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Scaling Up Vector Control for Malaria Prevention

Landscape of new vector control products

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Contents

Introduction

Description of methods

This "Landscape" was developed through email exchanges and discussions with colleagues working in the research, product development and regulatory fields, through on-line literature searches and meeting reports. The information is all public record. There may be a few products and processes under development and further from being ready for the field, not included here, as they are still proprietary information. For these few products not yet part of the public record, collaboration for operational research and field implementation and policy development can be discussed privately with the individuals involved. Contacts for many of these researchers and product development managers are provided in the last section of the document.

Contexts, combinations and opportunities

Few of the products or processes described here will be as universally scalable as Indoor Residual Spraying or an Insecticide Treated Mosquito Net. Rather, in the framework of Integrated Vector Management, programs will need to choose the right interventions for the right context. For example in the peri-urban environments around Lake Victoria, housing improvements and larval source management may be appropriate; for displaced persons in South Sudan, distribution of permethrin-treated blankets may be the intervention of choice; Attractive Toxic Sugar Baits may work in the Sahel, but not in Congo; there may be a combination of interventions other than mosquito nets for fishing communities around Lake Tanganyika; a topical repellent may work for a quick trip to gather rosewood stumps in the forests of southern Lao PDR, but not necessarily for weeks on end back in the village.

We also need to be cognizant of our new era of multi-sectoral engagement, especially in the context of the Sustainable Development Goals where we need to graduate from relying on a single intervention, such as episodic mass distributions of LLINs, to broader-based interventions using a combination of technologies and new partners outside our traditional health sector. For example, there may be engagement with the CDC "One Health Office" for collaboration with veterinary health services and cattle treatment for control of zoophilic vectors like *Anopheles arabiensis,* especially amongst pastoralists*;* with nutrition initiatives (e.g. USAID's "Feed the Future") for malaria prevention commodities as a core part of food security; with urban development initiatives for reducing vectors through improved housing and infrastructure; and with emergency response organizations for malaria in complex emergencies.

Finally, opportunities. The goal of this review is not to simply list what new products are currently available or on the near horizon, but to highlight where partners can be engaged and facilitate the development and adoption of these new tools. Rather than being passive recipients waiting for full WHOPES recommendations to "scale-up", there are opportunities for partners to engage product development consortia to meet the challenges of moving beyond our limited LLIN and IRS interventions. Some of these challenges involve capacity for public health entomology as described in recent WHO policy,[i] other challenges relate to capacity for social science and operational research, implementation and policy development necessary to bring these new strategies forward.

Pyrethroid attributes to be considered in new product development:

The current technology of Long Lasting Insecticidal Nets (LLINs) all use a pyrethroid (alphacypermethrin, deltamethrin, lambda-cyhalothrin, or permethrin) alone or in combination with the synergist Piperonyl butoxide (PBO), an insecticide chlorfenapyr, or juvenile hormone mimic pyriproxyfen. Before discussing the pyrethroid-based products, it is helpful to consider some attributes of the pyrethroids themselves.

Pyrethroid Types I and II. Pyrethroids were developed as a more photo-stable form of the natural pyrethrum insecticide produced by the flowers of the daisy *Chrysanthemum cinerariaefolium.* The earlier generation of pyrethroids, Type I, includes bifenthrin and permethrin developed in the 1970s. In the late 1970s and early 1980s a second type of pyrethroid with higher insecticidal properties was developed and referred to as Type II or *alpha-cyano pyrethroids*. These include alphacypermethrin, deltamethrin, and lambda-cyhalothrin. Both Type I and Type II act as sodium channel modulators on the insect nerve axon whereby the pyrethroid attaches to the insect sodium channel, keeping it open and preventing the nerve from repolarizing, thereby paralyzing the organism. This mode of action is classified as 3A by the Insecticide Resistance Action Committee.[ii] The other subgroup of sodium channel modulators, 3B, includes DDT. Thus, as described in more detail below, for certain types of "target site resistance" there can be cross-resistance within the insect to both DDT and pyrethroids. Type II pyrethroids also have additional toxic properties, including post-synaptic interactions.[iii]

Safety: Pyrethroid safety has been well documented in WHOPES evaluations[iv] and is not detailed in discussion of the individual pyrethroid-based products described below. One important issue is that the Type II, alpha-cyano pyrethroids can cause some skin irritation, known as *cutaneous paresthesia.*[v] Thus, treated materials that are in contact with the skin use only the Type I, permethrin. "Wearable spatial repellents" while containing Type I metofluthrin or transfluthrin described below, are engineered with a protective mesh so that the pyrethroid can volatize, but not be in direct contact with the skin.

Adhesion to textiles. Pyrethroids have low water solubility and are relatively stable chemicals which helps in the wash-resistant characteristics.[vi] Other chemicals such as pyriproxyfen and PBO may differ in how they react to the high-pressure extrusion or coating technology or how they migrate through the yarn or coating so their exposure to the mosquito can be in sync with the pyrethroid. The current criteria for an LLIN is 20 washes. Introduction of new chemicals with different solubility and adhesion properties may necessitate new criteria for "Long Lasting" with possibly less wash-resistance.

Heat stability. Pyrethroids are stable to very high temperatures and thus can be used in burning mosquito coils. This enables LLINs to be heat-stretched after treatment to stabilize the fabric without denaturing the chemical. This is not the case with other potential chemicals used for net treatment. For this reason, it may be important to maintain the technology of post-production treatment, including individual do-it-yourself kits.

Resistance. Pyrethroid resistance is the main driver for developing new vector control technologies. There are two main resistance mechanisms. The first is "target site" resistance where there is a configuration change at the sodium channel and the pyrethroid molecule does not bind and hold the

channel open. These changes to the sodium channel binding sites are classified as kdr mutations, referring to the knock down resistance seen in bioassays. The second major type of resistance is "metabolic" resistance where the P450 monoxygenase enzymes denature the pyrethroid molecule, preventing it from binding to the sodium channel. The synergist PBO acts by blocking the P450 enzymes and thus, eliminates one of the mosquito defense mechanisms. PBO does not influence kdr target site resistance. Two current insecticides, pirimiphos-methyl and chlorfenapyr are 'proto-insecticides' and must be oxidized by the mosquito P450 enzymes to become toxic. While PBO is good in interfering with molecular resistance to pyrethroids, it may be bad by inactivating the enzymes that make pirimiphos-methyl and chlorfenapyr toxic. Kdr is considered a relatively weak form of resistance compared to metabolic resistance, and it is usually only when kdr occurs at the same time as metabolic resistance that control fails. Even where all members of the population are homozygous for kdr, the alpha-cyano pyrethroids like deltamethrin are still effective unless a detoxification oxidase becomes significantly expressed. Use of focal IRS with an alternative insecticide class shows promise in returning deltamethrin effectiveness. This is facilitated by the fact that the resistance oxidases seem have a fitness cost in mosquito populations in the absence of pyrethroid pressure, adding to instability of intense resistance.[vii] Kdr is common in *An gambiae* s.s., present, but less common in *An Arabiensis,* and has not yet been detected in *An funestus.*[viii] To date, the only form of pyrethroid resistance in *An funestus* is metabolic resistance. The currently known kdr mutations confer cross-resistance across all pyrethroids, while it appears that some of the metabolic forms of resistance are specific to the particular pyrethroid.

