some describe this bias as a 'psychological barrier' in going forward with spatial repellent research. While the issue of acceptance within the vector control industry is clearly a legitimate one, the issue of non-compliance in uptake has also been raised; changing people's behaviour is a big challenge for spatial repellents. However, research has found compliance can be good provided spatial repellents meet expectations. A field study in Cambodia examined feasibility and acceptance of a metofluthrin emanator device. In a follow-up survey they found over 90% of participants were happy to use the product again, however 63% would not replace bed nets with spatial repellents. This suggests that there is a place for spatial repellents in vector control, not to necessarily replace but compliment the use of insecticides [51]. Previous studies have found good community compliance when proper education is provided [122]. Therefore, issues of non-compliance can be overcome, making it feasible that spatial repellents could be incorporated into grass rooted vector management programmes.

Although they may not always work, spatial repellents are popular, and therefore wide-scale uptake could be feasible if the right device is on the market. A survey carried out in an urban risk area for Aedes-borne diseases in Machala, Ecuador, found the most important factors to consumer decision-making when buying mosquito control products was their effectiveness and cost [123]. However, a qualitative field study in a rural part of Tanzania highlighted that ease of use and effectiveness were the two main reasons that LLINs were preferred over repellents [124]. Therefore, it would seem spatial repellents would be better accepted if they too required less maintenance and were longer lasting, a point which has been raised during interviews with industry experts. The cost of spatial repellents has also been raised, as there is no point in having control products which are too expensive [123].

Conclusion

There is evidence to show spatial repellents may be effective interventions against indoor biting mosquitoes, and if stronger epidemiological evidence were to be generated there would be strong arguments in favour of their use in control programmes. Depending on the exact formulation and device, they could be used instead of IRS, or in situations where IRS is unsuitable such as emergency shelters, or temporary accommodation for hunters, farmers or forestry workers. There is also considerable interest in the use of spatial repellents outdoors, however the evidence in this case is not as strong, and there are considerable technological barriers to overcome in developing a spatial repellent device that could provide protection outdoors. Spatial repellents need not be seen as a stand-alone intervention, and they have been tested in a number of push-pull systems. Evidence of epidemiological effect is still required, but these systems are very flexible and adaptable to a range of settings.

Recommendations on the Development of Spatial Repellents as Vector Control Tools

Background

There is a clear place for spatial repellents within vector control, however, industry experts and researchers agree that this would be complementary to current control efforts rather than as a stand-alone intervention in their own right. There are many improvements which would be desirable before spatial repellents play a larger role in vector control, however, even with current technology in certain situations they could make a real difference. The following analysis gathers the opinions of academic and industry experts on the work that might be required to take spatial repellents forward in terms of system preference, research and development and evaluation needs.

Improving Durability

Current spatial repellent devices are limited in their range, longevity and ability to provide full protection. This in part is to do with the AIs and formulations used, and their dispersal method. In order to be volatile, active spatial repellents often require a heat source to vaporize. Spatial repellents evaporate faster in higher temperatures, leading to reduced efficacy over time. Determining the rate AIs are released from coils and emanators in different environmental conditions is therefore a research need [3]. In poor, rural settings access to electricity or a heat source may not always be available, so there is room for research into passive spatial repellents which may be more suitable in these environments.

In general, mosquito coils and vaporizer mats last approximately for one night [125]. Research has also found mosquito coils to last between 8-9 hours [30]. This means that repellents and batteries frequently need replacing, at cost to the consumer. Ideally, better formulation with longer-lasting actives would be available for improved spatial repellent devices. An ideal spatial repellent device would have a longevity of anywhere between 1 month and a year. Although, this would likely depend on whether it was meant for indoor use or personal protection.

Passive spatial repellents containing metofluthrin, which vaporizes at ambient temperatures, incorporated into materials such as fabrics and plastic strips may provide longer-lasting repellency. Metofluthrin impregnated strips have been used in an experimental field study in Tanzania, which found a significantly lower *An. gambiae* density in treated versus untreated houses. The study also found an effective duration of repellency for 18 weeks [43]. Supporting research has found metofluthrin strips to last at least 6 weeks [43]. Another study found metofluthrin-treated fabric strips, hung in prayer huts with no walls in areas of Lombok, to successfully reduce outdoor biting by *Anopheles* and *Culex* mosquitoes [126]. In these communities, mosquito coils and vaporizing mats are not feasible due to the lack of electricity and their cost. This is a limitation to current spatial repellent devices and as a result, the idea of incorporating passive spatial repellents for use in eave screening and house modification has become very topical [46], and a frequently discussed topic during interviews with industry experts. Longer-lasting spatial repellents would be more appealing to consumers, given that ease of use is an important factor in consumer decision making for mosquito control products.

Similarly to the concept of house modification through eave screening, development of a spatial repellent material which could be incorporated into house modification, in the form of paints or building materials was also raised during an interview. An interesting take on this is the use of transfluthrin-treated woven baskets and hessian wall decorations, hung in outdoor social spaces to provide protection from *Anopheles* and *Culex* bites in Tanzania. This is an easy grass-roots strategy which has good acceptance and could complement other control strategies [84].

Further research into the development of more overall durable spatial repellents with improved longevity and formulation is needed. Other research priorities to improve spatial repellents include investigating the number of units needed in a house, and how volatile pyrethroids in spatial repellents may cause cross-resistance in mosquito populations.

Addressing Behaviour Change

When implementing novel control methods there are always cultural barriers which may threaten uptake. Changing people's behaviours can be a significant challenge for implementation of spatial repellent devices, as to be successful they must be in constant use. Therefore, qualitative research into community stand points is a very important part of spatial repellent research. These such studies have highlighted importance of efficacy, cost and ease of use in consumer decision making for spatial repellent devices [122-124], which must always be considered when furthering research and development. Understanding human behaviour in the acceptance of such tools has been identified as a possible knowledge gap going forward.

A good example of a preliminary qualitative study into the acceptance of a push-pull system was carried out in Peru and Thailand. The research identified that the community in Peru were already familiar with the idea of deterring insects, through what is known as a 'water bag', which they believe to keep flies away. In Thailand, participants said they would use electric fans to deter mosquitoes [52]. This research is valuable because it indicates these communities may be willing to try out spatial repellent devices as a means of vector control.

An additional point to employing spatial repellent devices successfully in a public health context, is to also market them towards the prevention of nuisance biting and pests. There should be an overlap in commercial and public health thinking when promoting spatial repellent devices.

It should also be mentioned that community uptake is likely to be greater if the spatial repellent devices are known to be safe. Even though traditional methods of burning of plants to release botanical insecticides and smoke, may have negative health effects, if a community feel that an unfamiliar tool is causing side-effects it may lead to incompliance.

Evaluation and Research Needs

A priority for spatial repellents going forward is to have clearly defined methodologies for testing, through updating WHO guidelines. This is a summary point within the 'Spatial Repellents for Control of Vector-borne Disease' (SRCPD) research programme, a Bill and Melinda Gates Foundation grant to the University of Notre Dame. A shift in vector control to include spatial repellents requires new laboratory and field assay tools, standardised end points and analyses, which are authorised and approved by global health organisations [98]. Current WHO field protocols need to be updated[127]. The need to improve reporting, methodologies and terminologies through standardising testing guidelines has also been highlighted in a systematic review of mosquito coils and passive emanators [102].

