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MOSQUITO CONTROL

Success, failure and expectations in the context of arbovirus expansion and emergence

Isabelle Dusfour and Sarah C. Chaney

Mosquitoes are considered humanity's most dangerous animal due to their capability to transmit a large number of deadly viruses and parasites, causing millions of illnesses and deaths annually, along with enormous economic loss (WHO 2020, Bradshaw et al. 2016). Among the 3,500 known mosquito species, however, only a few are vectors of these pathogens.

A vector is a mosquito that is able to pick up, amplify and transmit a pathogen from one vertebrate to another through blood feeding (Marcondes 2019). Only female mosquitoes are hematophagous (blood-feeders) and are therefore responsible for all mosquito-borne disease transmission. Yet not all female mosquitoes can transmit pathogens and some are better at it than others: the ability of any given mosquito to transmit disease from one vertebrate to another depends on its behaviour, how it fits into the ecosystem of the human-built and the natural world, and its internal biology. Each of these factors can be targeted with vector control strategies to interrupt the transmission of disease.

One way of reducing mosquito populations is to alter environmental factors necessary for mosquito breeding or to apply chemicals that target flying adults (adulticiding) or immature aquatic larval stages (larviciding). However, as we will see as we explore successes and failures of mosquito control, many chemical tools seem to have reached the end of their effectiveness as a stand-alone strategy. Despite decades of chemical control efforts over the past 50 years, the world has faced the intensification of dengue outbreaks, the re-emergence of yellow fever, the spread of chikungunya and Zika and the emergence of zoonotic diseases accompanied by the geographical expansion of major vectors (Wilder-Smith et al. 2017). Vector control departments are now faced with a challenge to expand beyond immediate prevention of human disease towards a global approach that encompasses the biology, behaviour and biodiversity of mosquito species, their ecology and what makes them effective or ineffective vectors—in

order to formulate a realistic, multi-faceted, environmentally friendly and efficient mosquito control strategy.

This chapter reviews what has been done so far to control *Aedes aegypti*, current challenges raised by the expansion of *Aedes albopictus* and growing threats of zoonotic viruses, and what innovations are under development to reduce mosquito-borne transmission of viruses. French overseas territories and the Americas are the focus here due to the special challenges they are facing to control mosquito vectors.

Controlling *Aedes* species in urban areas: *Aedes aegypti* and *Aedes albopictus*

Aedes aegypti and *Aedes albopictus* are the main urban vectors of arboviruses, the arthropod-borne viruses of yellow fever, dengue, chikungunya and Zika that threaten more than 3 billion people living in *Aedes*-infected areas worldwide (Wilder-Smith et al. 2017). *Aedes* species are optimally adapted for transmitting viruses from human to human: they can carry multiple arboviruses, are anthropophilic (prefer humans for blood feeding), bite during the day and feed multiple times, fly only short distances and prefer to breed in small human-made containers. Additionally, *Aedes* eggs are resistant to desiccation, giving them the advantage of spreading their offspring to new territories worldwide through human travel and commercial trade (Kraemer et al. 2019, Marcondes 2019).

Even though the two dominant *Aedes* vector species look very similar, their biology, ecology, behaviour and history of colonization reveal important differences. *Ae. aegypti* originated from forests of the western part of Africa and began spreading around the world through the transatlantic slave trade in the sixteenth century (Powell et al. 2018). This forest-dwelling species adapted to urban areas by becoming more anthropophilic and breeding specifically in human-made containers such as cisterns and buckets. This urban mosquito is closely tied to human habitation in all steps of its life cycle and is found less abundantly in rural areas and rarely in natural breeding sites. *Ae. aegypti* has colonized urban areas of subtropical and tropical regions around the world and is the main vector of the yellow fever virus, along with dengue viruses, and more recently chikungunya and Zika viruses.