This underlying biology has practical implications for pyrethroid-treated nets. Cross-resistance across all pyrethroids may not be the case where molecular resistance is the culprit. PBO will not give any advantage where the only resistance mechanism is kdr, and may actually be a disadvantage if pirimiphos-methyl or chlorfenapyr is used in the same dwelling for IRS. Where the main form of resistance is metabolic, e.g. with *An funestus*, there *may* be a difference in susceptibility among the pyrethroids. Our understanding of these issues is under close evaluation by PMI and rapidly evolving.

Finally, phenotypic bioassays are the definitive measure for resistance; biochemical or molecular assays do not necessarily correlate with control failure. Within the bioassays, we are beginning to see that 'frequency assays' with discriminating doses using either the WHO Tube Assay or the CDC Bottle Assay do not correlate well with control failure in the field[ix]. It appears that "intensity assays" using either the WHO Tube Assay or the CDC Bottle Assay that measure the "strength" of the resistance correlates better with control failure. For example, in Zambia, it was only when *An funestus* was able to survive 5 times the discriminating dose of the pyrethroid did they see the vector resting on freshly sprayed surfaces and new LLINs.[x] A WHO meeting in September 2014[xi] recommended that resistance testing guidelines be revised to include such intensity.

Behavioral impact of sub-lethal pyrethroid doses in spatial repellents. The volatile spatial pyrethroids transfluthrin and metofluthrin don't "repel" mosquitoes *per se*, i.e. they do not induce taxis away from the source of the pyrethroid. Rather they "disrupt" the mosquito's ability to locate the host. Therefore, a dose that may not be strong enough to kill her, may be strong enough to confuse her. However, recent studies in Kenya showed a different repellent reaction in the field-collected *An gambiae* s.s. than in *An arabiensis* and *An funestus* s.s. It might be that kdr mosquitoes exhibit less repellency to pyrethroids,

whereas those lacking kdr maintain high repellency irrespective of their possessing metabolic resistance factors to pyrethroids.[xii] However, in *Aedes aegypti,* insensitivity to the repellent action of transfluthrin is a heritable trait associated with resistance.[xiii] We are currently uncertain of the impact of pyrethroid resistance on the spatial repellents, transfluthrin and metofluthrin. This important issue is currently being investigated in the semi-field facilities at the Ifakara Health Institute in Tanzania.

Interventions

New Long Lasting Insecticidal Nets with different insecticides or combinations

ICONMAXX® is a 'dip-it-yourself' mosquito net treatment kit developed by Syngenta based on the slow-release capsule suspension (CS) of lambda-cyhalothrin. In September 2014 this received full WHO recommendation with an estimated duration of insecticidal efficacy of 30 to 36 months depending on the local settings. This technology is useful for converting untreated nets that may be widely available in the community, such as the 'bundling strategy' for treating hammock nets in Cambodia where the ICONMAXX was budgeted at $1.45 per kit. A full description of the Cambodia program can be found in a NetWorks Project report "Vector Control Assessment in the Greater Mekong Sub-region, May 2012"

While not a new product, and because individual treatment of nets has been largely superseded by factory pre-treatment, retreatment kits should be kept on the table for two reasons: treatment of specialized nets in the private sector, such as the hammock nets of Cambodia, and some of the specialized ornate, frilly, and kitsch custom nets popular in the private market. In many countries, the vast majority of nets in the private market are untreated. Until we find a solution to treat these during manufacture, the option for post-production treatment should be made available. A recent experimental hut trial in Tanzania concluded: "Nets treated with ICON Maxx and washed 20 times met the approval criteria set by WHOPES for Phase II trials in terms of mortality and blood-feeding inhibition. This finding raises the prospect of conventional polyester nets and other materials being made long-lastingly insecticidal through simple dipping in community or home, and thus represents a major advance over conventional pyrethroid treatments".[xiv] Second, while pyrethroids are heat stable (and thus effective in mosquito coils) in the future there may be some chemicals used for LLINs that are heat labile and can only be applied post-production after heat setting the netting material. These types of individual treatments may be an appropriate technology for these situations and so should be kept in consideration. The remaining research question is if bundling or other retreatment strategies are a cost-effective means of maintaining adequately high LLIN coverage.

Chlorfenapyr/alphacypermethrin the Interceptor G2® by BASF[xv]

This "Second Generation" combination net is currently undergoing WHOPES testing[xvi] and presented to the WHO Vector Control Advisory Group in November 2014.

Chlorfenapyr is a new class of public health pesticide, a pyrrole that acts by disrupting mitochondrial conversion of ADP into ATP, leading to cellular death and eventual insect mortality. There is no cross-

resistance to the other four classes of public health pesticides. In Benin exposure of *An gambiae* Vkpr (pyrethroid-resistant, fixed for kdr) and Yao strains (multi-insecticide resistant, Ace-1R allele 100%), indicated no cross-resistance between chlorfenapyr and kdr and *Ace-1R* resistance mechanisms. In India field-collected *Cx. quinquefasciatus* at two different sites, which were reported resistant to DDT, Malathion, bendiocarb and deltamethrin, showed 100% mortality, indicating absence of cross-resistance to chlorfenapyr.[xvii]

Chlorfenapyr is a common pesticide, registered in over 40 countries and has EPA approval for use in commercial kitchens. It is rapidly metabolized and excreted by mammals, birds, and fish, hence unlikely to bio-accumulate in individual organisms or bio-magnify between tropic levels.[xviii] Evaluations by WHOPES have indicated that chlorfenapyr is safe to use in vector control applications.[xix]

There are three points related to chlorfenapyr and LLINs. First, it is a slow-acting insecticide and will not immediately kill or knockdown the mosquito like the other four classes of mosquito adulticides that are nerve agents. Therefore, on nets, chlorfenapyr is combined with a pyrethroid, in this case alphacypermethrin (that BASF was already using on the 'first generation' Interceptor net). Second, chlorfenapyr is a "proto-insecticide" that is metabolized to the active form by the mosquito P450 mixed function oxidase enzymes, and thus should not be combined with PBO. Third, the rapidity of kill depends on the cellular respiration of the mosquito. Against night-active mosquitoes it will kill within 24 hours, while in artificial daytime bioassays it may appear slower. The low temperature constraint seems to be over-ridden by the circadian rhythm, as chlorfenapyr is as toxic in higher altitude Moshi as it is in costal Tanga Tanzania.[xx] Overall, one must be cautious in interpreting many of the bio-assays designed for fast-acting nerve toxins like the other four classes of mosquito adulticides when used with chlorfenapyr-treated materials as the mode of action is completely different. The WHO tunnel test on night-active anophelines is the most reliable bioassay for identifying the toxicity of novel insecticides such as chlorfenapyr.[xxi]

