



APMEN Case Study

Outdoor Biting by Malaria Vectors: What can we do to reduce it?

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1. Introduction

As context for this overview of tools to combat outdoor transmission of malaria, it is useful to remind ourselves that vector control remains the most important approach for malaria control in most malaria-endemic countries of the world. Most of the funds for malaria control globally go towards vector control, and the reason is easy to understand. For example, a study in Africa – where about 95% of the global malaria burden exists – showed that Insecticide Treated Nets (ITNs) and Indoor Residual Spraying (IRS) contributed around 78% towards malaria cases avoided over the period 2000 - 2015; the use of Artemisinin-Combination Therapy contributed a further 19% towards all cases avoided[1]. However, ITNs and IRS target indoor-biting/resting mosquitoes, and we have no equivalent effective tools for outdoor biting malaria vectors. In this document we discuss the interventions currently available and have varying degrees of effectiveness in reducing outdoor transmission.



Outdoor cooking and socializing in early evening provides opportunity for outdoor transmission of malaria

1.1. How does Asia differ from Africa regarding vector biting behaviour?

In Africa there are only a few primary vector species of *Anopheles* responsible for most of the malaria transmission, and these species overwhelmingly have a preference for biting indoors and resting indoors. In Asia the situation is very different. Here there is a much larger number of vector species, and most of them prefer to bite outdoors and also rest outdoors, and many of them also readily feed on cattle and other domestic animals. Whereas ITNs and IRS are highly effective for vector control in Africa, they are not nearly as effective in the Asia-Pacific region, where much of the transmission occurs outdoors.

1.2. So what can we do to reduce this outdoor transmission?

We are poorly equipped to combat outdoor-biting mosquitoes, and there is a major need to find new tools to apply when people are cooking and socializing outside the home in the evening or early morning, and working late or at night such as in forests or rubber plantations or at outdoor social functions.

1.3. What does the World Health Organization recommend?

Ministries of Health across the world take their lead from the World Health Organization (WHO) when it comes to recommendations for malaria control interventions and practices, based on committees and experts that review the available evidence emerging from research and practices globally. For vector control, WHO will only provide recommendations for interventions that have proven protective efficacy to reduce or prevent infection and/or disease in humans, and that are broadly applicable for populations at risk of malaria in most epidemiological and ecological settings[2]. Based on this approach of proven public health benefit, there are only two vector control interventions that WHO fully endorses, these being:

- A. Insecticide-Treated Nets (certain specified nets only) and
- B. Indoor Residual Spraying (pre-qualified products only).

However, WHO also provides conditional endorsement of two supplementary approaches, these being:

- C. Larviciding, and very recently also
- D. Spatial Emanators, for indoor use in combination with ITNs or IRS, and thus far only two specific pre-qualified products.

2. So, what are the options for reducing outdoor biting?

Despite the strictly defined recommendations of WHO for a limited number of intervention types, there are several other tools and approaches that can be used against outdoor biting mosquitoes that in most cases have not yet received adequate research evidence to persuade WHO to endorse such methods.

Below we outline most of these approaches that have been discussed to greater or lesser extent in the scientific literature. Where appropriate during the discussion below, we distinguish between WHO product endorsements which are based on impact of interventions on malaria reduction, and reduction in mosquito bites among specific individual people but as yet without proven protective efficacy to reduce or prevent infection and/or disease. The use of topical repellents is one example, where WHO has not given product endorsement for malaria reduction but many products have proven efficacy to provide individual protection for short-term risk (e.g. temporary forest goers) but not longer-term community protection. We explain this for each intervention class.

2.1. Repellents

2.1.1 Spatial Repellents/Emanators

As already mentioned, the use of specific spatial emanators for indoor use in combination with ITNs or IRS has recently been endorsed by WHO, for indoor but not for outdoor application. However, studies in semi-enclosed temporary shelters using transfluthrin-impregnated strips along the sides of open shelters in Cambodia[3] as well as in Sumatra using pyrethroid emanators or barrier screens[4, 5], and transfluthrin-impregnated hessian in sandals, chairs or barrier screen in several African studies[6, 7, 8, 9], showed high levels of reduction in mosquito biting rates. In contrast, other studies such as in Indonesia[10] showed inconclusive evidence of benefits from outdoor use of spatial emanators. Additional studies are ongoing, including in Papua New Guinea on the use of spatial emanators on open verandahs and semi-enclosed “outdoor” kitchens. Nevertheless, the current lack of adequate, consistent evidence of the value of spatial emanators reducing malaria burden under semi-enclosed and outdoor conditions has prevented WHO from formal endorsement of spatial emanators beyond strictly indoor use.