Aedes albopictus, the Asian tiger mosquito, originates from forests in Asia and has become the world's most invasive mosquito species, colonizing all areas of the planet over the last 30 years within its preferred temperature range. Even though its ecological niche seems similar to that of *Ae. aegypti*, this species tends to be more rural, develops in a larger variety of natural and human-made breeding sites and adapts to a wide range of temperatures due to its capacity to lay cold-resistant eggs that can survive winter temperatures during its diapause stage (Paupy et al. 2009). *Ae. albopictus* is also less selective about hosts and can be found feeding on animals as well as humans. It does not transmit dengue and yellow fever quite as efficiently as *Ae. aegypti* and has until recently been considered more of

a nuisance than a public health concern. However, *Ae. albopictus* revealed its true colours during the 2006–2007 chikungunya outbreak that hit the Indian Ocean Islands, Central Africa, India and Italy. *Ae. Albopictus*' growing distribution to more temperate latitudes and its ability to transmit about 26 different arboviruses between human and animal hosts makes it a growing threat in temperate regions (Paupy et al. 2009).

In some areas, the ranges of these two species overlap, sharing resources, often laying eggs in the same breeding sites and intermingling in ways that were never possible in their native ranges. *Ae. albopictus* has largely displaced the longer-established *Ae. aegypti* in many areas in the southeastern United States, creating complex interactions of competition, cross-mating and evolutionary pressures between these two invasive species (Bargielowski et al. 2013). The ongoing expansion of these two species to new locations in urban and rural communities makes them a central concern for public health. Due to the similarities between these species, control methods are often the same regardless of the presence of one or both species in the area.

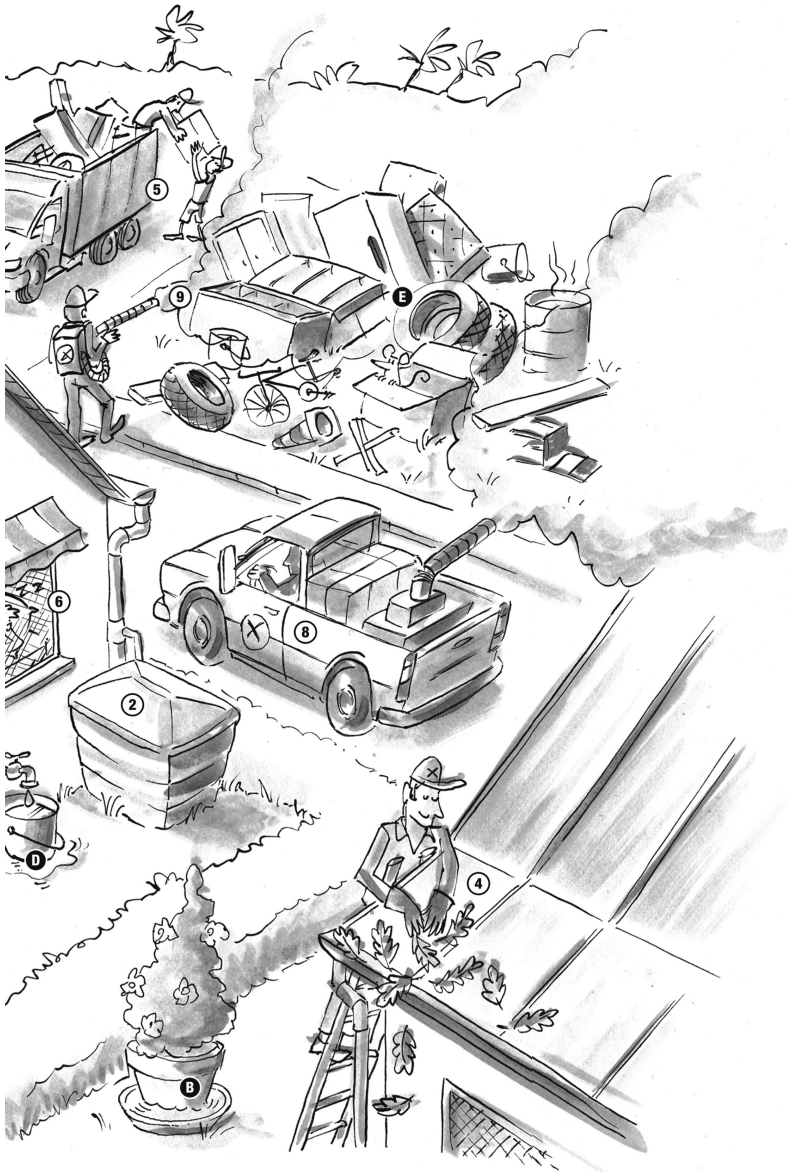
Vector control: where, when and who?