Many studies which evaluate the use of spatial repellents take the 'hut' or high throughput design, and pros and cons exist for each. The former design includes structures such as tunnels or screened enclosures, whereby a set number of mosquitoes can be monitored in a space to observe behavioural responses to olfactory stimuli [122]. However, as boundaries are defined, effects such as toxicity can effect data collection as mosquitoes may die from exposure before a behavioural response can be documented [122]. The latter method uses assays which expose mosquitoes to particular conditions, where exposure time, dosage and contact can be controlled. While these designs examine sub-lethal effects well, they are limited in evaluating of the spatial effect of the repellents [122].

Semi-field and field trials address potential gaps in these methods, although most focusing on the effect of spatial repellents, use outcomes such as mosquito house entry or biting rate as proxies for malaria transmission [11, 45, 47, 81]. There is a lack of large-scale, well-designed RCTs to provide evidence that they may have a direct effect on disease reduction [128]. This is largely owing to the lack of funding for research on spatial repellents, but without sound evidence for the use of spatial repellents funding will continue to be a challenge. In fact, the only two cluster-randomized RCTs on the effect of mosquito coils on malaria were found to be inconclusive in a Cochrane review [128]. The 2019 Unitaid grant to the University of Notre Dame should help expand the evidence base for spatial repellent impact against both malaria and dengue transmission[129].

In order for spatial repellents to be considered for public health interventions, standardised methodologies, but also better technologies should need to be deliberated to evaluate the efficacy of spatial repellents, such as video tracking. Such technologies have been used to investigate the interaction of *Anopheles gambiae* with LLINs, and could potentially be used to evaluate mosquito behaviour towards new spatial repellents [130].

It is often discussed in literature that SRs should be used in combination with other control tools. It is therefore important to measure the impacts of spatial repellents on bed net efficacy. Using low concentrations of volatile pyrethroids as spatial repellents continues to expose mosquitoes to insecticide classes already used for bed nets. Therefore, if used in conjunction with IRS and ITNs, they must use a different insecticide class to reduce the selection pressure for pyrethroid resistance [131]. Interest in spatial repellents is likely to increase with the movement towards integrated vector management being encouraged by the WHO, playing on IVM to promote spatial repellents could help to lobby for their recognition in the public health sector.

New Actives

Discovering new actives should be a priority for research, they need to be longer lasting and cover a larger protective area. The most promising spatial repellent products are based on volatile pyrethroids and for this product class to offer long term value as a public health product, additional mode of action actives will be needed. To address this issue research needs to focus on finding novel molecules which disrupt mosquito-human contact either through excito-repellency or disrupting host detection. Rather than targeting the odour receptors which result in confusion or avoidance behaviour, researchers at Vanderbilt University have discovered a new molecule class which hyper-stimulate odour receptors through allosteric agonism of shared orco-coreceptors. It is thought that this class of molecule (VUAA1), overwhelms the mosquito olfactory system resulting in excito-repellency. This novel active has been tested against anopheline mosquitoes, but also stimulates the odour receptor Orco complexes of other nuisance insects such as flies, moths and ants. Spatial repellents would be more appealing to users if they were effective against multiple pests[132].

Malaria and arboviruses are considered as diseases of the poverty. Therefore, increasing tourism and agricultural yield with the use of spatial repellents against nuisance biting and pests, should drive economic development and reduce these diseases of poverty [133]. As well as gaining the funding, challenges to new actives includes finding new classes, formulating and product efficacy testing.

Potential Areas and Spatial Repellents

Inside the home, spatial repellents can build up more easily thus providing more protection. However, the concept of using spatial repellents for personal protection for outside use is also widely accepted. Most current spatial repellent devices are designed for stationary use, limiting their capacity to protect outdoors. Devices such as personal diffusers have little scientific evidence to back their claims [26], despite some studies finding they offer 70% protection for over 3 hours [38]. There appears to be a lack of experiments under normal environmental conditions to assess the efficacy of these devices, and it is clear that they often do not offer full body protection from bites. One study found two products dispersing volatile pyrethroids to provide reasonable protection to arms and legs, as long as participants were positioned in the plume of repellent [26].

However, when discussing potential for SRs, many interviewees said they could offer protection for outdoor workers. Outdoor workers would not be stationary, and therefore further investigation into the use of these devices under real-life conditions is needed. More research into transmission cycles through indoor and outdoor monitoring of human behaviour is needed for effective deployment of SRs.

A common theme in interviews was that spatial repellent devices could be particularly marketable as protection against *Aedes*. This is because *Aedes*-borne diseases are the fastest growing public health threat, meaning it is easier to get funding for controlling these diseases. Targeting spatial repellent devices against *Aedes* could be successful in urbanised areas, where people may be willing to spend more money on a product, this especially includes urbanized areas of Africa where SRs could contribute to dengue control. Current epidemiological trials make a clear point to investigate the potential of SRs in both rural (Indonesia, Kenya, Mali) and semi urban (Peru, Sri Lanka) environments.

Conclusions

In summary, research needs for SRs going forward should focus on improvement of lonveviety efficacy and delivery. To do this, considerations into behaviour change strategies and marketing approaches need be made. There are concerns surrounding the use of volatile pyrethroids in these devices as this exposure could continue to select for insecticide resistance genes in mosquito populations. There is therefore a need to reduce lethal effects of SRs containing volatile pyrethroids. To resolve these issues, research also needs to focus on development of new actives and formulating them.

Device type is also important, as it must be efficacious, fit for purpose and the right price for the consumer. Ideally a spatial repellent product should be operational both indoors and outdoors. Literature surrounding metofluthrin impregnated screens and strips looks promising due to the longevity and ease of the device.

Monitoring and evaluation of these products needs to include better guidelines for testing from the WHO, and also more high standard RCTs which can investigate their effect on disease transmission. The effect of spatial repellent products on current vector control tools such as bed nets, needs to be made clear through further research. Several knowledge gaps also exist in terms of human safety and environmental risk, including affects to risk groups such as pregnant women and to non-target organisms need to be assessed.

A final challenge for SRs going forward is gaining support and backing for funding. Following the recent Unitaid investment in SR trials [108, 134], a market shaping initiative to address the Access and Delivery challenges including funding may be necessary. This is similar to the approach Unitaid has taken to new, more expensive IRS and LLIN products, assisting funders and procurers in purchasing the new products as part of initial scale up efforts [135, 136]. Marketing these tools in a public health context but also in terms of controlling biting nuisances may encourage consumers to purchase them. However, it is difficult to market a spatial repellent tool across multiple countries when factors such economic status, climate, epidemiology and the vector vary. When implementing SRs for vector control, community acceptance also needs to be considered.

Overall, it would seem that there is optimism for SRs going forward, both as a supplementary tool to other malaria vector control methods and in humanitarian health emergencies particularly for *Aedes*-borne virus outbreaks.

