Hidden recipe for disaster: non-target effects of chemical malaria vector control on other biological and mechanical infectious disease vectors

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Summary
Public health insecticides play a critical role in malaria control and elimination programs. Many other arthropods, including mechanical and biological vectors of infectious diseases, have similar indoor feeding and/or resting behaviors as malaria mosquitoes, and may be exposed to the same insecticides. In this Personal View, we show that little is known about the insecticide susceptibility status and the extent of exposure to malaria interventions of other arthropod species. We highlight there is an urgent need to better understand the selection pressure for insecticide resistance in those vectors, to ensure current and future active ingredients remain effective in targeting a broad range of arthropod species, allowing us to prevent and control future outbreaks of infectious diseases other than malaria.

Key Messages

Several arthropod genera share the same indoor environment
Malaria mosquitoes share the indoor environment with other mosquito species, houseflies, tsetse flies, kissing bugs, ticks, fleas, biting midges and cockroaches, amongst others, many of which can or are already transmitting infectious diseases mechanically or biologically.

Exposure to chemical malaria vector control tools
Those other arthropod species encounter public health insecticides that are incorporated in bednets and are used in indoor residual spraying campaigns. Factors such as spatial-temporal patterns in feeding and resting behaviors, as well as other activity patterns, will govern exposure to malaria vector control tools.

Under-recognized future public health problem
Resistance to insecticide classes currently used in malaria vector control is common in many other arthropod species. Yet time-location patterns of those species and contact rates with malaria vector control tools remain poorly understood. Understanding the selection pressure for insecticide resistance is essential to ensure current and future active ingredients remain effective in targeting a variety of arthropod species.

Integrated vector management is needed
Although malaria control efforts remain essential, several other biological and mechanical disease vectors need to be included in entomological surveillance and insecticide resistance management programs, if we are to prevent or control outbreaks of a variety of infectious diseases.

Introduction

Vector-borne diseases (VBDs) are diseases caused by bacteria, parasites or viruses transmitted by arthropods such as mosquitoes, triatomine bugs, sandflies and ticks. VBDs account for approximately 17% of the global burden of infectious diseases and cause an estimated 700,000 deaths annually.[1] Malaria remains one of the deadliest VBDs, accounting for 241 million cases and claiming the lives of about 627,000 people globally in 2020 alone, with Sub-Saharan Africa carrying the highest burden (95% of total cases and 96% of total deaths).[2] It is caused by *Plasmodium* parasites transmitted from human to human by the bite of the female *Anopheles* mosquito. Other mosquito-borne diseases such as dengue and Zika, transmitted by other species of mosquitoes, have (re)emerged and become an important global public health problem since the 1970s.[3] To illustrate, an estimated 1.5 million Zika cases were recorded in Brazil in 2015,[4] and there are an estimated 100 million symptomatic cases and 10,000 deaths globally every year due to dengue.[5] Sandflies are responsible for an estimated 1.5 to 2 million cases and 70,000 deaths annually due to leishmaniasis,[6] and triatomine bugs (also known as kissing bugs) infect an estimated 6 to 8 million people with Chagas disease every year, resulting in approximately 50,000 deaths.[7] The control and prevention of many vector-borne diseases depends largely on the control of arthropod vector populations as for most diseases (e.g., West Nile virus, Zika, chikungunya, Saint Louis encephalitis and Ross River virus) there are no vaccines and/or (prophylactic) drugs available.

Vector populations can be targeted at the arthropod's immature stages, or its adult stage. Most vector control interventions target adult arthropod populations, which will therefore be the focus of this review, however, similar messages will apply for the control of the immature stages. Chemical fogging and space spraying are mostly used to target mosquitoes of the genus *Aedes* and *Culex,*[8] sandflies,[9] triatomine bugs,[10] and tsetse flies.[11] Indoor residual spraying (IRS), whereby insecticides are sprayed on walls and sometimes on roofs of human dwellings and/or in animal shelters, and long-lasting insecticidal nets (LLINs), which kill and/or repel mosquitoes and provide a physical barrier that reduces vector-host contact, are mostly used to control *Anopheles* malaria mosquitoes.[2]

All aforementioned methods are insecticide-based, and the World Health Organization (WHO) has approved five chemical classes of insecticides for the use in IRS products (pyrethroids, organophosphates, carbamates, organochlorines, and neonicotinoids), two for the use in ITNs (pyrethroids and pyrroles) and two for the use in fogging (organophosphates and pyrethroids).[12] Worryingly, the rapid emergence and spread of insecticide resistance has led to observed resistance in malaria vector species to nearly every WHO-approved chemical class, and insecticide resistance is one of the major challenges in malaria control and elimination programs.[13] To tackle insecticide resistance, WHO recommends having robust insecticide resistance management plans in place (such as seasonal rotation of the different insecticidal classes),[14] and new active ingredients (e.g. tenebenal and several unknown active ingredients) are being developed and tested.[15] This development currently focusses on new insecticides for LLINs (long-lasting insecticidal nets) and IRS products, which is no surprise given their success

story in malaria, the threat of insecticide resistance, the continued malaria burden, and the goal to eradicate this disease.[2]