There is no evidence of resistance to chlorfenapyr in mosquitoes, including *An culicifacies* and *An stephensi* in India,[xxii] laboratory–reared *An funestus* in South Africa,[xxiii] *An arabiensis* in East Africa,[xxiv] and *An gambiae* in West Africa.[xxv] Moreover, BASF, with their large agricultural resources, closely monitors for the emergence of pesticide resistance across a broad range of arthropods and has not found any substantiated evidence of chlorfenapyr resistance.[xxvi]

Experimental hut trials for proof of concept of a chlorfenapyr combination net with the dipped chlorfenapyr/alphacypermethrin (not yet the formulated LLIN Interceptor G2) were published from Benin and Tanzania.

In Benin[xxvii] nets treated with chlorfenapyr and alphacypermethrin killed significantly more *An gambiae* than nets treated with alphacypermethrin, but not significantly different from nets treated with chlorfenapyr alone. The nets treated with the mixtures provided personal protection against *An gambiae* biting by a greater margin than the alphacypermethrin treated net whereas the chlorfenapyr treated net was not protective. A similar trend in mortality and blood feeding inhibition between treatments was observed in *Cx. quinquefasciatus* to that seen in *An gambiae*, although the effects were

lower. The study concluded that the effectiveness of ITNs against pyrethroid resistant mosquitoes was restored by the mixture: the alphacypermethrin component reduced human-vector contact while the chlorfenapyr controlled pyrethroid-resistant mosquitoes. The complementary action of these unrelated insecticides demonstrates that the combination on nets has potential for preventing malaria transmission in areas compromised by the spread of pyrethroid resistance.

Likewise in Tanzania,[xxviii] experimental hut trials with the mixture of chlorfenapyr and alphacypermethrin (again a dipped net, not the LLIN formulation) killed 58% of *An arabiensis*, compared with 50% for alphacypermethrin and 49% for chlorfenapyr, though the differences were not significant. Blood-feeding inhibition was highest in the mixture with a 76% reduction compared to the untreated net (P = 0.001). The investigators concluded that mixtures of chlorfenapyr and alphacypermethrin should restore effective control of resistant populations of *An gambiae* malaria vectors, provide protection from blood-feeding, and may have benefits for resistance management, particularly in areas with low or moderate frequency of pyrethroid resistance.

At the Global Collaboration for Development of Pesticides for Public Health (GCDPP) 2014 meeting, Mark Rowland showed a graph of hut trial data from Benin showing higher mortality for Interceptor G2 compared to Interceptor (Alphacypermethrin only). At the November 2014 Vector Control Advisory Group meeting (in press), an update on Interceptor G2 was presented with data from hut trials in Benin and Burkina Faso. Hut mortality data for Interceptor G2 were superior to Interceptor.

Summary:

The Interceptor G2 appears ready to reach the market soon, certainly before September 2016. Priority for deployment will be in those areas where pyrethroid resistance has caused traditional pyrethroid-only LLINs to fail (not always a straight-forward assessment). There are no known drawbacks to its deployment. The cost of the Interceptor G2 is not currently available. The remaining research questions, as for all combination LLINs, is the additional cost-benefit, especially in areas of intense pyrethroid resistance.

Permethrin/pyriproxyfen[xxix,xxx] the Olyset Duo® by Sumitomo

The Olyset Duo® is being developed in collaboration between IVCC and Sumitomo.[xxxi] The net, based on the traditional permethrin-imbedded polyethylene Olyset Net, combines the Juvenile Hormone Mimic pyriproxyfen with permethrin. Sumitomo has long marketed pyriproxyfen as a larvicide "Sumilarv®"[xxxii] (technically a "pupacide" as it inhibits adult emergence). Pyriproxyfen is safe to humans (and approved for use in drinking water) and while there has been some resistance reported in agricultural pests, there has been no evidence of cross-resistance to other classes of insecticides used for vector control.[xxxiii] In addition to prevention of adult emergence, pyriproxyfen also inhibits oogenesis and sterilizes the mosquito. Studies with adult *Ae albopictus* showed that tarsal contact with pyriproxyfen suppresses egg production and hatchability in adult females and the auto-dissemination of pyriproxyfen into larval breeding sites by adult mosquitoes may suppress the mosquito population density.[xxxiv]

There have been two field studies with the Olyset Duo®:

In western Kenya[xxxv] the Olyset Duo® was compared with a net treated with pyriproxyfen alone, against a pyrethroid-resistant wild population of *An gambiae* s.s. High mortality of blood-fed mosquitos was observed 3 days post-collection in the houses where pyriproxyfen was used. Reduction in the number of ovipositing females, number of eggs, and number of progeny per female was also observed. The permethrin repellency reduced mosquito bites, providing personal protection. Further studies on wild pyrethroid-resistant mosquito populations such as *An arabiensis* and *An funestus* s.s. will be the next steps in assessing the Olyset Duo®.

In Southern Benin[xxxvi], experimental hut studies against pyrethroid resistant *An gambiae* and *Culex quinquefasciatus* were made with the Olyset Duo®, the traditional Olyset Net (permethrin alone) and an LLIN with pyriproxyfen alone. Laboratory tunnel tests were performed to substantiate the findings in the experimental huts. Overall mortality of wild pyrethroid resistant *An gambiae* s.s. was significantly higher with Olyset Duo than with Olyset Net (50% vs. 27%) and Olyset Duo was more protective than Olyset Net (71% vs. 3%). The oviposition rate of surviving blood-fed *An gambiae* from the control hut was 37% whereas none of those from Olyset Duo® and the net with pyriproxyfen alone laid eggs. The tunnel test results were consistent with the experimental hut results. Olyset Duo was more protective than Olyset Net in the huts against wild pyrethroid resistant *Cx. quinquefasciatus* although mortality rates of this species did not differ significantly between Olyset Net and Olyset Duo. There was no sterilizing effect on surviving blood-fed *Cx. quinquefasciatus* with the pyriproxyfen-only treated nets. Overall, Olyset Duo was superior to Olyset Net in terms of personal protection and killing of pyrethroid resistant *An gambiae*, and sterilized surviving blood-fed mosquitoes.

Summary:

Like the Interceptor G2, the Olyset Duo appears to be close to market and will likely be deployed before September 2016. And like the other combination nets, the remaining questions relate to the added cost-benefit in areas of intense pyrethroid resistance.