Conclusion

Spatial repellents are a potentially effective tool against vector-borne disease, but at present most products are targeted to the consumer market. This report examines the potential role of SRs in public health (with the focus on malaria prevention) and evidence of their efficacy, through published and grey literature, and the opinions of academic and industry experts. Industry members have indicated an appetite for development of further spatial repellent products. In the humanitarian sector, spatial repellents are of interest because of the potential for a quicker rollout that than interventions like IRS, which can take weeks to months to set up and deliver.

Literature Review and Ongoing Research

There is no current consensus on a clear definition of spatial repellents. Generally, they are defined as chemicals that, when air-borne, prevent biting by blood-seeking insects such as mosquitoes. The chemical should, therefore, create a space where human hosts are not bitten and protect against potential disease transmission. The mode of action of spatial repellents will depend on the active ingredient used, but they should disrupt host seeking behaviour or cause mortality on exposure. Chemicals that have been shown to have spatial repellent effects include volatile pyrethroids such as metofluthrin and transfluthrin; botanical compounds such as terpenoids; and volatiles found from human skin and skin bacteria such as 1-methylpiperazine.

Spatial repellent actives have been incorporated into a wide range of devices, including coils, heat activated vaporisers, passive emanators based on impregnated plastic, paper and hessian materials. Laboratory and semi-field trials have shown good levels of efficacy against important vector species such as *Anopheles gambiae* and *Aedes aegypti*. Although spatial repellents aim to disrupt host seeking and feeding behaviour, many laboratory tests have concentrated on their killing effect, perhaps because of the predominance of volatile pyrethroids in the early development of spatial repellents.

The World Health Organization (WHO) has produced guidelines for testing spatial repellents which recommend that movement away from a host stimulus should be the main outcome, but very few studies were found that used those methods. Semi-field testing may be more appropriate for testing spatial repellents, as the build-up of the volatile within a three-dimensional space can be better simulated. There has been considerable work on semi-field testing of spatial repellents within push-pull systems. Push-pull systems use spatial repellents to push vectors away from a human host but combine this with an attractant baited trap. An outline protocol for testing of spatial repellents in a semi-field system is presented here, based on WHO recommendations and some subsequent published work.

For spatial repellents to become an accepted part of the malaria vector control arsenal, most experts agreed that data from randomised controlled trials showing an impact on disease transmission, as well as entomology, would be necessary. At present, there are data from semi-field trials showing repellency, and also where pyrethroids are concerned, mortality data from laboratory trials. So far one trial has shown an epidemiological effect; a 52% reduction in malaria from the use of spatial repellents. The follow-up study by Syffaruddin et al, cited several times in this review[75] confirmed impact of a transflulthrin passive emanator. A trial using the same device for a dengue-endemic community in Iquitos Peru is awaiting final results. Modelling studies, [17] [137] suggest spatial repellents could have a potentially large public impact, which may be particularly useful in helping design the next generation of spatial repellents.

Economic Considerations and Commercialisation

A wide range of products are commercially available for use as spatial repellents/insecticides, primarily for the consumer market rather than as a public health intervention and they vary in efficacy. There is an established route to market for spatial repellent products in the "developed" market, but this is not clear for the developing market, or for use as a vector borne disease intervention.

The high cost of spatial repellents was a recurring theme amongst those interviewed and was seen as a serious barrier to their potential future use in vector control. However, further modelling work is needed to determine the likely costs of available actives, in different presentations, under varying settings. Current products are largely aimed at developed markets, and the individual product cost reflects this. Some representatives from industry stressed that the high research and development costs had to be weighed against the relatively small potential market that is currently expected for spatial repellents. However, the repellent market is significant – around $11 billion and spatial repellents are considered part of this. We are aware of other large companies who have significant interest in developing spatial repellent products.

The commercialisation model for spatial repellents would be very different to LLINS or IRS, because there is a vibrant repellent consumer market worldwide. A high volume "developed" market should, in theory, bring production costs down, and therefore support provision of cheaper spatial repellent products in developing markets. But this needs further examination and consideration.

Evidence suggests the end-user is more likely to use the product if they have bought it rather than it being donated by NGO or government campaigns and therefore this should be considered when considering implementation and "route to market".

Regulatory and Policy Issues

Spatial repellents are usually included with insecticides in most regulatory guidelines, which presents a problem where the product is not designed to kill mosquitoes but prevent biting. However, there are regulatory hurdles for getting any product to market, and these did not overly concern most manufacturers. What was desired was a greater acceptance of data produced according to WHO guidelines at the national level, as these better characterise a repellent effect, rather than insecticidal effects. There was a common recommendation from both academics and industry to update the WHO guidelines, to include more up to date methods and input from industry on the outcomes that would be most useful if the data were to be presented to both the WHO PQ system and national regulatory bodies. The WHO guidelines include a dedicated section for spatial repellents, but it does not as yet supersede national-level requirements. The WHO guidelines are not flexible and suggestions were made for fast-track applications for products using safe active ingredients and to replace the requirement of RCTs in the field with alternative smaller scale robust efficacy testing.

Target Product Profiles

To develop the target product profile of spatial repellents for public health use, a pragmatic approach was used, where an "achievable" product, with currently available spatial repellents, was considered alongside the ideal product. The interviewees gave a variety of opinions on what would be the ideal spatial repellent product. We have provided further consideration, beyond the interviewee comments. Themes pulled out from interviews included a product which was low-cost, with at least 90% protection from biting, a light-weight portable product, a requirement for products that provide protection outdoors as well as indoors (not necessarily one product that can do both), with an effective duration of 3 to 6 months.

Please note, as described above, since the start of this review, the concept of Target Product Profiles has evolved and many of the details below may better fall under the higher-level framework of Preferred Product Characteristics.

Table 1. Conceptual target product profile, as determined by interviewees, for a spatial repellent to be used as a public health intervention. We have provided further consideration, beyond the interviewee comments.

<table>
<tr><th></th><th>Acceptable</th><th>Ideal</th></tr>
<tr><td rowspan="2">Target</td><td>80-90% reduction in biting by Anopheles or Aedes mosquitoes.</td><td>Close to 100% reduction in biting by all mosquitoes.</td></tr>
<tr><td colspan="2">Further considerations: ideally, a product would target all indoor or outdoor biting mosquitoes, including Culex. It may also have an effect on other species such as sand flies, bed bugs, etc. A product (or combinatory product) with broad effectiveness against a range of insects perceived to be the most "troublesome" is more likely to appeal to the end-user, improving uptake and compliance.</td></tr>
<tr><td rowspan="2">Setting</td><td>Humanitarian crises, mobile workers, low transmission settings. Spatial repellents should also be effective indoors, and in semi-open structures, and readily accessible in low-income and rural settings</td><td>Humanitarian crises, mobile workers, low transmission settings. Spatial repellents should be effective outdoors as well as indoors, and should be compatible with existing tools including LLINs.</td></tr>
<tr><td colspan="2">Further consideration: a spatial repellent product would ideally be effective in many different household settings within different types of communities, as well as the settings mentioned above by the interviewees.</td></tr>
<tr><td rowspan="2">Delivery</td><td>Passive device without requirement for batteries or electricity.</td><td>Passive device without requirement for batteries or electricity.</td></tr>
<tr><td colspan="2">Further considerations: there are many relevant communities that have access to electricity either via the grid or a generator. However, solar power is becoming more popular in rural settings and could provide a way of powering spatial repellent devices.</td></tr>
<tr><td rowspan="2">Active, Duration and Range of Effect</td><td>Insecticidal active ingredients that are currently available.