2.1.2 Topical Repellents

Topical repellents are applied directly to the skin in a variety of formulations that include sprays, creams, lotions, oils, and also incorporated into soap. They vary widely in level of user compliance, efficacy, duration, and cost, with most of them not able to provide 100% protection lasting from dusk-to-dawn and usually not able to maintain sustained use. A Cochrane review indicated that “There is insufficient evidence to conclude that topical repellents can prevent malaria in settings where other vector control interventions are in place. We found the certainty of evidence for all outcomes to be low, primarily due to the risk of bias. A protective effect was suggested among high-risk populations, specially refugees, who might not have access to other standard vector control measures”[11]. Multiple studies are ongoing to improve the evidence-base. For now, WHO does not give general endorsement of topical repellents, although such repellents do have a niche as an intervention tool especially among high-risk groups who have increased behavioural or occupational exposure to malaria vectors, and who are not as likely to be protected by either LLINs or IRS, for example protection for short-term exposure by forest-goers in Myanmar[12]. Other groups may include refugees, miners, soldiers, or migrant workers. Many commercial brands of topical repellents, including those based on the active ingredient diethyltoluamide (DEET), IR3535 and picaridin have proven efficacy for individuals and will have a protective effect lasting several hours, but need to be used regularly if the intent is to prevent malaria infection rather than short-term relief from high biting burden.

2.1.3 Repellent-Impregnated Clothes

Many studies have been conducted on the use of treated clothing, not just for protection against mosquitoes but also ticks, the military being a prime focus group. Examples include semi-field studies in Thailand that showed that etofenprox-treated clothing prevented more than 50% of mosquito landings[13]. However, in general, while there are some studies that demonstrate protection against pathogen transmission, they are surprisingly few, and the level of protection provided varies depending on type of treatment used, the age group of participants, the geographical location of the study, and other variables[14]. Additional studies are required to provide the necessary evidence for WHO to be able to endorse the general use of repellent-impregnated clothes for reducing malaria burden.

2.1.4 Repellent-impregnated Blankets/Top-sheets and Baby-Wraps

Although more relevant for indoor situations, there are circumstances where people sleep outdoors, such as, displaced populations in the acute phase of humanitarian emergencies, Forest-Goers in Asia but also in Africa to escape the heat of poorly-ventilated huts, and use thin blankets or sheets as protection against mosquitoes. Studies in Pakistan[15] and Kenya[16], using blankets impregnated with synthetic pyrethroids either alone or in combination with piperonyl butoxide, have shown that it does provide significant personal protection from mosquito bites. A recent study in Uganda on permethrin-treated baby-wraps showed a significantly reduced percentage of malaria cases among babies in the intervention-group compared with babies not wrapped in treated wraps, but the study also showed a higher percentage of skin-rash reaction to the treated wraps within the treatment group[17]. Etofenprox, now used to treat military uniforms in some countries, has lower dermal absorption and higher wash resistance than permethrin and is now being investigated as an alternative for treated clothing and babywraps. The use of repellent-impregnated blankets/sheets and baby-wraps remains a poorly-studied intervention and there is not enough evidence as yet regarding the impact of its use in reducing malaria burden, and therefore has not received WHO endorsement.

2.2. Larval Source Management (including larviciding)

Larval Source Management (LSM) refers to the practice of managing specific breeding sites of vector mosquitoes to reduce adult populations. It requires that knowledge exists of which species are the primary vectors in the targeted area, as preferred breeding sites vary widely between different species. It involves locating and mapping areas where mosquitoes breed, such as like puddles, ponds, rain-filled ditches, rice paddies and other water impoundments. LSM can be achieved through various interventions, including:

- Eliminating or modifying breeding habitats, such as draining standing water, filling in low-lying areas, or removing containers that hold water.
- Biological control such as by introducing natural predators of mosquito larvae, for example fish that feed on mosquito larvae, or using bacteria like *Bacillus thuringiensis israelensis (Bti)* (which produces a toxin harmful to larvae).
- Larviciding by applying chemical insecticides and insect growth regulators.