The most familiar stage of the mosquito, the winged adult, is the form that is responsible for disease transmission. However, the mosquito's life cycle involves both aquatic and aerial stages, all of which can be targeted by mosquito control methods for preventing disease. The World Health Organization (WHO) provided the first guidelines for dengue control and prevention, including vector management, in the 1990s, but the importance of *Aedes* control took a new turn with the strong support given to the Global Vector Control Response by member states during the World Health Assembly in 2017 (WHO 1997, UNICEF/UNDP/World Bank/WHO 2017). These guidelines include protocols for environmental management of natural and human-made mosquito breeding sites, chemical and biological control agents for treatment of larval and adult stages and best practices for encouraging community engagement (WHO 2012). Mosquito control activities are most successful when multiple approaches are combined and coordinated with other health, environmental and community sectors to produce an integrated approach to mosquito management.

Vector control measures targeting the aquatic larval and pupal stages focus on the removal of human-made containers where *Aedes* mosquitoes prefer to lay eggs, or these watery habitats can be treated with chemical or biological compounds (i.e. *Bacillus thuringiensis*) to arrest development or kill immature stages and consequently reduce adult population density (Achee et al. 2015). Preventive measures such as the regular removal of stagnant water (locations A–E, in Figure 14.1) or covering water storage containers are strongly recommended (control measures 1–5 in Figure 14.1). Deployment of larvivorous fish or copepods alone or in combination with other methods has shown low levels of efficacy (Lazaro et al. 2015, Han et al. 2015).



FIGURE 14.1 Suitable habitats for *Aedes* species and vector control methods. *Aedes albopictus* and *Ae. aegypti* breed in human environments. *Ae. albopictus* also develops in more natural habitats such as ponds, plants that hold water or tree holes (A). Both species are often found breeding in flower pots (B), gutters (C), water containers (D) and water collected in garbage of all sorts such as tyres, fridges and discarded containers (E). To reduce vector–human contact, several measures are used by people and public health authorities. Source reduction eliminates suitable places for females to lay eggs by properly covering



water storage (1, 2), removing stagnant water (3), cleaning household premises (4), avoiding garbage accumulation (5) and treating large ponds or reservoirs. To prevent human-vector contact, people at high risk can stay under bed nets even though *Aedes* mosquitoes are daytime biters, and screening can be installed in windows (6). Additionally, insecticide spatial spraying is performed indoors (7), outdoors (8–9) and occasionally by aircraft (10). The successful control of *Aedes* mosquitoes is based on the coordinated efforts of communities and public health authorities and by educating the youngest generation to take an active role in prevention (1). Illustration by Vincent Jacquet.

Interventions against adults aim to kill them in their aerial stage or interrupt female biting to prevent human–vector contact. Measures that target adult fertility and their ability to produce viable eggs aim to reduce future generations that may transmit disease (control measures 6–10 in Figure 14.1). Various adult behaviours can be targeted, including mating, host-seeking, blood-feeding, resting and egg-laying (oviposition). Current *Aedes* adult control in most countries around the world is based primarily on spraying chemical insecticides formulated for outdoor application via trucks or hand-operated backpacks or in targeted locations where adults can be found resting, such as vegetation for *Aedes albopictus* or indoor areas for *Aedes aegypti* (Achee et al. 2015, Faraji and Unlu 2016). Aircraft are also occasionally used as an emergency method (Britch et al. 2018, Likos et al. 2016).

An appropriate combination of vector control measures that target both immature and adult stages of the life cycle is recommended for maximizing density reduction and interrupting eventual virus transmission (Hierlihy et al. 2019). In areas with endemic arbovirus transmission, a low density of mosquitoes is achieved by routine larval control year round, with vector control teams implementing breeding site removal or treatment. During periods of high arbovirus transmission or epidemics, chemical applications, both indoor and outdoor, are used to control adults and reduce mosquito–human contact. Community involvement and participation in reducing breeding sites in urban areas requires sustained education and dedicated social mobilization (location 1, Figure 14.1). A combination of routine surveillance of mosquito breeding activity and disease cases in humans and potential animal hosts is essential for triggering early control strategies for preventing widespread disease transmission.