However, current and future insecticides are also needed to target other arthropod species to prevent and control vector-borne diseases other than malaria. For instance, the control of the Zika outbreak in Puerto Rico in 2016 was partly achieved by IRS and indoor space spraying,[16] and during the 2013-2014 Chikungunya outbreak in the Caribbean, insecticide-treated nets (ITNs) and insecticide-treated clothing and gear were the vector control interventions recommended by the WHO and Pan American Health Organization (PAHO).[17] ITNs and IRS have also been used in past to control sandflies during epidemic outbreaks of leishmaniasis in Nepal, India and Morocco,[18] and IRS is used to control fleas and plague in Madagascar.[19] Additionally, and the Pan African Tsetse and Trypanosomiasis Eradication Campaign in Burkina Faso and Ghana used aerial spraying of insecticides to control local tsetse fly populations to reduce the incidences human African trypanosomiasis.[20] Given the broad application of insecticides to control a range of infectious disease vectors, ignoring other arthropods during the malaria vector surveillance and malaria vector control decision-making process may have detrimental effects on our ability to control non-anopheline vectors in the future. Malaria vector control tools (IRS and ITNs) can have a non-target effect on other arthropods that share their ecological niche with malaria vectors. This effect is a recognized problem in other fields, such as pesticide use in agriculture,[21] and antibiotic use in public health,[22] and a recent study showed that persistent mosquito fogging has negative impacts on butterflies, ants, wasps and bees.[23] However, the non-target effects on other arthropod vectors has never been reviewed in detail, but it has been i) shown that e.g. ITNs reduce *Culex* mosquito populations[24] and IRS flea populations,[19,25] and ii) suggested that insecticide resistance observed in sandflies, *Aedes* spp., and *Culex* spp. may have been a result of adult anopheline vector control.[26–29]

The use of pesticides in agriculture to kill pest insects that affect crops may also have led to the development of resistance in malaria mosquitoes, and potentially other arthropod vector species. This occurs during the immature stage, when mosquito larvae can be exposed to pesticides through surface runoffs.[30] Whilst historically pesticides have been repurposed for vector control, recent novel active ingredients are developed for vector control only. For this reason, and the fact that most arthropod vectors we discuss below do not share a breeding habitat with malaria mosquitoes, we do not focus on this exposure route.

Here, we discuss how the use of current and future insecticides in malaria control and elimination efforts may lead to the future control failure of other arthropods, many of which have been responsible for epidemics in sub-Saharan Africa in the past (Table 1) and are known vectors of circulating and (re)emerging infectious diseases on the continent. The evolution of insecticide resistance in non-target organisms is a result of overlapping ecological niches, which results in exposure of non-target arthropods to insecticides that are used in malaria vector control. Understanding this exposure is critical, as epidemics of emerging vector-borne diseases have been on the rise over the past few decades, mainly as a result of socioeconomic, environmental, and climate changes.[31] Regarding the latter, it has been suggested that warming

temperatures are likely to promote greater environmental suitability for Zika, dengue and other arbovirus transmission sub-Saharan Africa, while the environmental suitability for malaria will reduce.[32] If this becomes a reality, our vector control efforts will have to shift from malaria vectors to including other mosquito species.

To be able to 1) perform surveillance on non-target insects, and 2) know whether the dosages used in malaria vector control leads to selection for resistance in non-target insects, it is important to identify the diagnostic insecticide doses and/or diagnostic times of other arthropod species compared to malaria mosquitoes. By combining information on arthropod biting and resting behaviors with the known diagnostic doses for DDT (an organochloride), malathion (an organophosphate), deltamethrin and permethrin (two pyrethroids) for those arthropods, we highlight the potential evolutionary consequences of intensified malaria vector control on the susceptibility of other arthropods to current and future insecticides.

Table 1. Vector-borne diseases that are or have been circulating in Africa.

Diseases	**Evidence of Outbreak/ circulation in Africa (Country & year)**	**References**
Yellow fever (*Ae. aegypti*; *Ae. africanus; Ae. simpsonii*)	Côte d'Ivoire (2001), Senegal (2002), Guinea (2002) and Burkina Faso (2004).	[33]
Zika (*Ae. aegypti; Ae. albopictus*)	About 25 countries across Africa have been affected by the virus so far	[34]
Dengue (*Ae. aegypti; Ae. albopictus; Ae. africanus; Ae. luteocephalus,*)	More than 20 countries in Africa including Burkina Faso, Senegal, South Africa, and Egypt have reported confirmed dengue outbreaks	[35]
Chikungunya (*Ae. aegypti; Ae. albopictus*)	Outbreaks in several African countries including Tanzania (1952–53), South Africa (1956; 1975–77), Nigeria (1964; 1969; 1974), Democratic Republic of Congo (1958; 1960), Angola (1970–71), Sierra Leone (1978), Central African Republic (1978–79), Zimbabwe (1957; 1961–62; 1971), Zambia (1959), Senegal (1960), Uganda (1961–62; 1968)	[36]
Rift Valley Fever (*Cx. pipiens, Cx. poicilipes; Ae.*	Egypt, the Gambia, Kenya, Madagascar, Mauritania, Mozambique, Namibia, Senegal, South Africa, South Sudan, Sudan, Tanzania, Zambia,	[37]