Devices should remain effective for 1 month.

Range of effect should be up to 2 m from the device.</td><td>An active ingredient (insecticidal or non-insecticidal) which is effective against susceptible and pyrethroid resistant mosquitoes.

Devices should remain effective for a transmission season (6 months to 1 year).

Range of effect over 2m from the device, with lasting sub-lethal effects that dampen biting behaviour outside this range.</td></tr>
<tr><td colspan="2">Further consideration: whilst range is important to consider, especially for an outdoor product, a product designed to be used within a household, should prevent household entry, and this is a more important measure than range per se.

Further consideration: Shorter duration devices (24 hour effect) may have a place where changing user habits is possible, and the reinforcement of effect may make these types of devices more acceptable to some communities.</td></tr>
</table>

	Acceptable	Ideal
Safety	Low human toxicity, particularly when used indoors Risks to non-target species in line with accepted standards for PHPs at the time of registration submission. Appropriate disposal routes and recycling for waste products	No human toxicity, particularly when used indoors Risks to non-target species in line with accepted standards for PHPs at the time of registration submission. Appropriate disposal routes and recycling for waste products
	Further consideration: ideally a spatial repellent product would have low toxicity and minimal environmental effects (e.g. on non-target organisms). The active ingredient must hold a registration with a major regulatory authority (EPA, EU, Japan) or WHO approval.	
Evidence	Safety data for consumer sector may be used to support use in public health settings.	Safety and efficacy data from randomised trials.
	Further consideration: although RCTs may not be necessary for all spatial repellent products, some smaller scale, robust, entomological data would be necessary to assess efficacy.	
Cost	Low-cost as possible to allow large-scale distribution.	Equivalent cost-effectiveness to LLINs or IRS.
	Further consideration: ideally a spatial repellent would be cheaper than LLINs or IRS. Some substantial modelling would be needed to fully understand the economics of what would be suitable for a particular product, in a particular setting.	
Logistics	Spatial repellents should be small and lightweight. Plastic waste should be kept to a minimum.	Spatial repellents should be small and lightweight. Plastic waste should be kept to a minimum. Release rates should be stable for the conditions of use.
	Further consideration: device constructed of biodegradable material, or with low environ-mental impact, would be preferred. Ideally the product would require little maintenance and infrequent replacement of actives.	

Knowledge Gap Assessment

A number of knowledge gaps were identified in our understanding of spatial repellents and their impact when used in vector control:

1. There is inconsistency in the definition of a spatial repellent, due to the likely different modes of action of different active ingredients currently used. For example, some have excito-repellency effects; others cause mortality and/or knockdown, some actively repel, causing the insects to move away from the source, others may cause arrestment behaviour, or prevent landing or feeding behaviour.

2. The confusion around the definition, and the use of different actives, has likely led to further inconsistencies in how spatial repellents are evaluated.

3. Some research suggests that resistant mosquitoes may still be repelled by insecticides and therefore could be useful in contexts where resistance is present. Other research suggests that the use of spatial repellents, where mosquitoes are subjected to sub-lethal doses of insecticide, could exacerbate resistance.

4. Some studies have shown that mosquitoes may be diverted from households with spatial repellents to households that do not have spatial repellents.

5. There was some concern that spatial repellents could create an accidental' push-pull situation, for example, using spatial repellents to drive highly anthropophilic anopheline and Aedes mosquitoes away from domiciles could potentially change their behaviour back to zoophily over time.

6. There is uncertainty around the correct placement of spatial repellents within a household, and how often they will need to be replaced. This will differ greatly between products. Interviewees felt that spatial repellents should last for the entire length of a transmission season.

7. There is some uncertainty around how large an area can be protected by spatial repellents, particularly in an outdoor setting.

8. There is a currently lack of understanding around the safety of active ingredients when used in a long-term spatial repellent context. Most studies have been done on animal models.

9. There is significant concern around the environmental effects of spatial repellents, particularly pyrethroid active ingredients, including the effects on non-target organisms.

10. Spatial repellents tend to be housed in plastic packaging. There is concern over the environmental effects of plastic use.

11. There is currently a lack of clarity around the registration and regulation of spatial repellents.

12. There is a lack of epidemiological evidence for spatial repellents.

13. There is a current bias in the vector control community for conventional methods. Even with epidemiological evidence, this view will be difficult to change.

14. Understanding human behaviour in the acceptance of such tools has been identified as a possible knowledge gap.

15. There is uncertainty around the effect of spatial repellents on the efficacy of bed nets.

16. Research is needed on the identification and development of novel actives.

Feasibility

There was clear consensus that spatial repellents have a place in vector control, but as a complementary tool, rather than a standalone tool. Although we need further evidence, including epidemiological evidence, and better products, there was clear support for the use of currently available spatial repellent products in certain settings, and this should be explored further. There a number of potential routes in which spatial repellents could be useful in vector control.

Firstly, without any further product development, current devices may be used in fast but short-term responses to vector-borne heath crises, including humanitarian relief situations or outbreak response. Spatial repellent devices with improved duration may well be suitable to protect people inside or around houses, perhaps as a replacement or even improvement on indoor residual spraying.

Spatial repellents require little in the way of behaviour change from users, so potentially may be more acceptable and easier to implement than bed nets that might require daily interaction. In areas aiming for malaria elimination, where other interventions such as bed nets or chemoprophylaxis may become unpopular, or inappropriate, spatial repellents have the potential for wider acceptance. Currently, there appear to be two significant barriers to adoption:

- Acceptability within the vector control community: there is currently inherent bias towards the use of standard control methods such as bed nets.
- Compliance and uptake within communities – however, there is evidence that compliance can be high (above 90% in some studies). A recent survey showed that effectiveness, ease of use and cost were most significant to consumers buying vector control products. Generally, spatial repellents should not require significant behaviour change, so compliance issues should be easily overcome so long as the product type is suitable.

It is difficult to know how well spatial repellents work in an outdoor setting. However, many interviewees felt they could be an important intervention to protect mobile populations, outdoor workers and refugees. Further work is needed to determine the range of activity for use in such a context. There was much support for the use of spatial repellents in the eaves of households, with evidence that this was an acceptable approach, from studies done in Kenya with undecalactone and PMD. There was evidence that spatial repellents can be used as part of a push-pull control strategy and there was support for this amongst interviewees.

It was felt that new active ingredients with different modes of action, are required, for example, agonists. This would also be beneficial for areas where resistance to pyrethroids is a problem. Botanicals are an alternative option currently, however, their efficacy appears to differ between species and contexts. Some interviewees felt that this means pyrethroids are the only viable option currently, however, there are several studies which demonstrate efficacy of non-pyrethroid actives. Further work is needed to determine which non-pyrethroid actives may be appropriate for use as spatial repellents.