The decision of when, where and how to control mosquito populations is best made through integrated entomological and epidemiological surveillance as part of a comprehensive management plan (UNICEF/UNDP/World Bank/WHO 2017, Roiz et al. 2018). Without the commitment of political, operational and community stakeholders, such a plan cannot be sustainably developed, validated, funded and implemented (Horstick et al. 2010). Furthermore, local governance and operational policies are structured differently depending on local transmission patterns and the available human capacity and resources. In the end, the successful early interruption of disease transmission depends on interagency preparedness and coordinated actions (Roiz et al. 2018).

Success stories in *Aedes aegypti* and disease control

The efficacy of vector control is measured at different steps: lowering density and/or human–vector contact, epidemiological impact and its sustainability over time. There is some evidence that mosquito density can be reduced for a period of time thereby preventing epidemics, but few studies have rigorously demonstrated the long-range efficacy of vector control interventions (Wilson et al. 2015, Bowman et al. 2016). Part of the challenge is demonstrating effectiveness of a

specific vector control strategy in a treatment area compared to a similar control area with no such intervention. Such experimental protocols are hard to justify during a public health emergency since the control area could be exposed to higher risk of infection and disease. This is part of the reason why clear evidence on the epidemiological impacts of vector control is scarce. However, there are three examples of sustainable success stories in interrupting yellow fever and dengue transmission.

Several reports claim stories of successfully eradicating yellow fever in the early 1900s in the Americas and the Caribbean when the yellow fever virus and its transmission by *Aedes aegypti* was first described (Soper 1963). Following reports of early successes in reducing urban yellow fever cases and the discovery of DDT (dichlorodiphenyltrichloroethane) as an effective tool in this effort, the Rockefeller Foundation embarked on a worldwide yellow fever and malaria eradication programme in the 1940s (Soper 1963). Combining vaccination with mosquito control, the Rockefeller programme paved the way for modern vector control techniques by relying on large-scale indoor residual spraying of DDT. The effects on *Ae. aegypti* populations were drastic and the species was believed to be eradicated in the Americas. For a decade no record of either the mosquito or any of the diseases it carried was published.

However, a subsequent progressive recolonization of the mosquito across the continent brought dengue fever and other arboviruses with it (Soper 1963). Pockets of urban yellow fever outbreaks were controlled with vaccination. Malathion and other organophosphorus compounds became the new adulticides of choice, combined with removing larval breeding sites and engaging community through education campaigns. During outbreaks, outdoor spraying of insecticides was favoured over indoor residual spraying.

The return of *Ae. aegypti* was accompanied by an increase in dengue outbreaks, as all four dengue serotypes colonized the Americas. One country was an exception: for 15 years from 1981 to 1997 Cuba managed to remain free of dengue and recorded very low densities of this mosquito. During this period in Cuba an intense programme of surveillance and control was enforced in two phases by combining adult and larval control. The first phase involved massive ultra-low volume (ULV) spraying of malathion by aerial and ground application both indoors and outdoors. Phase two involved nationwide breeding source removal with education programmes for the general population and law enforcement that focused on limiting suitable conditions for larval development in backyards and houses. This combination of vector control methods was accompanied by an emphasis on entomological surveillance, source reduction and larval control (Armada Gessa and Figueredo González 1986). However, in 1997 an increase in vector density, most likely due to weakening in surveillance, along with the introduction of foreign infections, caused the re-emergence of dengue on the island (Kouri et al. 1998).

Another example of success occurred in Singapore during the 1960s, when authorities combined strict larval control with law enforcement after the

emergence of dengue transmission in the island city-state (Ooi et al. 2006). The programme resulted in low incidence of disease and low entomological indices for 15 years. However, since the 1980s, dengue cases have increased in the city despite low mosquito numbers. Several reasons are hypothesized to explain this disease expansion: the absence of immunity, reduced vector surveillance for case detection, introduction of foreign cases, and possibly a shift in mosquito behaviour.

Aside from these examples, worldwide *Aedes* vector control efforts have not succeeded in sustainably reducing the arbovirus burden in recent decades.

