

One Health and a blood meal – integrative and ecologically sensitive approaches to mosquito-borne disease control

Najmul Haider¹, Muzamil M. Abdel Hamid², Francesco Vairo³, Chiara Montaldo³, Calvin Sindato^{4,5}, Leonard Mboera⁴, Alexei Yavlinsky⁶, Linzy Elton⁶, Liã Bárbara Arruda⁷, Timothy D McHugh⁷, Giuseppe Ippolito³, Alimuddin Zumla^{7,8}, Richard Kock¹ for the PANDORA-ID-NET Consortium

¹ The Royal Veterinary College, University of London, Hawkshead Lane, North Mymms, Hatfield, Hertfordshire

² Institute of Endemic Diseases, Medical Campus, University of Khartoum, Sudan

³ National Institute for Infectious Diseases, Lazzaro Spallanzani, IRCCS, Via Portuense 292, Rome 00149, Italy.

⁴ SACIDS Foundation for One Health, Morogoro, Tanzania

⁵ National Institute for Medical Research, Tabora, Tanzania

⁶ Institute of Health Informatics, University College London, United Kingdom

⁷ UCL Centre for Clinical Microbiology, Department of Infection, Division of Infection and Immunity, Royal Free Campus, University College London, London, UK

⁸ NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, UK, London, United Kingdom

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Abstract (Word count 184, Limit: 200 words)

The objective of this article is to discuss available strategies on Mosquito-borne diseases (MBD) control in the present age. The key outcome of this review is that new approaches are urgently required, as insecticide resistance has become more prevalent in recent years with at least one of the four major classes of insecticides reported ineffective in 80% of malaria-endemic countries. There is no single solution for MBDs. Recent promising initiatives to control MBDs targeting mosquitos include the use of insecticide impregnated mosquito nets, bacteria *Wolbachia* for biological control of *Aedes*-borne diseases and gene-editing of *Anopheles gene editing using CRISPR-Cas 9* and mass drug administration of ivermectin for malaria control. Mosquitoes infected with *Wolbachia* have reduced ability to transmit viruses including dengue, Chikungunya and Zika. Reduction in incidence between 71 and 90% of dengue cases in Australia, Brazil, Indonesia and Viet Nam was reported. A recent study showed successful gene editing of the malaria vector *Anopheles gambiae* leading to complete sterility and total collapse in 7-11 generations. *Wolbachia* mediated vector control seems to be the current-best implementable non-invasive technology for *Aedes* related diseases control. Integrated vector management still appears the best option to combat the vectors and MBDs globally.

Current word count: 3431

Background

Pathogens transmitted amongst humans, animals, or plants by arthropod vectors have been responsible for significant morbidity, mortality and economic loss throughout recorded history globally. Such vector-borne diseases (VBDs), including malaria, dengue, yellow fever, plague, trypanosomiasis, and leishmaniasis, represent the major cause of human diseases and deaths in the past four centuries (Gubler 1998; Mack 2016), while mosquito-borne diseases (MBDs) correspond to the most important VBDs.

There are more than 3,500 species of mosquitoes, in 37 genera. They are an important source of food for thousands of species of animals, including bats, birds, frogs, and dragonflies (Fang 2010). Although humans are source of blood meals, they are not the first choice for most mosquitoes (Fang 2010). For their own nourishment, both male and female mosquitoes feed on nectar and other plant sugar, while only the females use blood as a source of protein for their egg production cycle (Townson 1993). Despite being recognised for their important role in disease transmission, only approximately 100 species of three genera represent vectors of medical and veterinary importance: *Anopheles*, *Culex* and *Aedes* (Harbach 2014; Tandina *et al.* 2018) while *Haemagogus*, *Sabethes*, *Mansonia* and *Culiseta* can transmit diseases occasionally (Williams *et al.* 1964; Molaei *et al.* 2006; Boggild & Liles 2017; Lorenz *et al.* 2019).