While larval source management (LSM) does not specifically target outdoor-biting malaria vector species, the breeding site preferences of several primarily outdoor-feeding species in Asia (eg. *Anopheles dirus*, *An. stephensi*) and Africa (e.g *An. arabiensis*, *An. stephensi*) do lend themselves to targeted focal LSM efforts that would selectively impact outdoor-biting vector populations.



Larval source management by filling or removing *Anopheles* mosquito breeding pools is an opportunity for communities to become directly involved in self-help vector control.

The World Health Organization does not recommend LSM as a core vector control intervention (which it limits to ITNs and IRS) although it does endorse the use of LSM as a Supplementary strategy for species having breeding sites that are “few, fixed, and findable”[18]. As the species indicated earlier in this paragraph tend to breed in confined small pools rather than rivers or extensive bodies of water, it does render LSM for these species an effective approach for vector control in the proximity of households and working sites (eg. water wells in rubber plantations against *An. dirus*, traffic ruts or rain-pools around homesteads against *An. gambiae* and *An. arabiensis*, and construction site pools for *An. stephensi*).

Larval source management is best done at whole-village level scale rather than isolated individual households, because mosquitoes will easily fly from breeding sites beyond the area treated by a single household.

2.3 Attractive Targeted Sugar Baits (ATSBs)

All mosquitoes need to occasionally feed on nectar or other sugar-rich substances for energy, and this fundamental need is exploited with the ATSB technique. This is done by combining a toxic substance with a sugar component (e.g. fruit juice) as feeding stimulant, sometimes supplemented with an attractive aromatic compound scent lure, sealed within a bag which allows mosquitoes to pierce the thin plastic membrane to access the content. The flat bag bait station is suspended on the outside (or even inside) surface of a dwelling at a height out of reach of small children and domestic animals, usually two bait-stations per household. This method is receiving significant research attention in Africa but thus far has not been tested in Asia. Insufficient findings are available for WHO to make a recommendation, but the method will need refinement, such as extend the lifespan of the membranes and improvements in both the attractant and the toxicant. This method, if accepted, would be better applied at village scale for collective effect at scale rather than for deployment by individual households for personal protection.



2.4 Endectocides

Endectocides refer to drugs that kill endoparasites, such as parasitic worms, and also ectoparasites (including mosquitoes) that feed on treated hosts (including humans, cattle, pigs, or others). The most familiar example is Ivermectin, initially developed as a veterinary anthelmintic product in 1981. The ectoparasiticidal effects quickly became apparent[19], including that mosquitoes feeding on Ivermectin-treated animals and humans were subject to high mortality and debilitating effects even when the lethal dosage declined over time, such as reduced longevity and lowered egg production[20]. Ivermectin is generally administered as a commercially-available single-dose injection, whether as a standard dose but most effectively in the form of long-lasting formulations (domestic animals), or as a tablet for human consumption. Multiple trials have provided strong evidence of the effectiveness of Ivermectin in cattle[20, 21, 22, 23, 24, 25, 26, 27], water buffalo[21], pigs[28, 29], and humans[30, 31, 32, 33] for achieving high levels of mortality among various malaria vector species both in Africa and Asia, with negligible or no negative side-effects on the treated host.

While >70% mortality of mosquitoes for two weeks post-feeding at Ivermectin-treated animals was a routine finding in many studies, mortality rates diminish as residual dosage declines over time, although in many cases still high rates such as >40% mosquito mortality in week 4.

The high level of absolute mortality could be extended by using newer generation products now available commercially. Endectocides are a particularly attractive option for control of multiple outdoor-biting malaria vector species, because so many of the vectors across the Asia-Pacific region are predominantly zoophilic, exophilic and exophagic, especially as many rural households in many areas of Asia are closely associated with cattle, so that a few individual animals are typically confined close to the household and resting in the shade under the raised floor of stilt-supported dwellings, or in some countries even inside one of the rooms of the house.