Reasons for failure: chemical and social

These experiences present many lessons to inform future surveillance and control strategies. Investigating the reasons for what has failed to sustain long-term effects is crucial to developing strategies for stopping the transmission of *Aedes*-borne diseases. The massive elimination campaigns of the 1940s in the Americas relied heavily on chemical control methods and top-down organization, neither of which are feasible or sustainable today. The authoritarian campaigns were successful for a period of time but led to neglected surveillance and vector control programmes once the vector was thought to be eradicated. *Ae. aegypti* has now recolonized all of South America, reaching all the way to its southernmost temperature limit in Argentina where it recolonized the capital, Buenos Aires, in 1991 (Zanotti et al. 2015).

With our current understanding of the long-term environmental consequences of chemical insecticides, the mass spraying of DDT and similar materials is no longer an acceptable strategy, and not only because of environmental concerns. Indeed, chemical control methods for both larvae and adults are reaching the end of their effective use for sustainable control because *Aedes* populations worldwide are becoming resistant to a wide range of compounds. Early evidence of resistance was found with DDT, followed by resistances to a range of organophosphates including the larvicide temephos (Moyes et al. 2017). Malathion remains a useful compound for mosquito control, but its toxicity to mammals restricts its use. The biological insecticide *Bacillus thuringiensis* var. *israelensis*, for which no resistance has yet been observed, has largely replaced temephos.

Pyrethroids, then, have become the insecticide of choice: inexpensive, harmless to wildlife, and applicable indoors as spatial and residual spray, outdoors as ultra-low volume (ULV) aerosol, and even impregnated in cloth material. These advantages are leading to a monotherapy conducive to the widespread development of resistance (Moyes et al. 2017). In addition, since 2010, pyrethroids are the only approved compounds for adult insect control in the European Union. In the absence of any alternative, some areas such as French overseas territories have arrived at a chemical control dead-end.

Aside from the widespread mosquito resistance, the method of spraying large quantities of insecticide in the environment is itself controversial because of the

lack of evidence for efficacy, high cost, slow operational response, low community acceptance, and the potential impacts on non-target organisms in the environment (Esu et al. 2010, Knauer et al. 2017). Selective pressures exerted on *Aedes* populations from vector control are compounded when the same pyrethroid insecticides are used against pest mosquitoes, found in household insecticides and impregnated gardening and personal protection materials, driving pyrethroid resistance even further and possibly preventing its reversal (Macoris et al. 2018, Gray et al. 2018).

We have arrived at the point where both chemicals and the methods for applying them may be ineffective for controlling *Aedes*, with few acceptable alternatives existing. At the very least, chemical applications for emergency tools could be regained by mandating non-chemical alternatives for non-emergency situations, or by developing novel compounds that target the vectors with other modes of action and that are more selective for mosquitoes (Dusfour et al. 2019). In the absence of novel tools that are validated, recommended or available, one possibility is to increase the use of pyrethroid-impregnated materials (in window curtains, for example) and the reinstatement of indoor residual spraying with pyrethroids (Samuel et al. 2017, Banks et al. 2015). These options are less harmful for the environment as they are localized to the indoors and effective against non-resistant strains of *Ae. aegypti* which prefer to rest indoors. For *Ae. albopictus* mosquitoes that tend to rest outside households, these alternatives would not be effective. In the absence of efficient compounds against adults, the only other effective options are the application of larvicides or the alteration of larval breeding sites for large-scale mosquito population control. Typically, water collection areas or containers are drained to eliminate putative breeding sites, covered to prevent egg-laying, filled in with sand to keep moisture for gardens without stagnant water or manipulated in such a way that mosquito larvae cannot develop or grow.

Because *Aedes* females prefer to lay eggs in small human-made containers of water, households (especially those without reliable piped water) are an important source of breeding grounds for the mosquito. Community engagement, therefore, is essential for comprehensive larval control. However, such engagement has not shown long-lasting success outside of the Cuban and Singaporean examples, both of which involved strong, authoritarian enforcement. Even though education and promotion plans were integrated into strategies, top-down approaches push the population to rely on authorities and to ignore their own personal role and responsibility in source reduction (Perez-Guerra et al. 2009, Mieulet and Claeys 2014). This behaviour is exacerbated by the belief that neighbours are not doing enough and individual efforts are made in vain (Ibarra et al. 2014). The mosquito is generally and universally hated mainly because of its bite: people are often more motivated by the nuisance they cause than by diseases they transmit (Dickinson and Paskewitz 2012). Reducing *Aedes* breeding sites, however, does not always have a direct and noticeable effect on the perception of overall nuisance, since bites may continue even from a diminished population or from other mosquito species. In contexts where other, more critical health