Pyrethroid plus PBO:

There are two LLINs entering the market that combine a pyrethroid with PBO:

- Deltamethrin /PBO[xxxvii]: PermaNet® 3.0 by Vestergaard. Described as "the first long-lasting insecticide-synergist combination bed net."[xxxviii] It is now under consideration by the WHO Vector Control Advisory Group. It has deltamethrin on the walls of the net and a combination deltamethrin+PBO on the roof, and has an interim WHOPES recommendation as an LLIN. The combination net showed increased bio-efficacy compared with pyrethroid-only LLINs in areas where malaria vectors have p450-based metabolic resistance mechanisms.

- Permethrin/PBO: Olyset Plus® by Sumitomo. Like the Vestergaard product, Sumitomo has added the synergist PBO to its pyrethroid–treated net, although for the Olyset Plus, the PBO is incorporated into every fiber and not just the top panel of the net as in the PermaNet 3.0. In the laboratory, Olyset Plus® performed better than Olyset Net® against a susceptible *An gambiae* strain with a 2-day regeneration time owing to an improved permethrin bleeding rate. It also

performed better than Olyset Net® against multiple-resistant populations of *An gambiae* in experimental hut trials in Cameroon and Benin.[xxxix]

Summary. Both of these combination PBO LLINs are currently being deployed. The main question is if these will be deemed more cost-effective than either the original PermaNet 2.0 or Olyset Net or the next generation nets such at the Olyset Duo and Interceptor G2 or other new active ingredients and combination under development but not yet made public by the manufacturers.

Other combination ITNs:

Pyrethroids and repellents (DEET or IR3535)[xl]

Studies were done with binding combinations of permethrin plus DEET or IR3535, and etofenprox plus DEET, onto netting material employing a new multi-layer polymer-coating technique. Protective repellent efficacy, toxicological effectiveness and residual activity of 12 LLIRN types have been evaluated by laboratory testing against adult *Aedes aegypti*. Permethrin or etofenprox did not influence spatial repellency of DEET or IR3535 on LLIRNs. Vice versa, DEET and IR3535 increased spatial and excitatory repellency and reduced landing and probing frequency on LLINs resulting in strongly enhanced biting protection, even at low concentrations. This LLIRN is currently under development by UXTABEL.

Pyrethroids and Organophosphates

Studies were done in West Africa on a Chlorpyrifos-methyl/lambda-cyhalothrin combination net in 2005, but there has been little further development. Chlorpyrifos-methyl is an organophosphate developed by Dow AgroScience (DAS) for use as an indoor residual spray[xli] under the trade name Reldan™. For business reasons, the product was shelved, possibly connected with potential liability issues around chlorpyrifos, one of the most popular pesticides in the US, as in the termiticide Dursban™ which has since been taken off the market.[xlii] In the 2005 study[xliii] *An gambiae* and *Culex quinquefasciatus* resistant to pyrethroids and organophosphates (kdr and insensitive acetylcholinesterase *Ace.1*^{R}) were tested. Several treatments and application rates on intact or holed nets were evaluated, including single treatments, mixtures, and differential wall/ceiling treatments. All of the treatments were effective in reducing blood feeding from sleepers under the nets and in killing both species of mosquito, despite the presence of the kdr and *Ace.1*^{R} genes at high frequency.

Organophosphates and repellents

Other combination nets have been tested in experimental huts and tunnel tests, including repellents and carbamates (propoxur) and organophosphates (pirimiphos-methyl) [xliv]. In the experiments with the organophosphate, mixtures (PM+DEET and PM+KBR3023) induced 95% mortality for more than two months compared with less than one week for each compound used alone, then reflecting a strong synergy between the repellents and pirimiphos-methyl. A similar trend was observed with the blood feeding rates, which were significantly lower for the mixtures than for each component alone. The results suggested synergistic interactions between organophosphates and repellents to increase the residual life of impregnated materials and improve the control of pyrethroid-resistant mosquitoes. From

recent discussions with Syngenta, the WHOPES-approved manufacturer of pirimiphos-methyl, because of potential oral toxicity they are no longer pursuing an organophosphate-treated mosquito net.

Summary

From previous communications with DAS and more recent discussions with Syngenta, commercial investment for LLINs treated with organophosphates appears unlikely.

SmartPatch

The SmartPatch is being developed through the European Union's Framework 7 Health Innovation initiative support to the MCD Project (Mosquito Contamination Device)[xlv], a consortium that includes the Ifakara Health Institute, Biogents (manufacturers of mosquito traps) In2Care, and Penn State University. In addition to the SmartPatch the MCD project is developing Eave Tubes and passive release outdoor odor lures.

The SmartPatch is a supplementary netting patch (30 x 80 cm) impregnated with non-pyrethroid insecticides placed on top of a bed net. The goal is to develop a simple, cheap and easily implementable technology that can be added to existing LLINs, transforming them into combination insecticide products to control pyrethroid-resistant mosquitoes.[xlvi] The SmartPatch has been submitted to VCAG and is currently undergoing further testing in Tanzania.

Other innovations to make mosquito nets more consumer-friendly

- The Boko Bed Net Project. "Boko" means 'I am well' in Twi. There is an interesting project by the "Green World Health Net" who aim to reduce malaria rates by teaching people to make their own solar panels and solar systems to power fan and light consoles inside mosquito bed nets, making them more comfortable to sleep under. The additional benefit is to provide renewable electricity to villages that have none and creating business opportunities to make and sell solar panels as well as cell phone and battery chargers.[xlvii]

- Free-standing mosquito nets. There are a number of commercial manufacturers of self-supporting mosquito nets such as "SansBug"[xlviii] that are on the western market, and may find some penetration in malaria endemic zones.

Summary: While there is certainly work by the major manufacturers to make the netting more durable, there is also work by others to make the nets easier and more comfortable to use. There is a renewed interest by some entrepreneurs and consumer-product companies, including SC Johnson, to re-look at the design of the mosquito net to see if it can be modified for improved acceptability and use. The company BestNet was trying to do this with printing logos and other patterns on their nets but the product has since lost WHOPES approval.