Deploying endectocides by way of cattle holds particular advantage as cattle owners are far more likely to readily agree to their animals being treated, due to the secondary benefit of clearance or reduction of internal parasites.

While WHO has not yet provided formal endorsement for the use of endectocides, a substantial body of research evidence is accumulating that shows the efficacy of the use of especially Ivermectin in humans and in domestic animals for reducing malaria in target populations, and so it seems likely that such endorsement will be made in the foreseeable future. In its current application, the use of endectocides would probably be best as a tool for village-level suppression of mosquito populations and malaria reduction, supporting people across an entire village to participate for optimal impact.



Many households in Asia are closely associated with cattle that create good opportunity for vector control by way of endectocides

2.5. Outdoor Residual Spraying (ORS)

Outdoor residual spraying (ORS) aims to directly reach and reduce exophilic and zoophilic species, many of which are important malaria vectors, especially in the Asia-Pacific Region[34, 35, 36, 37, 38]. The surfaces treated in ORS include the outside shaded portions of walls under the overhang of the roof, and in particular any partial walls or surfaces forming part of animal pens in the vicinity of the homes. Some operators also spray natural vegetation with long-lasting residual insecticides but this is discouraged due to impact on non-target insects and other organisms. Very little published research is available to provide guidance on the merits and impact of ORS. Given the strong contribution of outdoor-biting and resting mosquitoes to malaria transmission in many geographic settings, there is a need for more research on the potential value of ORS against such exophilic and exophagic vectors.

Given the lack of evidence, WHO does not provide any recommendation regarding ORS. More research is encouraged. Until such evidence emerges, where funds are available such focal spraying can be applied at sites described above, in situations where malaria transmission is intense.

2.6. Fogging/Space Spraying

Fogging or Space Spraying differs from Outdoor Residual Spraying in that fogging achieves fast-acting mass-effect through a cloud of ultra-low volume sprays or thermal fogging which aims to impact mosquitoes while they are in flight and also penetrates cracks and crevices or hidden spaces, but generally is short-acting and therefore usually deployed as an emergency measure during outbreak situations, typically for dengue or other arbovirus epidemics. By contrast, indoor or outdoor residual spraying is usually a more preplanned standard application of an insecticide with long-lasting properties yielding a more sustained residual vector population suppression effect lasting months. Very little evidence is available to indicate any benefit of space spraying for reduction in malaria. Given this lack of research evidence, and for reasons of financial and labour costs as well as the scale at which the method would have to be deployed for malaria control, space spraying is not used by malaria control programmes. An additional concern is that such general application of insecticide outdoors significantly impacts non-target organisms due to fog drift across neighbourhoods[39].

WHO discourages the use of outdoor adulticide spraying for *Anopheles*[40]. Used in the context to control outdoor transmission, this technique is also one that is not likely to be of significant benefit for personal protection, and any malaria control effect would best be achieved by being done at village level.

2.7. Mass-trapping

This method is based on the concept that saturating an area with enough traps that sustainably capture adult mosquitoes over an extended period of time will depress the target population to very low levels that do not maintain disease transmission as long as the intervention is continued. However, to get close to the cost-effectiveness of ITNs as the Gold-standard malaria vector intervention, the traps delivery, operation and maintenance would have to cost a maximum of USD4.25 to USD 27.61 per unit per year (2005 values), and the traps would have to have a stronger attractive effect than humans, conditions that are unlikely to be easily met[41].

Clear evidence supporting the deployment of mass trapping is available for *Aedes arbovirus* vector interventions [42], which have much lower flight ranges for re-colonization and greater concentration around human dwellings than *Anopheles* malaria vectors.



Mass deployment of mosquito traps for malaria control is an expensive and labour-intensive option not cost-effective in relation to many other malaria vector control options

In addition to traps deployed against mosquitoes foraging for blood or nectar meals and for oviposition sites, traps are also used for deployment of larval control product, referred to as 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 (PPF), 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*.

From the available literature it appears that deployment of mass-trapping for malaria vector control is not a cost-effective option at present, but should be considered as an option for arbovirus control, either as generally-distributed traps across islands or as a barrier to reduce or prevent incursion into high-priority mainland situations. This is not a technique that would be practical or affordable for deployment by individual people for outdoor-biting personal protection, and WHO is also silent on the value of this technique for malaria control.