and safety concerns dominate, mosquito-borne diseases may not take priority in the lives of the community so that communication tools developed by vector control authorities may be ignored or misunderstood (Mieulet and Claeys 2014, Anderson et al. 2020). Being sensitive to local beliefs and instilling a basic understanding of disease transmission and the mosquito life cycle are also critical for mobilizing the population to act as participants in mosquito control and participate in bottom-up interventions (Ibarra et al. 2014, Paz-Soldán et al. 2011, Frank et al. 2017). Developing effective social strategies to support vector control strategies has therefore become a key recommendation and the WHO has published recommendations for guiding and supporting socially sensitive vector control teams (Bartumeus et al. 2019, Parks and Lloyd 2005).

A team of vector control specialists cannot possibly monitor all potential breeding sites when larvae can develop into adults in only two weeks under optimal temperature conditions; therefore, involving communities in control and surveillance is essential for efficiently covering or disrupting all possible breeding sites (Gubler and Clark 1996). Successful examples of community engagement also highlight the importance of regular surveillance protocols to monitor mosquito activity, disease incidence and mosquito resistance and then sustain these efforts over time (Bardach et al. 2019, Sulistyawati et al. 2019). This integrated approach has been advocated for decades but requires intensive and constant efforts from all stakeholders, even during periods when there is no disease transmission. The best results require political commitment, sustainable allocation of resources for planning and surveillance, as well as the training of public health authorities as part of an integrated and holistic approach for mosquito control. Despite decades of *Aedes* vector control experiences, widespread comprehensive and sustained strategies of mosquito control are not currently the norm in most endemic areas (Roiz et al. 2018). As a consequence, sound strategies have by and large failed to be implemented or sustained (Gubler 2005, Roiz et al. 2018, WHOPES 2010).

In the face of dramatic recent increases in dengue and other arboviruses, few success stories and little solid evidence for effective mosquito control, many questions are left open about the future prevention of vector-borne diseases (Bowman et al. 2016). For decades, the challenges and the calls for action have been stated in publications and reports—yet dengue remains a neglected disease. With a 30-fold increase in the past 50 years, dengue is finally being taken seriously (UNICEF/UNDP/World Bank/WHO 2017, WHO 2012). The re-emergence of yellow fever, the Zika outbreak and the emergence of other novel sylvatic arboviruses carry a warning to authorities and the public about an imminent threat. *Aedes*-borne arbovirus transmission is finally drawing the attention of researchers to develop new tools for surveillance and control.

The future of control against *Aedes* and disease

The global community is facing new challenges in controlling arboviruses. At the same time, modern vector control is still placed firmly in the dream

of past successes, expecting old tools and old methods to be efficient against new diseases, impacting only the targeted vector, while being environmentally friendly, sustainable and acceptable by communities all over the globe. Clearly, new tools and strategies are urgently needed.

As the number of available and effective compounds continues to decrease, it is of primary importance to regain the efficacy of pyrethroids and avoid further development of resistance. Integrated vector control must include monitoring insecticide resistance and measuring current insecticide efficacy in a comprehensive plan (Dusfour et al. 2019). Available control compounds are scarce but remain crucial for emergency control during outbreaks. As mentioned earlier, the efficacy of spatial sprays is debatable but pyrethroids could be used for indoor residual spraying or impregnation of materials. To reduce the selection pressure for resistance, alternative tools must be developed, validated and deployed.

To ensure the quality and effectiveness of proposed products and tools, the WHO has established the Prequalification Team (PQT), which replaces the WHO Pesticide Evaluation Scheme (WHOPES). The PQT supports the development, evaluation and adoption of novel control methods. An independent Vector Control Advisory Group provides additional guidance to product developers, innovators and researchers, including guidelines on the acquisition of epidemiological data, study design and new vector interventions. This group also provides advice to the WHO Strategic and Technical Advisory Group for neglected tropical diseases.