Entomopathogenic fungi

Entomopathogenic fungi such as *Beauveria bassiana* and *Metarhizium anisopliae* are widely available commercially for garden and agricultural pests including locust control in Africa,[xlix] where in 2009 FAO spent over $2m to spray an oil-based formulation of *Metarhizium anisopliae,* known as "Green Muscle" to control locust swarms in Tanzania, Malawi and Mozambique.[l]

These fungi have an advantage over the current fast-acting insecticides by disrupting feeding and killing the mosquito later in her life, but before she is infectious, reducing the selection pressure and potential development of resistance seen in the other fast-acting chemical insecticides.[li] In addition to being 'resistance proof' fungi can be considered 'resistance breaking'. Studies show that multiple mosquito species/strains exhibiting resistance to all classes of chemical insecticide currently approved for use remain completely susceptible to fungus.[lii] Furthermore, there is evidence that pre-lethal fungal infection can reduce expression of insecticide resistance, returning otherwise resistant mosquitoes to a more susceptible state.[liii] [liv] These features create strong potential for use of fungal entomopathogens within novel resistance management strategies. Recent studies indicate that *Beauveria* co-infection or super infection does not influence the development of *Plasmodia* within the mosquito.[lv]

Fungi act through contact so lend themselves to deployment strategies similar to many chemical insecticides (IRS, treated materials, resting targets, etc.). Application of entomopathogenic fungi, may be through spray, through application to resting areas such as clay pots[lvi], sugar-feeding sites[lvii], and to eave screens as described below. Work is ongoing to improve formulations and persistence.[lviii]

Bueaveria has been registered by EPA since 1995 for all food and feed crops. There are no known health or environmental risks. Since 1997 there are seven approved pesticide products containing this active ingredient.[lix] Additional tests have been conducted as part of EPA registration for use in indoor environments. The fungus has passed all tests at maximum challenge including acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, acute eye irritation, and primary dermal irritation. Additionally, the delivery systems tested so far (oil-based formulations or powders bound to netting using electrostatic forces) prevent spores from being liberated into the air. Air quality sampling in real village houses in Tanzania have been conducted and have not detected any powders from electrostatic netting placed in eave tubes within the house itself.[lx]

Direct costs of fungus depend on amount of fungus used per house. For full IRS, fungus is probably in the same region as one of the more expensive chemical products and has persistence of 3-6 months. For use in eave tubes, the fungal active ingredient is about $0.02 per tube (< 20 cents to treat a house once eave tubes are installed). Studies in Tanzania indicate persistence of 2-3 months for spores in eave tubes. The fungal active ingredient to keep a house treated all year round using eave tubes would be around $2. Eave tubes seem to be the real breakthrough in making this technology viable. There is considerable scope for production of spores in country. Production requires good quality control, but the level of technology and capacity is roughly equivalent to running a brewery. Once produced and stored properly, the spores can last for years.[lxi]

Summary:

Like many of the technologies described in this Landscape Review, the use of entomopathogenic fungi will likely be supplementary to LLINs, although, if the formulations can be improved, it is conceivable that it could be a replacement IRS application. Currently eave tubes seem to be the best presentation and have been submitted to the WHO Vector Control Advisory Group for consideration. Registration dossiers exist and experimental use is permitted in Tanzania, Benin and Kenya. According to the developers, commercial quantities can be produced and if funding was available a larger trial of eave tubes and spores could begin almost immediately. Overall it is highly likely that entomopathogenic fungi in some format will be ready for deployment in the near future.

Novel strategies for larvicide

Larvicides and environmental management was the original malaria vector control strategy, but was surpassed by IRS and later LLINs that can be more easily applied across wide areas with standard approaches and with much less technical expertise, time and effort. Larval control is especially difficult in the rural African context where the malaria vector larval habitats can be difficult-to-locate temporary pockets of water. As WHO recommends, larviciding should only be considered where the larval habitats are "Few Fixed and Findable" and only as a supplement to IRS and LLINs.[lxii] PMI supported larviciding in urban settings in the Urban Malaria Control Program in Dar es Salaam from 2006 to 2008, but discontinued support to focus on interventions with higher public health impact. Larviciding strategy is fraught with challenges where implementation with non-quality controlled product often outpaces evidence. [lxiii]

Still, there are developments in the field of larviciding that can improve its effectiveness.

Improved application technology. Misting or ultra-low volume spraying for area-wide application of the WHO-recommended *Bacillus thuringiensis israelensis, strain* AM65-52, WG has been effective against *Aedes* container larval habitats.[lxiv] While this type of wider application technology for larvicides has had limited use against malaria vectors[lxv], it is under consideration for a number of peri-urban situations. Likewise, pyriproxyfen has been applied through truck mounted ULV providing effective control of container larval habitats 23 meters from the road.[lxvi]

- The US Navy Entomological Center of Excellence in Jacksonville, Florida (in the process of becoming a WHO collaborating center for application equipment) is working with manufacturers of larvicides, including Valent BioSciences (the manufacturer of *Bti* AM65-52) on improved application equipment, primarily for use against *Ae aegypti* and *Ae albopictus*.
- The most recent WHOPES meeting of the Global Coalition for the Development of Public Health Pesticides recommended that the Global Plan for Insecticide Resistance Management be revised, including a recommendation to reconsider Larval Source Management as a part of the insecticide resistance management strategy. In the past larviciding has been challenged by formulation/persistence and 'cryptic larval habitats' that went un-found by the applicators. Area-wide applications, with these different application systems and with longer-acting larvicide formulations may change the cost-effectiveness calculations and enable broader use of larval control, especially in peri-urban areas and as part of an insecticide resistance management strategy. One word of caution, depending on the spectrum of the specific larvicide, there is potential impact on non-target organisms.
- Auto-dissemination. Initially developed for *Aedes* container-breeding mosquitoes, this is far less

ready for deployment for anophelines. The principle of auto-dissemination is that female mosquitoes pick up traces of the Juvenile Hormone Mimic pyriproxyfen, carry it to breeding sites and deposit sufficient toxicant into the water while laying eggs, resulting in inhibition of mosquito larval development. Still under development, it is unsure if it will work against *Anopheles* that often oviposit in larger bodies of water than the container-breeding *Aedes*.[lxvii lxviii]

Durable Wall Linings

Insecticide-treated polyethylene netting hung on the inside walls of dwellings kills mosquitoes in a way similar to IRS but assures a uniform dosing and can be formulated into slow release, longer acting presentation[lxix]. The first generation Durable Wall Linings incorporated deltamethrin. To address the widespread problem of pyrethroid resistance, more recent presentations incorporate other chemicals, including the organophosphate insecticide pirimiphos-methyl.[lxx] A new non-pyrethroid DWL product will be field-tested in Muheza, Tanzania in 2015-2016.

Summary: More information on Durable Wall Linings will become available through the PMI-supported trial in Tanzania. While the lining appears to be acceptable in traditional houses, there remains the question of acceptability in the growing proportion of modern houses with cement and brick walls.

Topical Repellents

There are six topical repellents approved by the EPA (who has developed an excellent public website for issues related to topical repellents)[lxxi].

Topical repellents (applied to the skin) are widely used around the world to provide individual protection against mosquito bites. A recent review[lxxii] and meta-analysis[lxxiii] indicate that on their own, there is little evidence that topical repellents provide a public health impact. The main challenges are compliance and correct use. However, there may be situations, when used in combination with other personal protection measures, or over relatively short exposure times where topical repellents can provide protection. Four recent community-based trials of topical repellents include:

- para-menthane-diol (PMD)in Bolivia.[lxxiv] A double blinded, placebo controlled cluster-randomized clinical study was done to determine the effectiveness in reducing malaria by combining PMD with ITNs vs ITNs alone where the vectors fed in the early evening. The study included 4008 individuals in 860 households for a total of 15,174 person-months. There was a highly significant 80% reduction in *P vivax*, and although there was an 82% protective efficacy against *P falciparum*, the numbers were too small to be significant. Reported episodes of fever with any cause were reduced by 58% in the group that used repellents. The authors concluded that the combined use of ITNs and repellent was justified.