There were several suggested recommendations for improvement of spatial repellent devices:

- Durability – they need to last longer (ideally between 1 month and 1 year for a household setting), and achieve high levels of efficacy under different environmental conditions
- There is a place for spatial repellents that are passive and those that require electricity, depending on the local setting (e.g. sub-Saharan Africa where there may be no electricity, or solar panel electricity; and Brazil where grid electricity is provided).
- Spatial repellents may be incorporated into building materials or paints. This would require long lasting formulations to be developed. Some formulations can achieve up to 8 months repellency.

Other challenges that would need to be overcome to make spatial repellents effective vector control tools include economic, regulatory and implementation concerns. At present most spatial repellent devices come at a high cost. They are primarily marketed to consumers in developed areas, and include expensive materials, batteries or require electricity, all of which reduce their potential use in less developed areas where disease transmission is often highest. Ideally, spatial repellents would need to demonstrate an equivalent cost per person protected to bed nets or indoor residual spraying to be considered by funders and programme managers. In addition, there are technical questions around safety and their impact on insecticide resistance that would need to be addressed before widespread roll-out could be advocated.

Recommendations and Next Steps

- Define the acceptable modes of action for spatial repellents in context of vector control.
- Define the testing guidelines/evaluation suitable for spatial repellents with different modes of action.
- Further work is needed to determine the effect of spatial repellents against resistant mosquitoes:

  i. What is the effect of an insecticidal spatial repellent on the behaviour of resistant mosquitoes?

  ii. What is the effect of a non-insecticidal spatial repellent on the behaviour of resistant mosquitoes?

  iii. Does exposure to sub-lethal amounts of insecticidal spatial repellents result in increases behavioural, and/or physiological resistance?

  iv. What is the effect of exposure to a spatial repellent on mosquito behaviour, post-exposure?

- Further work is needed to determine the possible diversionary effects of spatial repellents in different community/household contexts, and whether spatial repellents change mosquito behaviours from anthropophily to zoophily, and vice versa, over time; and the likely consequences on transmission of this effect.
- Modelling studies and small-scale experimental studies are needed to determine the optimum length of time required before replacement for spatial repellents in different transmission settings and ecological/environmental contexts.
- Small-scale experimental studies should be done to determine the best positioning of spatial repellents (e.g. eaves, doorways, further inside, etc.).
- Further work is needed to understand the safety of active ingredients when used in a long-term spatial repellent context. Inhalation data would be a necessity.
- Small-scale experiments are needed to determine how large an area can be protected by spatial repellents, particularly in an outdoor setting.
- Work is needed to understand the effect of different active ingredients on non-target organisms under different ecological settings.
- Spatial repellent devices/dispensers that do not use plastic, or use biodegradable plastic need to be identified and considered going forward, to minimise environmental effects of plastic.
- A better understanding of the regulatory and registration requirements is needed for spatial repellents. This will involve discussions with the WHO VCAG, competent authorities and regulators for each country of relevance.
- Further studies are needed to determine the epidemiological evidence to support the use of spatial repellents.
- Work is needed to tackle the current bias within the vector control community for conventional methods.

- Research is needed to understand human behaviour and how best to promote behaviour change within different communities to ensure high levels of compliance.
- An investigation on the effect of spatial repellents on the efficacy of bed nets is needed.
- Research on the identification and development of novel actives should be a priority.
- More funding for research into spatial repellent research is required and further engagement with funders should be done.
- Encourage national regulatory bodies to identify spatial repellents as needing their own separate set of guidelines for evaluation.
- Encourage the WHO to revise current guidelines to allow fast-track product acceptance where certain criteria are met (currently undefined).
- Discuss the whether RCTs are needed in all cases, or whether there is an alternative, noting that while an RCT may be needed to define the product class, this be as broad as possible to include a range of spatial repellent products.

Notice

All data will be held by *arctec* for a minimum of 10 years. During that time it shall remain available solely at the request of a nominated executive of IVCC and under no circumstances be released to a third party. This report is designed for internal developmental use, product registration or as evidence of full independent efficacy testing in defence of any official regulatory or legal inquiry. It must not be used for advertising purposes. In no way does any comment made in this report constitute an endorsement of any product by *arctec*, LSHTM or Chariot Innovations and no such claims, directly or by inference, made by any company or individual will be permitted to this effect. All information given in this document is confidential and must not be released to other parties.

Please note that the original document submitted by *arctec* to IVCC in November 2018 has been edited and updates with additional references that became available in 2019 and 2020

Appendix 1.
Question Guide for Interviews

1. Can you tell me about yourself and your company/research interests?
2. What experience do you have working with spatial repellents?
3. Are SRs a priority area of research or development?
4. Do you have any ongoing projects involving SRs?
    a. If possible ask for more details – may require CAs to discuss.
5. Are you aware of any products currently available for use using SRs?
6. Do you think current spatial repellent products are effective?
7. What sector (consumer, pest control, vector control) do current product best serve?
8. Commercial SRs need to go through testing for national regulators, whereas public health tools usually follow a WHO-PQ path to regulation. Do you see this dual system as a barrier, or would the type of products involved be too different to require regulation by both systems?
9. Are you aware of any regulatory issues that may need to be addressed before SRs can be more widely adopted?
10. What do you see as the most significant challenges for SRs to become effective vector control tools in a public health context?
11. What are the potential barriers (to being effective tools against malaria)?
12. What are the potential barriers (to being effective tools against *Aedes*-borne diseases)?
13. Do you think spatial repellents would be a more challenging area to apply for research funding (than traditional VC tools such as bed nets)?
14. What would your ideal spatial repellent product look like?
15. Do you view SRs as viable potential tools for public health vector control?
16. What needs should public health SRs address?
17. How would a spatial repellent aimed at the public health vector control market differ from a commercial domestic use product?
18. What are the big knowledge gaps to be closed before SRs can become effective vector control tools?
19. What areas are SRs most weak (e.g. efficacy/apparent efficacy, cost)?
20. What evidence would you want to see to convince you that SRs were a useful tool in the public health VC toolbox?
21. Do you think SRs could be effective against malaria?
22. Do you think SRs could be effective against *Aedes*-borne diseases?
23. What problems do SRs solve that are not addressed by current tools (e.g. bed nets and IRS)?
24. Do you think SRs should be developed with a view to use as public health interventions?
25. The WHO currently has guidelines for spatial repellent evaluation covering laboratory, semi-field and field trials (published 2013). Do you think these need updating?
26. What in your opinion should be the priorities for research on SRs?
    a. If unsure, allow to choose from: new actives, new delivery systems, efficacy testing (against vectors); efficacy testing (against disease transmission)

Appendix 2.
Use Case Analysis

Use Case Analysis of Spatial Repellents

IVCC inputs from Dan Strickman, Jason Richardson, Richard Adey, Mike Macdonald, Julian Entwhistle, Fred Yeomans, and Christen Fornadel.

External reviews by Nicole Achee, Dan Kline, Tom Putzer, Kara MacCarthy. External reviewers had significant comments, most of which were incorporated into this document. However, the responsibility for the content of this document is solely that of IVCC.