2.8. Genetic Modification Techniques

2.8.1 Sterile Insect Technique

The classic Sterile Insect Technique (SIT) involves generating massive numbers of eggs of the target species, separating the sexes during one of the immature stages (for example, pupal stage, where sexual size differences allow sieving smaller male pupae from larger females and then irradiating millions of the males for mass release into the target area, where sterile but competitively effective males outnumber and outcompete wild males thus resulting in a population crash. However, unless regional eradication is achieved, such releases of large numbers of sterile males will have to continue indefinitely to sustain the effect and avoid local resurgence due to natural increase and also immigration from neighbouring areas. In addition, it would have to be done for each vector species transmitting malaria in a particular area, making this technique too expensive and impractical for most areas where malaria is transmitted by multiple co-existing vectors. It is clearly not a technique which can be undertaken by individual villagers for personal protection, but requires major investment and deployment at large scale.

2.8.2 Gene Drive Population Manipulation

Gene drive is the latest quantum jump in technological advancement that – together with vaccines – represents significant potential as a breakthrough intervention to combat malaria or other mosquito-borne diseases. The objective of gene drive technology is to usually to pursue one of two alternative pathways: either achieve population suppression (pushing a target mosquito species towards local elimination) or to achieve population replacement with a genetic strain in which female mosquitoes have reduced or no susceptibility to infection by a specific pathogen such as Plasmodium or an arbovirus, as examples. However, such genes have a high likelihood of being removed from the population through natural selection over successive generations, and therefore rely on “gene drive” methods to force the desired gene in a greater than normal 50% Mendelian ratio into the next generation. Therefore, it becomes necessary to select two genetic components, one being the gene holding the desired population control effect (the effector or cargo gene), and another “selfish gene” that in combination will “drive” the desired gene into all or most offspring, not only 50% in each generation. This can now be done using CRISPR technology [43, 44, 45]. The attraction of this technique is that the technology is narrowly species-specific, and therefore will spread within and impact only members of a particular target species. The technology has now also reached a stage where it is no longer necessary for sustained long-term continuous releases of genetically modified mosquitoes, but at least in theory could be a single introduction into a wild population which then spreads by itself via normal reproductive mating. For potential application in malaria control, this gene drive technique has now been successfully demonstrated in two members of the *Anopheles gambiae* complex and also *Anopheles stephensi* [45, 46] but as yet limited to laboratory or small-scale field settings. Research is still ongoing and at present aimed at African malaria vectors. Again, this will be a technique for specialized institutional deployment for community-level malaria-reduction impact and not a tool which individual villagers could deploy for personal protection.

2.9. Raised platforms

Mosquito host-seeking and feeding is driven by multiple factors, and it does seem that there are certain shared behaviours that apply to many, and possibly all, malaria vector species. These include that at humans seated or standing outdoors, vectors have a strong preference for feeding on ankles and feet (which is why for human landing catch sampling of malaria vectors the collectors focus exclusively on lower parts of the leg) but that this preference for ankles and feet breaks down if the person lies down after which the body is bitten randomly, evidence that the behaviour actually relates to a height above ground preference[47].

Several publications based on different malaria vectors in different parts of the world have demonstrated this height-above-ground effect. Work on *An. farauti* in Papua New Guinea showed significantly higher biting rates near ground level than on wooden beds only 35 cm off the surface and that these mosquitoes also showed clear preference for biting below the ankle[48]. All of this supports general statements such as that made by Gillies & Wilkes back in 1976 already, who worked in The Gambia and observed that, despite almost complete lack of wind, "one of the most striking features is the very high density of many species of mosquitoes flying just above the ground in the layer of air from 0 to 15 cm above the ground". Their results show that all five *Anopheles* species collected, including *An. gambiae s.l.*, flew in greatest numbers below 1 m above ground[49].



Many malaria vector species prefer to bite very close to ground level and so raising yourself even one metre above ground-level – as in houses built on stilts - results in a major reduction in malaria risk.