- PMD - Lemon grass oil in Ghana. A trial in Northern Ghana showed high user acceptance, a protective efficacy of over nine hours and was associated with a decrease of absolute malaria prevalence by 19.2% in the repellent village and by 6.5% in the control village (45.5 to 26.3, and 29.5 to 23.0, respectively).[lxxv] The commercial company that manufactures the product, “No Ma”[lxxvi] continues to pursue its adoption and is currently in discussions with VCAG.

- Picaridin in Cambodia. There is an on-going randomized control trial of the repellent picaridin in North-East Cambodia. In terms of *efficacy*, when applied properly the picaridin provided a five-hour protection rate of 97.4%, not decreasing over time. Picaridin 20% performed equally well as DEET 20% and better than picaridin 10% but had higher acceptability as compared to DEET.[lxxvii] While still awaiting final analysis of the serological tests, preliminary results did not reveal a significant reduction in the malaria prevalence in the intervention arm as compared to the control arm. Repellent coverage (measured through a two-weekly bottle exchange program) was reported to be reasonably high (80% exchange > 4 times). Self-reported repellent use in the intervention arm is in the range of 70-80% and people reported using more repellent in forested sites. However the overall prevalence of the study is lower than initially expected and no significant difference between the control and the treatment arms could be detected. [lxxviii]

- DEET in Lao PDR. A double blind, household randomized, placebo-controlled trial carried out in southern Lao PDR to determine whether the use of repellent and long-lasting insecticidal nets (LLINs) could reduce malaria more than LLINs alone. The study included 1,597 households, and 7,979 participants. The analysis found no effect from the use of repellent on malaria incidence. [lxxix]

Summary: The challenge with topical repellents remains ease of application, user acceptability and price. While the Ghana and Bolivia trials did indicate some community-wide protection, there is skepticism that outside a trial situation, communities could be convinced to appropriately use topical repellents night in and night out for weeks or months on end to achieve a community-wide impact. The meta-analysis cited above by Wilson et. al. *Are topical insect repellents effective against malaria in endemic populations? A systematic review and meta-analysis* published in the Malaria Journal elicited a strong disagreement by Prof. Mark Rowland who commented: "The point is that in some populations, some cultures, and in some epidemiological situations, repellents *were* shown to protect against malaria. That cannot be denied, and therefore the overall [negative] conclusion is wrong and misleading".[lxxx] In conclusion, especially for personal protection during limited-time exposures, topical repellents should not be ruled out. Moreover, the challenges of proper application to all exposed areas may be overcome through the use of "wearable" spatial repellents as detailed below.

Treated clothing and other materials

Insecticide-treated clothing, including with micro-encapsulated permethrin is a well-developed technology, especially for military uniforms and outdoor recreational clothing. A 2014 review[lxxxi] showed there is clear evidence for preventing biting through the treated clothing, but not exposed areas, such as hands, not covered by the permethrin-treated clothing, where topical repellents are recommended. Trials on disease reduction focused on malaria and leishmaniasis. Here, the results are more varied and depends on how the materials are used. Insect Shield[lxxxii] is one of the largest commercial producers of treated materials for military and civilian use and is currently working with partners in Thailand to develop protective clothing for malaria prevention. There has also been recent work on the potential of treated school uniforms for dengue prevention in Thailand.[lxxxiii]

As treated clothing only prevents "bite through" and not other exposed areas of skin, future development of treated clothing will likely focus on spatial repellents such as transfluthrin or metofluthrin. As these can cause skin irritancy, "wearable spatial repellents" are being developed where

there is no direct contact with the skin. One very highly engineered version of a wearable spatial repellent is the SC Johnson OFF!® Clip-On™ that emanates metofluthrin with a battery-powered fan.[lxxxiv] While a clip-on fan may not be appropriate for many malaria endemic settings, there are a number of groups and companies in advanced development of passive wearable spatial repellent technologies, but the results are not yet part of the public record. It is highly likely that some of these products will be available for deployment within the next few years. Product managers from these individual companies can be contacted for further information.

Treated blankets and sheets

A subset of the treated clothing is the use of permethrin-treated blankets and scarves. Permethrin treated blankets or top-sheets were first studied among Afghan refugees in North West Pakistan in 1999.[lxxxv] More recent work in 2014 demonstrated the potential of treated blankets to provide substantial personal protection even against pyrethroid resistant mosquitoes, and that they may prove particularly useful where LLINs are unsuitable or net usage is low.[lxxxvi] One micro-encapsulated permethrin-treated blanket has been approved by EPA and is currently being considered for use in emergency relief operations.[lxxxvii] This product has recently been considered by the WHO Vector Control Advisory Group and may be available for broader field evaluation soon.

Summary. Like many of these technologies, treated blankets may be best utilized as "niche" products for emergency relief rather than for a general, stable, population. There are opportunities for partners to collaborate with the manufacturers and with OFDA or UNHCR to improve access and use of treated blankets, especially for emergency relief operations.

Spatial repellents

There are major investments by donors, academia and the private sector on the development of spatial repellents for both indoor and outdoor protection. In the recently released "The 50 most critical scientific & technological breakthroughs required for sustainable global development" by the Lawrence Berkley National laboratories, repellents were ranked #16 and 17.[lxxxviii] Undoubtedly this will be an area of prime interest for collaboration over the next few years.

Mosquito behavior elicited in response to airborne compounds including movement away from a chemical stimulus, loss of host detection, anti-feeding as well as knockdown and mortality are collectively referred to as "spatial repellency". Spatial repellents do not require physical contact of the mosquito with a treated surface but act in the vapor state at a distance.[lxxxix] Current spatial repellents include metofluthrin, transfluthrin, linalool and the undecalactones. Metofluthrin and transfluthrin have the unique characteristic of volatizing at room temperature and thus not requiring a heat source like a coil, electric mat or lamp.[xc] Transfluthrin is widely used in mosquito coils and mats and may have slightly more insecticidal rather than repellency actions.[xci] Linalool was seen to have some repellency when presented as a candle, but more recent tests in Tanzania concluded that the tested 73% d-linalool agar gel emanators do not provide protection against malaria vectors.[xcii] Lactones, derived from fruit and dairy products are a promising new class of spatial repellent that show efficacy similar to or greater than that of DEET but has the added advantage of a pleasant smell.[xciii]

Mosquito coils[xciv], lamp and other emanators[xcv]