Overview

This document was developed from a much longer consideration of spatial repellents and condensed in order to make the analysis more accessible. The primary intended audiences are those in industry and funding organizations who might make decisions about project investment or design. It was initiated by the Innovative Vector Control Consortium in October 2019 in response to discussions about the value of investment in spatial repellents. Those discussions quickly led to the realization that spatial repellents are a family of products that could serve any of a number of purposes. The purposes to which a particular spatial repellent is applied might influence the ideal characteristics of the product. The use case analysis is intended to provide a framework for the various ways in which spatial repellents might be used, influencing funding decisions and the specific content of target product profiles (TPPs). Consideration of the use cases might also result in new designs tailored especially for those uses.

Activities implied by the analysis:

1. Review of other published and unpublished assessments of user needs.
2. Quantitative modelling of efficacy required to achieve public health benefit under a variety of environmental conditions.
3. Interviews with experts on each user group to test assumptions about their behavior and needs.
4. Technical development of better methods to monitor performance of spatial repellents in order to provide quality control and to continuously provide positive feedback to users.
5. Test cases of regulatory requirements for documentation, storage, and disposal; survey of regulatory authorities' familiarity with the spatial repellent product category.
6. Review of TPPs to be assured that they take account of use case analysis.
7. Examination of requirements of distribution systems, particularly publicly funded ones, to determine how those requirements might influence spatial repellent product design.
8. Determine the needs of those who make a decision to accept use of a spatial repellent and the needs of those who actually apply the spatial repellent.

Definition:
Defining spatial repellency and spatial repellents raises a number of questions about what kinds of products would be included in this category. The problem of definition is complicated by at least five factors:

1. Common spatial repellents (e.g., coils, heated paper strips) cause mosquitoes to avoid an area, but they also kill mosquitoes that receive a sufficient dose of the active ingredient.

2. Exposure to at least some active ingredients causes persistent changes in behavior of the mosquitoes.

3. The modes of action of chemical active ingredients in spatial repellents vary. Some are much less efficacious than others.

4. There are legitimate modes of action not based on chemical exposure, including electric fields, magnetic fields, and probably sound.

5. Although commercial spatial repellents are used for personal, household, farm, or workplace protection (i.e., preventing bites to individuals within the protected area), there is a strong hypothetical case for community protection based on vector population reduction and interference with mosquito life cycle. Recent trials using chemical-based spatial repellents support this hypothesis.

Draft guidelines from the WHO provided the following definition:
The term 'spatial repellency' is used here to refer to a range of insect behaviours induced by airborne chemicals that result in a reduction in human–vector contact and therefore personal protection. The behaviours can include movement away from a chemical stimulus, interference with host detection (attraction inhibition) and feeding response.

The WHO's definition is precise and informative for the immediate needs of creating evidence for policy decisions concerning existing kinds of products. IVCC is invested in creating evidence for policy decisions, but it is also concerned with more upstream development of new kinds of products. A more general definition of spatial repellent is proposed:

A spatial repellent affects vectors at a distance from the point of application [in contrast to contact repellents]. The effect on a vector is dependent on exposure, which is dependent on distance from the application site. Generally, the intention of a spatial repellent is to prevent entry of the vectors into a space occupied by one or more people or animals; however, exposure to a spatial repellent may affect other aspects of the vectors' life cycle [e.g., detection of host cues, initiation of blood-feeding] and therefore affect their competence to transmit pathogens. Although the likely mechanism of action is exposure to volatile chemicals, other mechanisms are conceivable, such as sound, magnetic fields, or electrical fields.

Outcomes
We identified 10 use cases for spatial repellents and describe potential users for each case. Use cases have been divided into two broad categories based on the marketing and distribution strategy in which spatial repellents would be deployed – 1) commercial and 2) public.

1. In commercial use cases, individual persons will make decisions to use their own discretionary money to buy and use spatial repellents based on a variety of inputs. The decision to purchase might be influenced by community outreach, including subsidy by government, NGOs or other distributors.

2. In public use cases, spatial repellents will be funded and procured centrally (at national or local level), through public health policy that was created by a public authority. Examples of responsible authorities include the World Health Organization, the US Centers for Disease Control and Prevention, or a national or subnational vector control program.

Similar to other vector control interventions, such as LLINS, the choice to use and/or properly apply a spatial repellent is in the hands of an individual, giving those individuals considerable influence over the success or failure of an intervention. For most commercial spatial repellent use-cases, individuals would be responsible for positioning spatial repellents in the area at-risk for vector exposure; therefore, perception of effectiveness would be important in driving decisions for continued use. For public use-case scenarios described here, new strategies for spatial repellent deployment may be needed to ensure access meets coverage required for efficacy – these to include community health workers. Were a program to use community health workers for distribution, some of the commercially-based spatial repellents might become public-funded ones. In that case, there would need to be a selection process for the most suitable spatial repellents and possibly a change in labeling and packaging.

The impact of spatial repellents on disease is still under study, though results so far suggest that efficacious spatial repellents can significantly decrease transmission of pathogens, malaria parasites being the model most thoroughly examined so far. Impact of spatial repellents against *Aedes*-borne viruses is currently being evaluated, but results are still being generated or analyzed. Results from trials of mosquito coils and simple passive emanators indicate that spatial repellents can have an impact on disease (malaria). Larger trials have been funded to demonstrate and measure an effect on disease more definitively. The entomological efficacy of some current and near-term spatial repellents suggest a level of efficacy and range of protection that would overcome the limitations of earlier products.

Centrally funded campaigns have generally not included spatial repellents, except for limited uses as a stop-gap in emergencies or for mobile migrant workers in self-help "forest packs." The lack of public health programs using spatial repellents may be due to several factors associated with generation of evidence for policy, technical limitations on range of efficacy and/or duration, and cost for implementation.

The use case analysis proposes that there are three broad categories of barriers to overcome before spatial repellents can be confidently deployed for malaria elimination or control of diseases like dengue, Zika disease, chikungunya, yellow fever, lymphatic filariasis, Chagas disease, leishmaniasis, or livestock-associated illnesses. Current development and large-scale trials are attempting to overcome these challenges.

1. **Technical:** Current spatial repellent products have a broad range of efficacy in terms of duration and range of effect. That efficacy is clearly sufficient for many consumers, as billions of mosquito coils are sold. Spatial repellent products exist that last for up to 45 days and that are effective for an entire room. The minimally effective level of efficacy will vary between each use case. For example, a traveler would not need a long-duration spatial repellent and the range of efficacy might be much less than that needed in a house. The ideal spatial repellent from the standpoint of a public health application would combine the efficacy of the most effective spatial repellents with the simplicity and acceptability of coils. Development is still aspirational for a long-lasting spatial repellent that protects an entire house from a single point source in the home.

2. **Lack of evidence for use by the public health community:** The key question for this kind of

access may become where and when to use spatial repellents. Ongoing generation of evidence will be helpful in overcoming this barrier.

3. **Supply:** Appropriate stockpiles, availability in the correct locations, and suitable costs are all necessary for the successful use of spatial repellents at large scale for maximum impact. These processes and infrastructure would have to be created for new spatial repellent products, though in many cases it would be expected that existing supply systems would be able to accept new products. A key element to operating vigorous supply systems is the policy for use of a spatial repellent, facilitating a public health market.