These findings do not suggest that we should encourage a mass shift in cultural behaviour to motivate people to start building houses on stilts, but it does suggest that in particular situations with high-intensity outdoor biting associated with high malaria transmission, it might be helpful to construct small platforms outside the home where people can relax during evenings, thereby reducing outdoor biting intensity. Such raised structures should be clear below, so that mosquitoes fly through unobstructed below the platform. Having walls around the platform has the effect of mosquitoes bouncing upwards in their attempts to bridge the obstacle, thus rendering the platform less effective.

2.10. Zooprophylaxy

In some regions, as in Asia-Pacific, most of the primary malaria vectors are both exophilic and zoophilic or opportunistic feeders[34, 38], although in Africa the most important vectors are strongly anthropophilic[38, 50], except *An. arabiensis* which is exophilic, exophilic, and readily feeds opportunistically on both humans and cattle[50, 51, 52]. Cattle are known to be powerful attractions to many vector species and cattle-baited traps will often yield much higher catches of vectors than similar human-baited traps or Human Landing Catches[53]. So on the one hand, having cattle in close proximity to the household could mean a dilution of mosquito bites because they are diverted to the cattle (zooprophylaxis), but on the other hand the cattle also attract many more mosquitoes to the household area than would have been there in the absence of the cattle (zoopotential). The answer to this conundrum, and whether the impact of cattle around households reduces malaria transmission or not, remains unresolved and a source of contention[54, 55, 56].



Having cattle close to households can either attract some malaria vector mosquitoes closer to humans, or reduce bites on humans if the mosquitoes also feed on cattle

Except for the use of endectocides in domestic animals as a proven high-potential tool to target outdoor-biting vectors – as discussed earlier in this document - the concept of traditional zooprophylaxy for control of outdoor biting is probably not a method to encourage at this time, except for experimental purposes, due to the uncertainties and variability of results based on a multitude of confounding factors.



3. Strategies and approaches that underpin successful interventions

Below we point out two important enabling approaches, namely Social Engagement and also Integrated Vector Management, which are cross-cutting principles to support specific interventions, even though they are not inherently focused on outdoor biting. These two approaches should be followed to make the uptake and scale of impact of specific interventions much more effective.

3.1. Social Engagement & Behavioural Change

Creating social awareness of the need to be conscious of outdoor biting and where possible to reduce exposure is a valid and important form of malaria transmission intervention and vector avoidance, although difficult to measure its impact. Behaviour Change Communication (BCC) is a long-standing practice implemented by most malaria programmes and seeks to optimize uptake and acceptance of behaviour that facilitates and improves malaria reduction efforts[57, 58, 59, 60]. Empowering communities in planning and implementing interventions is essential. For communities to accept and implement vector control or related interventions on a sustainable basis, the community itself must define, believe in, and commit to strategies to interrupt transmission[61]. Such community support is therefore more of an underpinning attitude and behaviour, rather than a specific tool in itself, but critically important if malaria reduction is to be achieved. Such community engagement and appropriate behavioural adaptation is needed for any of the methods and approaches mentioned in this overview of outdoor biting.

3.2. Integrated Vector Management (includes LLIN's and IRS)

Integrated vector management (IVM) is defined as "a rational decision-making process for the optimal use of resources for vector control" and includes five key elements: 1) evidence-based decision-making, 2) integrated approaches 3), collaboration within the health sector and with other sectors, 4) advocacy, social mobilization, and legislation, and 5) capacity-building[62]. It promotes an approach that encourages the use of multiple tools and strategies that complement each other to provide a higher likelihood of sustained impact on the target vectors and disease, rather than an over-reliance on one or a few interventions that may yield selective and imperfect impact. So, for example, for reduction in outdoor transmission, an IVM approach would encourage consideration of a strategy that would combine a range of complementary interventions that support and enhance the impact of any one intervention, and might include use of spatial emanators, topical repellents, endectocides if appropriate, larval source management, taking into account budgetary constraints and local environmental context, together with social behaviour change communication to encourage particular behaviours that promote personal protection and mosquito population reduction, that collectively would bring together a portfolio of actions reducing outdoor transmission.

At first impression, IVM seems an obvious and sensible approach, but in reality it is not well adopted and practiced in the malaria sector, unlike in the agricultural sector. Budgetary constraints and cost factors still dictate that only one (mostly ITN's) or a few vector control techniques are deployed, with lip service to supplementary applications. Where IVM has been diligently applied, the outcomes prove the value of such an approach.

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