Based on the failure to maintain long-term successes in past control efforts and the expanded knowledge that the research and vector control communities have accumulated over the years, a more integrated view of vector strategies and technological advances has led to a suite of novel tools and new methods to implement them. While professional teams are still mainly responsible for implementation, the general public is now involved at an early stage, becoming an obvious and necessary component to establish and sustain vector control knowledge and practices in the affected communities (Kolopack et al. 2015, Ernst et al. 2015). Research in citizen and social sciences such as anthropology are also accompanying the expanded use of social networks and integrating mobile and geospatial technologies for providing new potential for vector control (Sousa et al. 2017, Hamer et al. 2018). Better understanding of the community's perception, knowledge, practices, beliefs and reluctance/acceptance of mosquito control is crucial for developing appropriate local communication and media messages (McNaughton 2012). Education must be sustainably implemented beginning at a young age, and adapted to local beliefs, habits and infrastructure. People must mobilize not only for vector control but also for surveillance in cooperation with a coordinated public health framework.

The research and development of new tools for targeting vector species is revealing more efficient and environmentally friendly techniques. One category is based on the knowledge of the vector's biology, behaviour and ecology to trap

or otherwise prevent it from coming into contact with people. For example, there are autodissemination traps, which exploit the cryptic behaviour of oviposition, when adult mosquitoes pick up a residue of larvicide that they then spread to other breeding sites (Maoz et al. 2017). Toxic baits that contain a sugar-insecticide compound target behaviours of both adult male and female sugar-feeding (Revay et al. 2014). Those tools are currently under evaluation, and even though some have proven their efficacy in reducing mosquito density, none have yet demonstrated epidemiological successes. These tools are relatively easy to implement and can be widely distributed, although their chemical composition may require authorization in areas where they are not commercially available. The fact that such tools rely on community involvement may factor into their chances of success (Faraji and Unlu 2016). Other tools such as the trapping of large numbers of adults through attractant compounds and behaviour-modifying compounds have shown promise in lab tests. However, better attractant compounds are still needed to demonstrate significant reductions in mosquito density (Degener et al. 2015, Obermayr et al. 2015).

The second category of novel control technologies relies on genetic modification (GM) of the mosquito (Qsim et al. 2017). The objective here is to produce non-fertilized eggs or non-viable offspring, thereby reducing the density of future generations. The sterile insect technique can be achieved through several methods. One method focuses on producing sterile males by irradiation (SIT); another relies on genetically modified mosquitoes to carry a lethal gene (RIDL); a third method utilizes insect incompatibilities with *Wolbachia*-modified mosquitoes (IIT) (Crawford et al. 2020, Kittayapong et al. 2019, Thomas et al. 2000). The last has the advantage of inhibiting arbovirus multiplication and interrupting its transmission (Ryan et al. 2019). In addition, the RNA interference technique is being tested for mosquito control as both SIT and insecticidal tools (Giesbrecht et al. 2020). Whether alone or in combination, SIT, RIDL and IIT mosquitoes have proven to be of some efficacy in controlling insects in field trials, but so far such techniques have shown only preliminary evidence for controlling disease (Crawford et al. 2020, Bellini et al. 2013, Carvalho et al. 2015, Kittayapong et al. 2019).

The general public and government agencies are often sceptical about genetically modified or altered mosquito technologies and more evidence for their efficacy is needed before they can become part of a public campaign to improve their acceptance (Ernst et al. 2015, Kolopack et al. 2015). Such concerns were heightened with the discovery in Brazil that genetically modified *Ae. aegypti* transferred some of their GM genes into the wild population (Evans et al. 2019). In Europe, GM mosquitoes are highly regulated and access to such technology is controlled and limited. Because mosquitoes irradiated to produce sterile offspring (SIT) are not considered genetically modified, some have been used and tested in Italy and in Reunion Island, France. Guidelines and principles for evaluating fertility-altered mosquitoes are different from one country to another (Panjwani and Wilson 2016). In any case, all methods targeting mosquito fertility entail

significant costs to maintain dedicated infrastructure and personnel for long-term mosquito mass-rearing and release (Meghani and Boëte 2018). At present, none of the new tools are fully validated or widely available, leaving traditional insecticides and source reduction methods as the sole pillars for controlling mosquitoes in the context of disease epidemics.