Previous Work

History and Kinds of Interventions

Strickman, D. 2007. Chapter 23. Area Repellents. *In:* Debboun, M., S.P. Frances, and D. Strickman, *Principles of Insect Repellents: Principles, Methods, and Uses.* CRC Press, Boca Raton, Florida. [A wide variety of methods have been used to achieve area repellency, including chemicals which were effective but no longer used]

Kline, D.L., and D.A. Strickman, 2014. Chapter 12. Spatial or area repellents. *In:* Debboun, M., S.P. Frances, and D. Strickman, *Insect Repellents Handbook,* CRC Press, Boca Raton, Florida, pp. 239-252. [Passive emanators have been developed further and there is a need for trials to show impact on disease]

Current Promise and Challenges

Achee, N.L., and J.P. Grieco. 2018. Chapter 3. Current evidence, new insights, challenges and future outlooks to the use of spatial repellents for public health. *Advances in the Biorational Control of Medical and Veterinary Pests*, American Chemical Society Symposium Series 1289: 25-42. [There is a need for evidence, particularly on disease impact. The mode of action of area repellents offers a promising means of reducing pathogen transmission.]

Achee, N. L., Bangs, M. J., Farlow, R., Killeen, G. F., Lindsay, S., Logan, J. G., ... & Zwiebel, L. J. (2012). Spatial repellents: from discovery and development to evidence-based validation. Malaria Journal, 11(1), 164.

Efficacy and Guidelines for Testing

Lawrance, C.E., and A.M. Croft. 2004. Do mosquito coils prevent Malaria? A systematic review of trials. Journal of Travel Medicine 11: 92-96. [There is good evidence of entomological efficacy, but no evidence of disease efficacy]

Hill, N., H.N. Zhou, P. Wang, X. Guo, I. Carneiro, and S.J. Moore. 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. Malaria Journal 13: 208. [Transfluthrin coils provided 77% reduction, deltamethrin LLINs provided 91% reduction, and combination provided 94% reduction].

Syafruddin, D., B.S.A. Asih, I.E. Rozi, D.H. Permana, A.P.N. Hidayati, L. Syahrani, S. Zubaidah, D. Sidik, M.J. Bangs, C. Bogh, F. Liu, E.C. Eugenio, J. Hendrickson, T.A. Burton, J.K. Baird, F.H. Collins, J.P. Grieco, N.F. Lobo, and N.L. Achee. 2019. Efficacy of a spatial repellent for control of malaria in Indonesia: A cluster-randomized controlled trial. medRxiv 19003426. [24-cluster protective effect of 27.7% and 31.3%, for time to first-event and overall (total new) infections; not statistically significant. Subgroup analysis of 19 clusters where at least one malaria infection occurred during the baseline showed 36.0% and 40.9% (statistically significant at 1-sided 5% significance level; $p = 0.0236$) protective effect to first-infection and overall infections, respectively. Among 12 moderate- to high-

risk clusters, a statistically significant decrease on infection by the spatial repellent was detected (60% protective efficacy)].

Syafruddin, D., Bangs, M. J., Sidik, D., Elyazar, I., Asih, P. B., Chan, K., ... & Ishak, H. 2014. Impact of a spatial repellent on malaria incidence in two villages in Sumba, Indonesia. The American Journal of Tropical Medicine and Hygiene, 91(6), 1079-1087. [Systematic use of metofluthrin coils provided 52% reduction in malaria]

Maia, M.F., M. Kliner, M. Richardson, C. Lengeler, and S.J. Moore. 2018. Mosquito repellents for malaria prevention. Cochrane Database of Systematic Reviews 2. [Concludes that evidence base is weak and flawed, citing only two spatial repellent studies that met criteria for review]

Charlwood JD, Nenhep S, Protopopoff N, Sovannaroth S, Morgan JC, Hemingway J. 2016. Effects of the spatial repellent metofluthrin on landing rates of outdoor biting anophelines in Cambodia, Southeast Asia. Med Vet Entomol. 30(2):229-34

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

Use Cases

Principle Use Category	Use Case and End-user	Description	Vectors Potentially Affected
Commercial	Permanent structures Primary users: Household members	A residence used on a more or less permanent basis.	*Anopheles* that feed or rest indoors or outdoors where the SR is effective, container-developing *Aedes, Culex pipiens/ quinquefasciatus*, domestic Phlebotominae, sylvatic Triatominae that enter homes
Commercial	Temporary structures not in emergency settings Primary users: Nomadic populations	A residence used on a temporary basis, possibly constructed for use during a single period.	*Anopheles* that feed or rest indoors or outdoors where the SR is effective, sylvatic Phlebotominae (other vectors are assumed to be associated with long-term occupation of the structure)
Commercial	Semi-permanent structures Primary users: Mobile migrant workers	A residence that serves to house temporary workers on a seasonal basis (related to agricultural practices) or workers who take advantage of resources outside of their local area	*Anopheles* that feed or rest indoors or outdoors where the SR is effective, container-developing *Aedes,* sylvatic Phlebotominae, sylvatic Triatominae
Public	Emergency settings Primary users: Displaced persons/ refugees	Considered to go through three stages of settlement: Emergency (temporary oriented toward immediate survival), Transition (longer term but still temporary and with more centralized support), and Settlement (potentially for years and with structured support)	Anopheles that feed or rest indoors or outdoors where the SR is effective, container-developing Aedes, Culex pipiens/quinquefasciatus, domestic Phlebotominae, sylvatic Triatominae
Public	Military deployment Primary users: Enlisted and officers	Variety of permanent or temporary structures, may include tents, forward operating bases, latrines, and sentry posts	*Anopheles* that feed or rest indoors or outdoors where the SR is effective, container-developing *Aedes, Culex pipiens/ quinquefasciatus*, domestic and sylvatic Phlebotominae, sylvatic Triatominae

Principle Potentially Affected	Use Case and End-user	Description	Vectors Potentially Affected
Commercial	Public places Primary users: Facility maintenance personnel and managers	Structures occupied by people for work, entertainment, worship, education, or leisure. Ports and airports are important subcategories.	*Anopheles* that feed or rest indoors or outdoors where the SR is effective, container-developing *Aedes, Culex pipiens/ quinquefasciatus*, domestic Phlebotominae
Commercial	Travelers Primary users: Travelers	Temporary lodgings or when in a situation where exposed outdoors, such as open-air restaurants	Anopheles that feed or rest indoors or outdoors where the SR is effective, container-developing *Aedes, Culex pipiens/quinquefasciatus*, domestic Phlebotominae. From a commercial standpoint, bed bugs might be important.
Commercial	Prevention of movement of invasive vector species. Primary users: Shippers, vehicle owners, aircraft crew	Aircraft, shipping containers, and/or other vehicles used for commodity transfers. Human-occupied conveyances like aircraft and automobiles might require different kinds of spatial repellents with lower dosage rates. Ports and airports that serve as first points of entry for countries. On aircraft, critical areas include cargo holds and passenger entry areas.	Important invasive vector species include *Anopheles arabiensis, Anopheles stephensi, Aedes aegypti, Aedes albopictus,* and *Aedes notoscriptus.* Potential threats include *Culex tritaeniorhynchus, Phlebotomus* spp., mosquito vectors of Rift Valley fever, and others. From a commercial standpoint, routine inclusion of effective spatial repellents could be a large market.
Public	Outbreak First-response Primary users: Same as for other use cases with the addition of first responders (e.g., military called in to help with disaster relief)	In the event of an outbreak of a vector-borne disease, SR could be deployed quickly as a first response. Deployment would be in all the places listed in other use cases. The emphasis would be on rapid and widespread deployment. This use implies that there would be the capability to warehouse large quantities of the SR, ready for immediate use.	Any vector susceptible to the intervention might be considered. Historically, the species involved in severe, emergency outbreaks are *Aedes aegypti, Anopheles arabiensis, Anopheles stephensi, Phlebotomus* spp., *Pediculus humanus,* and *Xenopsylla cheopis.* The latter two vectors are not known to be susceptible to current SRs and are more effectively controlled by other means; however, if there were an effective SR it might be used until longer-term interventions could be put in place.
Commercial	Livestock Primary users: Livestock farmers Under many circumstances, livestock health affects human health, and therefore has public health implications.	The health and yield of livestock are affected by a complex of insects, some of which occur worldwide and others that are local. Some of these insects reduce yield by irritating animals, others transmit pathogens biologically, and others transmit pathogens mechanically. Examples include Rift Valley fever virus transmitted by mosquitoes and H157 *E. coli* by house flies. In addition, fly control is a standard part of sanitation in dairies and abattoirs.	Mosquitoes, *Culicoides* biting midges, phlebotomine sand flies, stomoxine stable flies, tabanids, horn flies, face flies, muscoid filth flies. It is expected that spatial repellents would not be effective against non-flying vectors/pests, like ticks.