mcintoshi, Ae. ochraceus, Ae. sudanensis, Ae. dentatus)	Zimbabwe	
West Nile Virus *(Cx. univittatus,Cx. neavei*, *Cx. quinquefasciatus)*	South Africa (1973-74)	[38]
Human African Trypanosomiasis (*Glossina* spp.)	Endemic in over 36 countries in Sub-Saharan Africa including Uganda and the Congo Basin (between 1896 and 1906), and Angola, South Sudan and the Democratic Republic of Congo (between the 1970s to the 1990s)	[39]
Leishmaniasis (*Phlebotomus* spp.)	Major outbreaks reported in west Africa (Ghana, Senegal, Mali and Burkina Faso)	[40]
Chagas (*Triatomine* spp.)	Gabon and Tanzania	[41]
Tungiasis (*T. penetrans*)	Endemic in sub-Saharan Africa (Tanzania , Uganda, Algeria)	[42]
Plague (*S. fonquerniei* and *X. cheopis*, amongst other species)	Prevalent in Africa (Democratic Republic of Congo, Nigeria, Madagascar)	[42,43]
Cholera (*Musca* spp. & *Blattaria* spp.)	Endemic and persistent throughout sub-Saharan Africa especially in Democratic Republic of Congo, Nigeria, and Guinea Bissau	[44]
Trachoma virus (*Musca* spp.)	Endemic in 29 of 33 countries in Africa	[45]

Different arthropods, overlapping niches

Here we show that different arthropods share a similar niche with the malaria mosquito. We focus on sub-Saharan Africa, where the malaria burden is highest,[2] and where, as a result, malaria vector control -and hence the selective pressure for insecticide resistance- will remain intense.[46] In addition to other biological disease vectors, we have included several other important arthropod species. These include mechanical disease vectors that can transmit foodborne illnesses, such as house flies (responsible for e.g. cholera, typhoid fever, diarrhea, and

salmonella),[47] and cockroaches (responsible for e.g. diarrhea, salmonella, hepatitis A, and typhoid fever).[48] Species that are not known to transmit diseases but could be a nuisance or a concern to local communities (e.g. ants, termites, bedbugs, and spiders) are included as well. Killing specimens of this latter category may be important to household members, and has been associated with the acceptance of vector control tools such as LLINs and IRS.[49]

The malaria mosquito (*Anopheles* spp.), our frame of reference

African malaria mosquito species are widely distributed across Sub-Saharan Africa.[50] The major malaria vectors in Africa are *Anopheles gambiae s.s.*, *An. funestus s.s.*, and *An. coluzzii*. More details on their exact geographic distribution can be found elsewhere [51,52] and is beyond the scope of this paper. They are targeted successfully by LLINs and IRS as they primarily feed and rest indoors, [51,52] which is referred to as endophagic and endophilic behavior, respectively. These species are also highly anthropophilic, meaning they prefer human blood over other blood meal sources,[53] and there is a close association between vectors and human presence.[54] *Anopheles* spp. tend to feed during the night while people are indoors and often asleep, but peak biting times vary between species, season and location.[52] As in any biological system, there are exceptions to general rules, and several *Anopheles* species are known to rest and/or feed outdoors, although those are commonly considered secondary vector species.[51] Increased pressure on the primary vectors indoors through intensified vector control may lead to those secondary vectors playing an increasingly important role in local malaria transmission over time.[51] However, the strong endophilic and endophagic behaviors in the primary malaria vectors was the reason for the development of the next generation of LLIN and IRS products, and acted as a stimulus for the current development pipeline for new active ingredients.[15]

Each section below is written as follows: the current and potential role in disease transmission (if applicable) is given for each arthropod genera, together with their known distribution in sub-Saharan Africa. Then their known resting (relevant for contact with IRS insecticides) and biting behaviors (relevant for contact with LLIN insecticides) are described, including known biting times, which are relevant to determine likelihood of contact with LLINs (i.e., indoor biting during daytime is unlikely to result in contact with LLINs, as no or only few users will be present under the net).