Zoonotic and epizootic mosquito control

While urban vectors and their associated arboviruses are at the centre of control efforts in both temperate and tropical areas, a growing concern is arising around zoonotic diseases. Viruses (and other pathogens) cycle between forest-dwelling mosquitoes and wild animals. Viruses such as Zika can be transmitted to humans when the virus enters an urban cycle with *Aedes* mosquitoes or it can be aided by bridge mosquitoes like *Ae. albopictus* that move between rural and urban habitats (Pereira et al. 2020). Many of these viruses infect humans as accidental and dead-end hosts, meaning that the virus may infect a human but is insufficiently amplified in the human body to be transmitted to another mosquito (Weaver and Reisen 2010, Wilder-Smith et al. 2017). Such is the case for West Nile virus, Usutu, Eastern equine encephalitis and Serogroup California viruses, which have all attracted attention in Europe and North America in the last few years (Gill et al. 2019, Lindsey et al. 2020, Vilibic-Cavlek et al. 2019, Calzolari et al. 2020). West Nile virus is of particular concern, and has received more research since its arrival and expansion in North America in the late 1990s.

With the emergence of more viruses using humans as dead-end hosts, controlling transmission has become an important challenge. The culprit mosquito species do not all belong to the genus *Aedes*, with *Coquillettidia*, *Culex* and *Culiseta* also implicated, mosquitoes with vastly different ecologies and some already recognized as nuisance pests (Sherwood et al. 2020, Hesson et al. 2019, Martinet et al. 2019). Several of these latter mosquito species transmit viruses to humans with varying abilities. Their physiological and ecological requirements are as different as are their life cycles over the seasons. Unlike *Aedes*, few are container-breeders, for example, creating complications for integrated vector control strategies in areas they coinhabit with other vectors. Such mosquitoes do not transmit disease as readily in their urban cycles, with the effect that there is not as much research about ways to include their habits in integrated vector control plans.

Controlling these other vector mosquitoes therefore presents difficult challenges. Personal protection and prevention measures such as topical repellents are recommended along with larval control; controlling adults or releasing sterile males are not recommended against West Nile virus (Hongoh et al. 2016, Campagna, Trudel and INSPQ 2018, CDC 2019b). Reduction of West Nile vectors by larvicides or adulticides often depends on mass spraying, a decidedly old-fashioned technique. Strategies tend to be implemented

in emergency mode relying on tools already in place for controlling nuisance or other vector mosquitoes (CDC 2019a, Werth 2019). With such outbreaks occurring with increasing frequency and greater severity, the means of controlling target mosquitoes or otherwise reducing disease transmission should be carried out with consideration for environmental impacts. To complicate matters, some of these species are already resistant to insecticides, leaving their efficacy unproven in both reducing mosquito numbers and transmitting diseases (Scott et al. 2015, Dunbar et al. 2018). Novel control methods need to be developed but the knowledge of these species is scarce, leaving the first-line strategy one of heightening people's awareness of using personal protections and developing efficient surveillance tools (Kading et al. 2020, Hongoh et al. 2016, Lindsey et al. 2020).

Conclusion

Since the discovery of the mosquito's capacity to transmit pathogens that cause diseases, humanity has tried to control these vectors to reduce the disease burden. The vectorial systems involve hosts, vectors and pathogens in the natural environment in a complex interplay that is constantly evolving under selective pressures. To reach a point where people and mosquitoes can achieve a sustainable and acceptable equilibrium that simultaneously preserves human health and protects the environment, one must aim to integrate all aspects of the ecology of mosquito-borne disease with the habits of the few mosquitoes that transmit those diseases. Just as the *Aedes aegypti* mosquito has fully adapted to living with humans, people must learn to adapt their own habits and urban environments to minimize their exposure to this and other dangerous mosquitoes. Targeted and integrated approaches for reducing the transmission of urban mosquito diseases have been advocated for decades but are unevenly applied due to their costs, limited human capacity, community apathy and weakness of the political will that is required to sustain these efforts during interepidemic periods. With the rising threat of mosquito-borne diseases, these approaches must be strengthened and adapted if we want to reduce pathogen transmission.

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