Who are the anticipated users of spatial repellents?

Commercial Users

In commercial uses, the choice of the product, the decision to purchase it, and the willingness to use it are anticipated to be the responsibility of individuals. The commercial users will most likely be occupants of households but can include travelers, and any other individual who decides to purchase regardless of a centralized distribution program, as well as individuals or group of individuals responsible for decision-making for an organization. For example, a hotel-resort might have an employee responsible for deciding which spatial repellent to use throughout the resort during a dengue outbreak.

Individual users are informed through varied sources including personal experience, experience of others trusted by the individual, retailer advice, marketing, advertising, outreach, or label information on packaging. Where the effectiveness of spatial repellents is recognized by public health authorities, individuals might also be influenced by official outreach campaigns advising their use.

Public Users

In public uses, the choice of the product, the decision to purchase it, and the deployment to use it are anticipated to be the responsibility of governments, NGOs and/or health authorities. The public users will most likely be a centralized distribution program, as well as individuals responsible for product procurement for an organization.

Public users are informed through public health recommendations by the World Health Organization, operational experience in the use case for which the spatial repellent is intended to be used, as well as by label information on packaging. Assuming that the evidence for disease efficacy and cost effectiveness are adequate (i.e., meet requirements for reduction of disease risk at a cost suitable for available funds) for some spatial repellents, their application to centrally-funded public-health programs will share a pattern of a responsible authority making a funding decision. That decision might be viewed as a directive by an implementor or the decision might be in response to a request by the implementor. At the level of actual use, people will either be following orders to apply the spatial repellent or considering whether to use it.

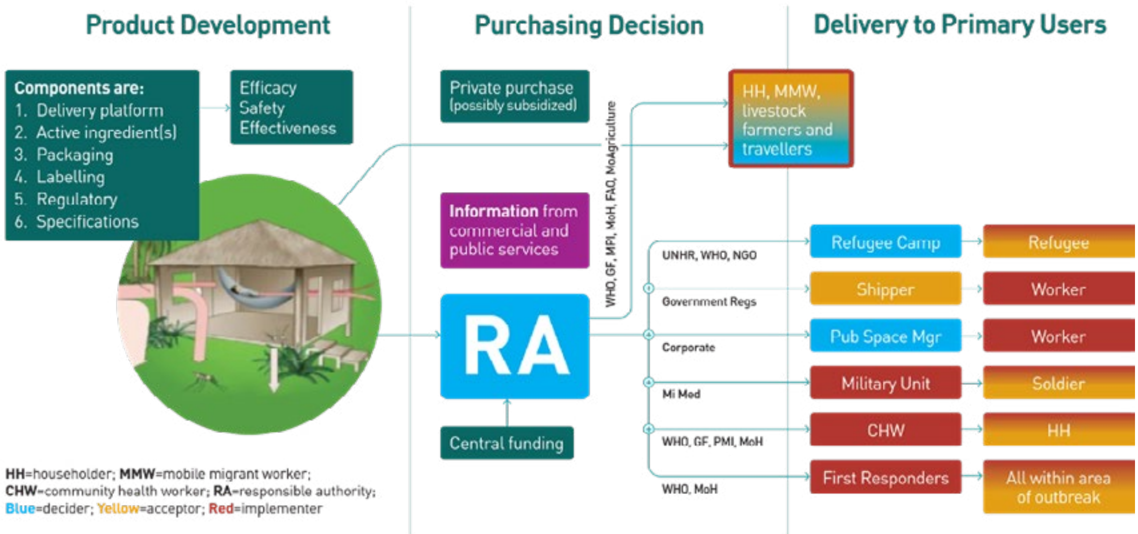
Relationships Between Commercial and Public Spatial Repellent Users

The diagram below attempts to summarize the relationships of stakeholders in the use of spatial repellents. At the left is the development of the spatial repellent product itself, which may involve considerable interaction with the user community in order to achieve the most appropriate spatial repellent to meet requirements of specific use-cases. In the middle is the purchasing decision, either done by individual commercial users or by public authorities. Whether an individual or a responsible authority, the purchasing decision will be made based on information gathered from various sources.

For the public user, the authority responsible for a purchasing decision is above the level of the primary user. The public authority would typically have the intention of representing the best interests of the primary users, but those intentions might be communicated in a variety of ways. At one end of the spectrum, the public authority might simply distribute the spatial repellent and hope that people use them. At the other end of the spectrum, the public authority might hold focus groups and outreach sessions that attempt to match the right spatial repellent with the right group of people.

For example, protection of a public space like a hotel resort involves decisions by a facilities manager, but the applicator is not going to have much decision authority over acceptance of the spatial repellent. In contrast, householders, refugees, and even soldiers will be in a position to govern use or not of a spatial repellent after distribution. Outreach and communication would presumably be most important when the individual ultimately decides whether or not to use the spatial repellent.

Given that a spatial repellent exists that is effective and economical for a given use case, following a purchasing decision it is still necessary to get the spatial repellent into the hands of the primary user. Commercial distribution has the advantage of using existing facilities and expertise for movement, storage, and sale of items. However, the availability of commercial distribution may not be adequate for all the people who need the spatial repellent. Public user distribution requires both the cooperation of industry for delivery of a viable spatial repellent product suited to the use case and the use of non-commercial delivery to the primary users. There is not a lot of experience with this kind of distribution, but other vector control programs have used various combinations of top-down campaigns during discrete time periods, more continuous programs making the items widely available, or encouragement to obtain the items through vouchers or similar mechanisms. Probably any public distribution would best be combined with education and outreach. The nature of the distribution system, whether commercial or public, would likely influence the design of the spatial repellent itself, for example the nature of labelling and packaging.



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