Other arthropods - biological disease vectors

Mosquitoes (*Aedes* spp.) can transmit arboviruses such as yellow fever,[55,56] Zika virus,[57,58] dengue virus,[59,60] and Chikungunya.[61] Outbreaks of these arboviruses have been reported in sub-Saharan Africa (Table 1) and *Aedes* mosquitoes are widely distributed across Africa.[62] *Aedes aegypti* was found to pre-dominantly rest indoors in Senegal,[63] and Sudan,[64] whereas a study conducted in Kenya showed that *Ae. aegypti formosus*, which is a sub-species typically found in Sub-Saharan Africa, was mainly exophilic (resting outdoors). Other studies in Mali,[65] and Malawi,[66] also reported *Aedes aegypti* resting indoors, but without surveilling the outdoor environment. The biting behavior of *Aedes* spp. is typically bimodal (during the early morning

and late afternoon) as demonstrated in various countries in Africa.[67,68] A study conducted in Kenya that simultaneously studied their indoor and outdoor feeding behavior observed that 80% of *Aedes* spp. fed outdoors.[68] Thus, *Aedes* spp. mosquito populations can be found both feeding and resting indoors, which means that part of *Aedes* mosquito populations will likely be exposed to insecticides that are applied to wall and roof surfaces (IRS). Of note is that these behaviors will likely depend on the local context (climatic factors, human behaviors, housing conditions, use of interventions, etc.). Given the typical feeding times of *Aedes* spp., they are probably less likely to encounter LLINs, simply because they feed during periods of time when people are not in bed. However, despite the importance of *Aedes* mosquitoes on arboviral transmission in sub-Saharan Africa, there remains a paucity of evidence on their exposure to public health insecticides, although recently several African countries started to report the insecticide susceptibility status of both *Ae. aegypti* and *Ae. albopictus*.[69–71] Given the lack of detailed data, it is difficult to quantify the extent of the resting and biting behaviors of *Aedes* spp. indoors and outdoors. Worryingly, this applies to the genera we will discuss below as well.

Mosquitoes (*Culex* spp.) can transmit arboviruses such as Rift Valley fever, and West Nile virus[72,73] and lymphatic filariasis.[74] Major outbreaks of these arboviruses have been reported in sub-Saharan Africa (Table 1). *Culex* spp. mosquitoes are also widely distributed in sub-Saharan Africa.[65,75–77] C*ulex quinquefasciatus* was found to rest more indoors in Nigeria,[78] but more outdoors in Kenya.[79] *Culex* mosquitoes have also been observed to rest indoors in South-eastern Tanzania,[80] but outdoor collections were not performed. *Culex* spp. typically bite during the night as shown in a study in Equatorial Guinea.[81] In the same study, the outdoor biting rate of *Culex* mosquitoes (mostly *Cx. quinquefasciatus*) was slightly higher than the indoor biting rate.[81] Overall, these resting and biting behaviors, although again limited quality data exist, suggest that *Culex* mosquito populations have a high likelihood (likely higher than *Aedes* spp.) to be exposed to IRS and LLINs indoors.

Kissing bugs (*Triatoma* spp.) are important vectors of Chagas disease.[82,83] Recently, Chagas disease has been detected in Gabon and Tanzania (Table 1) and its vector is found in many countries in Africa (e.g. Guinea and Sierra Leone).[84] These regions could serve as a hotspot for many species of triatomine bugs due to their climatic suitability,[85] but this needs to be validated empirically. To the best of our knowledge, evidence on indoor feeding and resting behaviors of kissing bugs in Africa is not available. Observations made in Brazil showed that adult triatomines rest mostly indoors,[86] whereas a study in Texas, USA, showed that they mostly rest outdoors.[87] Given that Triatomines typically rest inside cracks and crevices indoors, and the fact that such resting habitats are plentiful in Africa where many communities live in traditional mud-walled homes, it is likely they will be found resting indoors. Since Triatomines are generally nocturnal, [88] and biting their human host while they are asleep,[89] they will be exposed to indoor insecticides when host-seeking. A review on the behavior of kissing bugs in the United States suggests that they usually hide during the day and feed at night in homes.[90] Their nocturnal

biting and potential indoor resting behaviors suggest that part of African triatomine bug populations could easily come into contact with LLINs, when they are looking for a host, and IRS products during their resting phase.

Tsetse flies (***Glossina* spp.**) can transmit human African trypanosomiasis, also known as sleeping sickness.[91] Over the past decades, there have been several outbreaks of human African trypanosomiasis across Africa (Table 1) and tsetse flies are widely distributed in sub-Saharan Africa,[39] which indicates that they still pose a serious health threat. To our surprise, little is known about the resting and feeding behaviors of Tsetse flies. They were found resting more outdoors than indoors in Zimbabwe,[92] but other studies only state the flies were found to rest both indoors and outdoors, without further quantifying these behaviors.[92,93] They are usually actively searching for bloodmeals during the day,[93] and have been observed to bite indoors during the day when people are active indoors.[92] Albeit little, the evidence of tsetse fly populations found resting indoors does suggest that they can be exposed to IRS products. However, due to their apparent daytime biting behavior, they are unlikely to encounter LLINs.