Mosquito coils are found everywhere throughout the tropics and in carefully controlled situations have been shown to provide both an entomological and epidemiological impact. For example recent trials on the island of Sumba, Indonesia[xcvi], using a specially manufactured 12-hour metofluthrin coil that was placed in homes and monitored throughout the night provided a 30% reduction in mosquito bites and a 60% reduction in malaria (not disaggregated between *Pf* and *Pv)* transmitted by *An sundaicus.*

There are two important points to consider here. While the principle of spatial repellents was established, the use of coils to emanate the chemical is still questioned. There is a renewed interest in mosquito coils by some influential donors, but there are serious hurdles. First is compliance. Experience shows that homeowners will sometimes burn a coil for a few hours while the evening-biting *Culex* are a nuisance, but then break off the coil to save the bits and pieces for the next time. Second is quality, with vast differences in active ingredients and impurities. Third, and most important are issues of the smoke and particulates. The USAID WashPlus project lists a series of publications on mosquito coils and indoor air pollution.[xcvii] It is unlikely that mosquito coils will become a prominent strategy for malaria vector control, although there is some development work on the use of repellent treated joss-sticks to be used on home altars in South East Asia for control of *Ae aegypti.*

While burning coils may not be in the future, other presentations for indoor spatial repellents are in an advanced stage of development by a number of manufacturers. These can be “passive” systems, where transfluthrin is applied three times per week to a specially designed PET film poster (approximately 10x30 inches) and “active” systems, where the transfluthrin is included in a device, such as a specially-designed candle system, some type of illumination device, or a device that will produce air currents across the treated substrate, to disrupt the boundary layer and enable faster diffusion of the repellent. The candle-based presentations and illumination devices are showing promise in experimental systems and prototypes may very well be available for broader field-testing in the near future.

One “passive” system of note is the SC Johnson WOW™ project in Ghana,[xcviii] a business concept that creates access to pest control products that can help prevent malaria in at-risk populations at the “base of the pyramid”, as well as home-cleaning and personal care products valued by rural consumers. Products include the Raid dual action home freshener and insect repellent using transfluthrin.

Transfluthrin was also impregnated into cloth strips and placed around human volunteers conducting human landing catch in an outdoor environment in urban Dar es Salaam. Overall, the treated strips conferred 99 % protection against *An gambiae* (1 bite versus 159) and 92 % protection against *Culex spp.* (1478 bites versus 18,602). No decline in efficacy over the course of the study could be detected for the very sparse populations of *An gambiae* ($P = 0.32$) and only a slow efficacy decline was observed for *Culex spp.* ($P < 0.001$), with protection remaining satisfactory over 3 months after strip treatment. Diversion of mosquitoes to unprotected humans in nearby houses was neither detected for *An gambiae* nor for *Culex spp.* [xcix]

A second passive system has been developed by Sumitomo and marketed under the trade name SumiOne™c. This passive emanator using metofluthrin has had a number of field trials including against

Ae aegypti in Australia[ci] and against *An gambiae* in Bagamoyo, Tanzania.[cii] In the Tanzania trials, metofluthrin-impregnated plastic strips were hung in 10 houses with another 10 houses acting as control and followed for a 124-day period. Pyrethrum spray catches and CDC light traps were used to sample mosquito population indices. The pyrethrum spray collections showed significantly reduced *An gambiae* s.l. mosquito collection compared with that for the controls, even after 124 days. These low indices were observed despite the large openings found in Bagamoyo houses, which were predicted to have a considerable negative effect on the spatial repellency of metofluthrin.

Summary: spatial repellents, with both active and passive emanators, using transfluthrin, metofluthrin and other semiochemicals like the undecalactones, is an active area of research and development. There remain a number of engineering questions related to the emanator, such as the amount of chemical that needs to be volatized per unit volume of space and how this is affected by air exchange in typical houses in the different malaria endemic zones where this would be deployed. There is also a very critical entomological issue of how these two pyrethroid spatial repellents will perform against pyrethroid resistant mosquitoes, particularly those with kdr target-site resistance. Finally, there are a host of social science and implementation research in the deployment, use and replenishment of these devices. The basic fact is that if a chemical is volatized in a spatial repellent, there needs to be an adequate reservoir or some other means of replenishing the chemical. Overall, it is very likely that some type of indoor spatial repellent will become available in the near future.

Push-Pull systems

Originally developed for indoor use against *Ae aegypti*[ciii] whereby a spatial repellent (the *PUSH*) is combined with an attractant lethal trap (the *PULL*), there is interest to adapt this strategy for *Anopheles* vectors of malaria in Tanzania[civ] and in Kenya.[cv] Proposals are currently under development to examine active vs passive emanators, different repellent chemicals and different attractants and trapping devices.

Attractants, lure and kill technologies

There are three basic strategies for lure and kill technologies. The first attracts and kills the female as she is foraging for a blood meal; the second to attract and poison her when she is looking for a carbohydrate meal; and third to trap and kill her when she is looking for an oviposition site.

- Attractant traps for bloodmeal-foraging mosquitoes. These are the attractants and traps to be used in the Push- Pull systems noted above. There are a number of technical challenges related to attractants – to develop something that an anthropophilic mosquito would find even more attractive than humans. Most traps now rely on CO_2 to supplement the odor bait. This can be from cylinders, dry ice or sometimes produced by yeast fermentation. Most feel that none of these methods are sustainable and there is a search for attractants that can compete with humans that do not require CO_2. Work in this area includes molasses[cvi] and 2-butanone.[cvii] A second challenge is the placement of the attractant traps. The other two traps listed below target the mosquito while she is looking for a carbohydrate meal or an oviposition site; these attractants target her while she is looking for blood. It would not be beneficial to place something in the peridomestic environment that will actually *increase* the number of host-seeking females and result in greater feeding from humans. The third challenge is how an attractant will work in combination with a repellent, or rather

a 'disruptor', of her host-seeking receptors. If she comes in contact with a chemical that disrupts her ability to sense CO_2 or other odorants that mimic humans, will the attractant still work? Finally there are a host of social science and implementation research questions about the cost and maintenance of these traps.

- Attractant-bait Lethal Oviposition traps. Designed primarily for container-breeding mosquitoes such as *Ae aegypti* and *Ae albopictus*[cviii], the technology kills the ovipositioning mosquito, sometimes with a non-irritant insecticide like bifenthrin.[cix] While the technology is promising for *Aedes*, and there have been recent advances in determining habitat discrimination of oviposition sites by *Anopheles,*[cx] field deployment of an effective lethal oviposition trap for malaria vectors seems a long way off.