Sandflies (***Phlebotomine* spp**.) can transmit leishmaniasis.[94–96] This disease has been circulating in Africa (Table 1) and various sandfly species are widely distributed throughout the continent.[97] Studies conducted in Ethiopia found that sandflies (*P. orientalis*) rest more outdoors than indoors,[98,99] while a study in Central Mali showed that 99.2% of the collected *P. duboscqi* were resting indoors.[18] While indoors, it was suggested that they frequently seek blood meals at similar times and places as mosquitoes in Egypt, but solid evidence was not presented by the authors.[100] Based on the information above, it is likely that part of sandfly populations can be exposed to IRS and LLINs. This is further supported by the fact that IRS and LLINs have been successfully used in the fight against sandfly-transmitted leishmaniasis in Mali.[18] However, this should be an active area of investigation due to the limited amount of available data.

Biting midges (***Culicoides* spp**.) can transmit animal diseases in birds and blood sucking insects (*Haemoproteus* spp.),[101] horses (*Shuni virus*),[102] cattle and sheep (*Akabane virus and Simbu virus*),[103] which are all present in Africa. There is also evidence from Peru that they transmit *Iquitos virus* and *Madre de Dios virus* to humans.[103] Therefore, biting midges could potentially affect human health. To the best of our knowledge, there is only one study from Africa that investigated the feeding and resting behaviors of biting midges both indoors and outdoors. *Culicoides milnei* were found to both rest and feed more indoors than outdoors in many parts of Ethiopia, with a clear nocturnal feeding pattern.[104] If this observation is representative for the different *Culicoides* spp and across the continent, then biting midges will be exposed to IRS products while resting, and will encounter LLINs when they are actively looking for a bloodmeal when people are asleep. However, up to now, far too little attention has been paid to the resting and feeding behaviors of *Culicoides* spp.

Fleas (multiple spp.) can transmit a range of pathogens, including murine typhus, Bartonellosis, Tungiasis and the plague, all circulating in Africa.[42] Here we focus on the latter two diseases. *Tunga* spp., responsible for the transmission of Tungiasis, can complete their whole life cycle indoors[105] in dwellings with cracks in the walls and floors,[106] an environment that is common in resource-poor settings in sub-Saharan Africa. They penetrate a person's foot, or other parts of the body when people sleep on the floor. The flea's life cycle is also successfully completed in other hosts (e.g. cattle, rodents and domesticated animals,[107]). The fact that such animals are kept close to home, and even indoors in many African cultures,[108] can make fleas a major public health risk. *Xenopsylla* and *Synopsyllus* flea species, which are responsible for the transmission of plague in e.g. Madagascar, feed on humans, rodents and domesticated animals.[109] They are most commonly found on their principal host, the black rat (*Rattus rattus*),[110] but *X. cheopis* is the flea species primarily found on rats indoors.[111] The resting and breeding patterns of fleas in general suggest that indoor flea populations will be exposed to IRS products (in fact, IRS has been implemented since the 1940s to control plague[19,25]), and might come in contact with LLINs. The latter will depend on their diurnal activity patterns, which are unknown to the best of our knowledge.

Ticks (multiple spp.) can transmit a range of pathogens, including Crimean–Congo haemorrhagic fever,[112] Bhanja virus,[113] Thogoto,[114] Bourbon virus,[115] and African tick bite fever.[116] These diseases are all circulating in Africa.[116] Many different tick species can be found in a single country (e.g., over 70 species have been recorded in Sudan alone).[117] Ticks are commonly found living as ectoparasites of livestock.[117] Based on the ecology of a large variety of tick species in Africa, ticks are most likely to live and feed outdoors,[118] and will therefore not come into contact with LLINs and IRS. However, the brown dog tick (*Rhipicephalus sanguineus*), which originated from Africa,[119] is known to complete its lifecycle indoors.[120] If this species (or any other tick species) shows a similar behavior in Africa, it can be exposed to IRS products while it is hiding in the cracks of walls[121,122] and/or to LLINs when it is hiding in (or crawling around) furniture. [122]

Other arthropods - mechanical disease vectors

Houseflies (*Musca* spp.) can mechanically transmit diseases such as cholera, trachoma virus, shigellosis, salmonellosis, typhoid fever.[47] Houseflies are widely distributed and associated with humans all over the world.[123] and the diseases they mechanically transmit are all endemic in Africa.[44,45,124,125] A study in central Ethiopia showed that 76.7% of all *M. domestica* were caught indoors.[126] Therefore, part of housefly populations can be exposed to indoor vector control tools when they crawl over substrates (LLINs and IRS), but more detailed investigations are needed as their feeding and resting places inside homes may very well differ from those of blood-sucking arthropods.

Cockroaches (*Blattaria* spp.) can mechanically transmit diseases such as typhoid fever and cholera.[48,127] Cockroaches are present in nearly all climatic regions of the world[123] and the diseases they mechanically transmit are endemic in Africa.[44,125] In general, cockroaches are commonly found indoors, where there is abundant food, warmth and moisture.[127] Focusing on the African continent, we found one study validating cockroaches live inside homes.[128] Their general resting and activity (crawling) patterns suggest that part of cockroach populations can be exposed to indoor IRS products, and perhaps even to LLINs, but that will depend on their specific indoor activity patterns that likely differ from those of blood-sucking arthropods.

Other arthropods - nuisance genera

Other arthropods that dwell indoors are e.g., bed bugs (*Cimex spp*.),[129] spiders (*Oecobiidae* spp*., Lycosidae* spp*., and Gnaphosidae* spp*.)*, ants (*Formicidae* spp.), termites, crickets (*Gryllidae* spp.), wasps (*Bethylidae* spp.), lice (*Liposcelididae spp.*) and bees (*Halictidae* spp.),[130] some of which can be perceived as a nuisance (unpleasant) to residents. Although some of the citations used are not specific for sub-Saharan Africa, those genera are commonly found across continents. The prevalence of these pests in indoor human domiciles suggests that they can also be exposed to LLINs and IRS, again depending on their activity patterns. Understanding those patterns and their subsequent exposure to vector control interventions can be relevant for the acceptability of those same interventions, as homeowners are not always interested in killing mosquitoes indoors only.[131,132]

Figure 1. Schematic drawing of a traditional home in sub-Saharan Africa, showing the arthropods that potentially overlap with anopheline malaria mosquitoes in their resting behavior (left half), which may increase their likelihood to contact IRS products, and their feeding behavior (right half), which may increase their likelihood to contact LLINs.

Known insecticide resistance and susceptibility thresholds in African arthropods other than malaria mosquitoes

Given the considerable overlap in niche occupancy of anopheline mosquitoes and many of the above-described other arthropods, it is plausible that these non-target arthropods are also exposed to insecticides used in malaria vector control and potentially have evolved resistance. For mosquito species other than malaria vectors, there are few published studies on insecticide surveillance. Insecticide resistance to four of the main classes of public health insecticides that are used in malaria control (DDT's, pyrethroids, organophosphates, carbamates) has already been detected in *Aedes* spp.[29,69] and *Culex* spp. [27] mosquitoes in Africa. For sandflies, one study has been done in Sudan, which demonstrated resistance to carbamates and organophosphates. [26] Resistance to public health insecticides in other arthropod species appears to be less rigorously monitored in sub-Saharan Africa but has been observed elsewhere, including evidence of resistance to pyrethroids in kissing bugs in Argentina,[133] and resistance of house flies to pyrethroids and organophosphates in China,[134] Turkey[135] and USA.[136] Interestingly, it has been

shown that the target-site pyrethroid resistance mechanism (L1014F mutation, also referred to as a knockdown resistance (*kdr*)) is similar in *Anopheles gambiae s.s*,[137] *Cx. quinquefasciatus*, houseflies (*M. domestica*), and cockroaches (*B. germanica*).[138] This suggests similar evolutionary processes are indeed acting on a broad group of (indoor-dwelling) insects. Similarly, metabolic resistance via overexpression of cytochrome P450s is commonly found across different mosquito species,[139,140] and a span of other insects.[141] However, regardless of resistance mechanisms, a range of intrinsic insecticide susceptibility to anti-malaria vector control tools will be expected across all species of insects due to differences in size and cuticle thickness.[142]

In the absence of data on the presence of insecticide resistance in most non-malaria transmitting arthropods in Africa, it is impossible to know what the impact of the intense malaria vector control is on other arthropods occupying the same niches. However, we can assess whether exposure to current and future malaria vector control tools is likely to lead to the development of insecticide resistance. In order for insecticides to select for resistant organisms, the exposure dose needs to fall in the window of selection.[143] The window of selection describes the range of insecticide dosages between which selection for resistant mutants is likely, which on the lower end is the dose that leads to non-zero mortality in susceptible organisms and on the upper end less than 100% mortality in resistant organisms. The diagnostic dose in insecticide susceptibility assays is typically twice the concentration killing 99.9% of susceptible organisms (LC99.9), whereas mortality of resistant organisms is reduced at the LC99.9.[144] Therefore, this dose falls within the window of selection and selection at this dose is likely to be intense due to lack of competition from susceptible organisms.[143] While for most organisms there are no detailed dose-response curves of susceptible and resistant strains available to establish the window of selection, we can compare their known diagnostic dosages, if available, with those of malaria mosquitoes. If the diagnostic dose of a particular arthropod vector is similar, then we can assume these also face intense selection for resistance at dosages used for malaria vector control. If the diagnostic dose is much lower (i.e., a much lower concentration of insecticides is needed to effectively kill this arthropod), the selection pressure for resistance in this arthropod when exposed to malaria vector control tools will be less as it is more likely that even resistant organisms will be killed at the dosages used to kill malaria mosquitoes. If the diagnostic dose is much higher (i.e., a much higher concentration of insecticides is needed to effectively kill susceptible individuals), the selection pressure for resistance in this species when exposed to malaria vector control tools is lower because even susceptible organisms will have a probability to survive and thus decreasing the selective advantage for resistant mutants. [143]