- Attractive Toxic Sugar Baits[cxi]. These were first developed by researchers in Israel[cxii]. There are a number of groups working on ATSBs, in Florida, Africa and Israel[cxiii]. The technologies are similar with mixtures, usually of sugars and fruits that will attract carbohydrate-feeding mosquitoes, combined with an oral poison, often boric acid, spinosad or an essential oil such as garlic oil. One advantage of the ATSBs over the host-seeking trap above is that it should not increase the risk of human blood feeding even if these baits are placed on the sides of houses. There are a number of consortia developing the ATSB technologies for both the western markets, and with design (and pricing) changes for malaria endemic communities. One of these is the company Terminix,[cxiv] with a focus for now on the North American market, and the second company WestHam[cxv] working with the IVCC with a focus on Africa. Clarke is part of another consortium developing this technology for Africa under a grant from the BMGF for malaria vector control. The product managers for the WestHam consortium and the Clarke consortium are provided below.

Housing improvements

The link between housing and malaria has been known since the earliest days of malaria control in Italy at the turn of the last century, and have been shown more recently to have an impact on malaria.[cxvi] [cxvii] A review of the more recent literature presents strong evidence that 'good housing' is protective in many tropical countries.[cxviii] [cxix] [cxx]. A 2009 randomized-controlled trial of house screening in The Gambia showed that simple untreated screens on the doors and windows, and closing the eaves in typical rural African houses, reduced by 50% the prevalence of anemia in children.[cxxi] A 2013 study from Ethiopia, using locally bought materials, found that the same interventions reduced vector densities by 40%.[cxxii] The cost of housing interventions seems to compare favorably to current interventions.

Africa's economy is booming. Over the next decade its GDP is expected to rise by an average of 6% a year.[cxxiii] Today's increased personal wealth is enabling housing improvements, especially with metal-roofed houses replacing traditional thatched-roofed houses. Indeed in Rwanda the Ministry of Local Government has since 2009 conducted a rural housing improvement campaign known as the "Bye-bye Nyakatsi" (thatch house) campaign.[cxxiv] This economic and cultural transition presents an opportunity to document and to influence housing improvements that can reduce the threat of malaria and other vector borne diseases. It is estimated that over 144 million rural houses will be built in Africa by 2050.[cxxv] This construction wave is happening, with or without input from entomologists and vector control specialists. Now, groups including UNHabitat, Habitat for Humanity International and others in the RBM Vector Control Working Group Housing and Malaria work stream are coordinating efforts to include

housing improvements as complementary measures to current vector control tools.[cxxvi] Elements of housing improvement that are being investigated include eave tubes with entomopathogenic fungi,[cxxvii] ceilings, [cxxviii] insecticidal paints[cxxix] and insecticidal barrier approaches such as fences curtains erected as barriers set between the village and the vector breeding sites.[cxxx]

Summary. While housing improvements have not been considered as an "intervention" by most donor-supported malaria control programs, it may play a vital role in sustainable elimination. A meta-analysis on malaria and housing was recently released[cxxxi] and there are prospective trials beginning in the Gambia and Cameroon. There are efforts to develop a "WHO Position Statement" on malaria and housing to help spur developments in this field. There very well may be opportunities for broader partner contributions in this area, for example in collaboration with the USAID "Making Cities Work" initiative[cxxxii].

Systemic treatments/Animal treatments

The role of domestic animals in the epidemiology of malaria has been recognized since the earliest days of malaria control.[cxxxiii] For vectors with zoophilic tendencies there have been numerous attempts at zooprophylaxis[cxxxiv] and with dipping or sponging cattle with insecticide.[cxxxv] Pyrethoid spraying of cattle is a common method of tsetse fly control, but can have a negative environmental impact through its effect on dung fauna[cxxxvi].

Systemic insecticides[cxxxvii] are commonly used in veterinary medicine; fluralaner against ticks and fleas on dogs[cxxxviii] and fipronil in control of the sand fly vectors of visceral leishmaniasis through "feed through" baits for rodents [cxxxix] and oral dosing for cattle.[cxl]

Ivermectin, widely used for nematode treatment in cattle and humans, is also toxic to mosquitoes that feed shortly after the host has been given the drug.[cxli]. This strategy is gaining a great deal of attention for situations with highly anthropophilic and difficult to control vectors such as *Anopheles dirus* in the Mekong sub- region where the drug would be given to the at-risk human population,[cxlii] and to situations like west Africa with the more zoophilic *An arabiensis* where the drug would be given to both humans and their domestic cattle.[cxliii] An ivermectin research network has been established[cxliv] and field trials for ivermectin are under discussion but face a number of regulatory and business-related hurdles.

Vaccinating humans and domestic animals with antigens against the arthropod itself is another promising line of investigation. Among these antigen candidates, tick Subolesin (SUB) and the ortholog in insects, Akirin (AKR), have been used to induce a protective response in vaccinated hosts for the control of ticks, sandflies, poultry mites and mosquitoes (*Ae albopictus*).[cxlv]

Summary: Inclusion of animal treatments, especially topical insecticides, may be useful for zoophilic vectors like *An arabiensis* in Africa and an opportunity for broader engagement partners. [cxlvi] The CDC promotes the concept of "One Health" with a dedicated One Health Office where they write.

> *The One Health concept recognizes that the health of humans is connected to the health of animals and the environment. CDC uses a One Health approach by working with physicians, ecologists, and veterinarians to monitor and control public health threats. We do this by learning about how diseases spread among people, animals, and the environment*.[cxlvii]

Endosymbionts

Bacteria in the genus *Wolbachia* are prevalent in many insect species with a number of *Aedes* (but not *Ae aegypti)* and *Culex* species found naturally infected.[cxlviii] Anophelines, which are not natural hosts, can be infected in the laboratory. *Wolbachia* strategies include both population suppression and decreased competency. There have been recent advances for *Aedes* and dengue, with field releases in Australia.[cxlix] Establishment of *Wolbachia* infections in *Anopheles* populations appears to be much more difficult, but there was recent success in laboratory infection of *An stephensi* that resulted in reduced susceptibility to *Plasmodium*.[cl] However, more recent work indicates that *Wolbachia* interaction with *Plasmodia* can be strain and species specific, in some cases enhancing parasite development.[cli]

Similar to the *Wolbachia* strategies, there is a large body of work exploring the relationship between microbiota of the mosquito midgut and how this influences vector competency to suppress development of *Plasmodia*.[clii]

Genetic-based population suppression or replacement

Strategies with genetically modified mosquitoes (transgenesis) and their endosymbionts (paratransgenesis) also aims to either suppress the population through self-limiting genetic changes or to replace the population with individuals less competent to transmit the pathogen.[cliii] There have already been field trials of population suppression using the strategy of Release of Insects with Dominant Lethality (RIDL) with releases of genetically modified *Ae aegypti* in the Cayman Islands, Malaysia and Brazil.[cliv] In *Anopheles*, there has been laboratory development of a RIDL system producing flightless female *An stephensi.*[clv] Potential population replacement of *An stephensi* refractory to *Plasmodia* has also been developed.[clvi] While transgenesis, direct modification of the mosquito vector, or paratransgenesis, modification of an endosymbiont, are very active areas of research, there remain many technical and regulatory hurdles before these can be applied in the field for malaria control.[clvii]

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