Given the fact that DDT, pyrethroids and organophosphates have been used for decades in vector control,[145] we focus on comparing the known diagnostic doses for DDT (an organochloride), deltamethrin (a pyrethroid), and malathion (an organophosphate) between arthropods. The diagnostic dose of DDT in WHO tube bioassays for *Aedes albopictus* and *Ae. aegypti* is similar to that for *Anopheles* spp., but *Ae. aegypti* only has to be exposed for 30 minutes (rather than the typical 1h exposure).[146] Looking at deltamethrin and malathion, the

diagnostic dose is lower for *Aedes* spp.[147] than for *Anopheles* spp.[144,146] In other words, *Aedes* spp. may be slightly more susceptible to insecticides than *Anopheles* spp. The mosquito, *Cx. quinquefasciatus*, requires a similar diagnostic dose as *Anopheles* mosquitoes [144] but a longer exposure time (4 hours) to DDT, a lower dose but similar exposure time for deltamethrin, and a similar dose and exposure time for malathion, [146] indicating this species may naturally be more resistant to DDT, but is equally or less resistant than *Anopheles* spp. for the other two insecticides.

The WHO insecticide susceptibility testing guidelines also include other arthropods, namely bedbugs and the castor bean tick.[146] Bedbugs (*C. hemipterus)* require a 1h exposure to a lower dose of DDT,[146] therefore, if resistant bedbugs have the ability to survive the relatively higher dosages used for malaria control, bedbugs are likely to develop resistance to this insecticide. Although the reported diagnostic doses for castor bean tick (*Ixodes ricinus)* are lower than those for *Anopheles* ssp., they require a continuous exposure during testing.[146] Bedbugs also require a continuous (deltamethrin) or a 16-day exposure (malathion).[146] These longer exposure times mean that genetically susceptible organisms of these species are more resistant to the vector control tools than *Anopheles* mosquitoes, and selection is therefore not expected to be intense. However, to be able to draw more firm conclusions, we will need to know more about the insecticide bioavailability in their environment and contact rates and times in the field. Unfortunately, there are many gaps in our knowledge for the other arthropod species discussed in this Personal View. Comparisons across species is additionally problematic, because bioassays differ in methodology and thus exposure, with different species being exposed in WHO tubes,[144] CDC bottles,[148] jars,[149] vials,[150] or bigger bottles[151]. Standardized toxicology studies such as the topical application bioassays that control for organism biomass,[152] are needed to compare susceptibility of species at a given insecticide dose (lethal dose), while behavioral field studies would give us an estimate of contact time and rate with malaria vector control tools. While we can create some hypotheses, it would be impossible to understand how a range of public health insecticides affect a range of arthropod species in the absence of such standardization.

Non-target effects of other vector control tools

While most of our discussion has been centered around insecticide use in LLINs or IRS, this message does not only apply to current and new active ingredients that are being developed for the use in LLINs and IRS. For a range of other vector control methods/technologies, including those that target early indoor biting, outdoor biting and/or outdoor resting mosquitoes, the same selective pressures may lead to resistance in other arthropods. This may therefore result in a loss of efficacy of interventions that aim to kill i) host seeking mosquitoes (e.g. insecticide-treated window or eave screens,[153] insecticide-treated eave tubes,[154] spatial repellents[155]), ii) resting mosquitoes (e.g. insecticide-treated wall liners[156]), iii) sugar-feeding mosquitoes (e.g. attractive targeted sugar baits containing insecticides[157]), iv) flying mosquitoes (e.g. insecticide-treated outdoor barrier screens[158]), and v) blood-feeding mosquitoes (e.g. by endectocides, a drug lethal to arthropods that feed on treated animals and/or humans).[159] While the latter is not an

insecticidal application, mosquitoes can develop resistance to endectocides, like they do to insecticides.[160] A wide roll-out of these insecticide- and drug-based tools is likely to expose other arthropods to the same interventions, which could lead to both insecticide and drug resistance in those arthropods.

Non-target effects on vectors of animal diseases

Our message is not limited to infectious diseases that affect human health. The One Health approach recognizes that there is a relationship between the health of humans, animals and ecosystems.[161] Our current malaria control and elimination approaches may very well impact arthropods that transmit a range of animal diseases, such as visceral leishmaniasis (transmitted by sandflies [162]), Crimean-Congo hemorrhagic fever, anaplasmosis and theileriosis (ticks [117]), animal African Trypanosomiasis (tsetse flies [163]), Canine Chagas disease (kissing bugs [164]), and Bluetongue virus (biting midges [165]). It is very common in many African cultures to keep animals close to home, and even indoors.[108] This means that vectors responsible for transmitting those diseases to animals may also be exposed to LLIN and IRS products depending on their activity patterns, which could have long-term consequences for animal health, socio-economic status and food production.[161]

Conclusion

Non-malaria transmitting arthropod species, many of which are (potential) vectors of various infectious diseases affecting both humans and animals, share their ecological niche to a certain extent with malaria vectors, as they co-occupy the indoor environment. As such, they are likely exposed to bed nets (as shown for e.g. *Culex* mosquito species[24]) and indoor residual spraying (shown for e.g. fleas[25]), two core insecticide-based malaria control interventions. As insecticides and antibiotics have been shown to lead to resistance in non-target organisms in the field of agriculture,[21] and medicine,[22] respectively, it is highly likely that LLINs and/or IRS will contribute to the emergence and spread of insecticide resistance in other arthropods, as has been suggested by others.[26–29]

Fortunately, the implementation of insecticide resistance management (IRM) strategies is high on the agenda,[166] and may result in other arthropod species not developing resistance to insecticides. However, we cannot simply assume this will be the case, as we have not quantified the level and impact of exposure. Detailed ecological and behavioral data (i.e., preferred place of resting and feeding, time of feeding, contact time with nets and/or walls) and information on insecticide resistance mechanisms, and the diagnostic or lethal dose for insecticides are not readily available for most of those arthropod species. We have seen with malaria vectors across Africa that their feeding and resting behaviors[51,167] as well as insecticide susceptibility levels[168] can differ across small spatial and temporal scales due to factors such as climatic conditions, land use, availability of animal hosts, flight range, level of bednet use, IRS acceptability, seasonality, and cultural practices. As such, it is not difficult to imagine that this will also hold true for other arthropod vector species. This will require local tailored surveillance and implementation plans,

with details on which entomological indicators to collect, surveillance tools and methodologies to be used for the different arthropods, sampling locations and sampling frequencies. Existing frameworks (such as the Entomological Surveillance Planning Tool[169] and WHO's Global Vector Control Response 2017–2030[170]) could serve as a blueprint, and the WHO and partners could develop a comprehensive manual for monitoring insecticide resistance in arthropod vectors and selecting appropriate interventions, as they did for mosquitoes.[166] And with an increased focus of the malaria control community to also target outdoor biting and/or resting malaria vectors, assessing the overlap in behaviors between malaria vectors and other arthropods in the outdoor environment should not be ignored.

Priority areas for implementation should be guided by factors such as the real need to control and/or prevent (re)emerging diseases, or a pre-emptive need to understand the selective pressure of malaria vector control on arthropods of interest. Implementation can be funded by domestic funding as e.g. seen in Thailand with the mobilization from local districts,[171] and/or international donors.[13]

In summary, the missing information on arthropods' behaviors and insecticide susceptibility levels makes it difficult to predict the effect of malaria vector control on other arthropod genera. This is very worrying, given our limited insecticidal arsenal[12] to fight arthropod vectors and the fact that there are no drugs or vaccines available to control or prevent many of these vector-borne diseases. While non-chemical control measures (e.g., environmental management to reduce vector populations[172]) and strategies that address the social determinants of health (e.g., improved house designs to reduce human-vector contact[173]) can have a significant impact on disease burdens and are urgently needed,[174] we will have to rely to a large extent on insecticides to control and prevent future vector-borne outbreaks over the next decades. As such, for Integrated Vector Management (IVM)[175] to be really successful, we have to improve our understanding of the distribution, ecology, behavior and insecticide susceptibility status of all other relevant arthropod species, to ensure we develop the most future-proof and holistic vector control strategies.

Conflict of interest statement

The authors declared no conflicts of interest.

Contributors

KPP conceived this Personal View. NBJ performed the literature search. NBJ, SH and KPP wrote the manuscript and approved of the final version.

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Search strategy and selection criteria

References used in this Personal View were selected from reading peer-reviewed publications from Pubmed, NCBI, and Google Scholar, using search words such as “non-target effect”, “infectious disease”, “Africa”, search words that relate to arthropod behavior (e.g., “endophilic”, “exophilic”, “exophagic”, “resting”, “feeding”, “biting”) and by combining those search words with both the common (e.g., “kissing bug”) and scientific names (e.g., “Triatoma”) of each arthropod we discuss. Search words related to information on insecticide susceptibility included “insecticide resistance”, “diagnostic dose”, “CDC bottle bioassay”, “WHO tube test”, “DDT”, “deltamethrin” and “malathion”.

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