Table 1: The Mosquito genus capable of transmitting diseases to humans and animals

Sl no	Genus	Pathogens/Diseases
1	<i>Anopheles</i>	Malaria, Lymphatic filariasis, O'nyong-nyong virus
2	<i>Culex</i>	Lymphatic filariasis, Eastern equine encephalitis virus, West Nile virus, Usutu virus, Rift Valley fever
3	<i>Aedes</i>	Yellow fever, dengue, Chikungunya, Zika , Rift valley fever virus, <i>Dirofilaria</i> worms
4	<i>Haemagogus</i>	Yellow fever
5	<i>Sabethes</i>	Yellow fever (Lorenz <i>et al.</i> 2019)
6	<i>Mansonia spp</i>	Usutu virus
7	<i>Culiseta spp.</i>	Eastern Equine Encephalitis Virus

Although the elimination of such vectors could represent a significant impact on human health, the importance of insect biomass in the food web cannot be underestimated. Recent indicators of a decline in insects are of great concern at a time when biodiversity generally is also showing dramatic collapse (Hallmann *et al.* 2017). Food is a critical limiting factor among populations, thus, animals that feed on insects are likely to be impacted and this is replicated along food chains with potentially catastrophic consequences to the human population (Møller 2019).

The loss of mosquitoes on future pollination is unquantified, but a significant loss in pollinators would have a serious impact on food production and natural ecologies. There are few studies of insect decline (Hallmann *et al.* 2017; Møller 2019), but a recent study in Germany, showed a decline of 75% of the insect population over 27 years (Hallmann *et al.* 2017). This trend was measured within environmental protected areas, suggesting that current actions to preserve the biodiversity are inadequate for the purpose of insect conservation.

Nevertheless, some level of intervention is unavoidable as MBDs remains a significant burden on human and animal health and the scale can be exceptional (Table 2). For example, over 80% of the Burundi human population (~8.7 million of people) was infected by malaria in 2019 (WHO Africa 2020) whilst significant losses of non-human primates (n=1277) occurred in Brazil during recent yellow fever epidemics (Fernandes *et al.* 2017; Klitting *et al.* 2018).

Table 1: The major Mosquito-borne diseases incidence in 2019 (Adapted from European CDC) (ECDC 2020) and WHO Africa (WHO Africa 2019)

<i>Country</i>	<i>Diseases</i>	<i>Mosquito species</i>	<i>Total Cases</i>	<i>Death</i>
Burundi	Malaria	<i>Anopheles</i>	8,724,757	3233
Philippines	Dengue	<i>Aedes</i>	420,453	1565
Vietnam	Dengue	<i>Aedes</i>	320,702	54
Brazil	Dengue	<i>Aedes</i>	220,100	591
Brazil	Chikungunya	<i>Aedes</i>	174,140	NR
Malaysia	Dengue	<i>Aedes</i>	127,407	176
Sri Lanka	Dengue	<i>Aedes</i>	103,924	NR
Bangladesh	Dengue	<i>Aedes</i>	101,354	162
Thailand	Dengue	<i>Aedes</i>	86,418	NR
Cambodia	Dengue	<i>Aedes</i>	65,000	NR
Ethiopia	Chikungunya	<i>Aedes</i>	54,908	0
Reunion (France)	Dengue	<i>Aedes</i>	18,206	NR
Singapore	Dengue	<i>Aedes</i>	16,003	NR
Thailand	Chikungunya	<i>Aedes</i>	11,484	0
Republic of Congo	Chikungunya	<i>Aedes</i>	11,434	0
Australia	Dengue	<i>Aedes</i>	1,419	0

NR= No Report

In some cases, vector control is not advisable or not likely to be effective, since the elimination of a particular vector can induce adaptive evolution of the pathogen. In the case of West Nile virus, loss of the primary vector led to infection of non-anthropophilic mosquitoes, which then adapted to become a potentially larger source of infection among non-human hosts (Kilpatrick 2011). After introduction of West Nile Virus in North America, it quickly adapted to infect the local mosquito species more efficiently than the original wild type viral strain (Kilpatrick 2011). Similarly, in Palmyra Atoll (WHERE IS THIS?), eradication of rodents was associated with the eradication of *Ae albopictus* (Lafferty *et al.* 2018), leading to an increase of the *Culex quinquefasciatus* mosquito which is a vector for lymphatic filariasis, West Nile virus and Japanese Encephalitis virus (Lafferty *et al.* 2018). This illustrates how poorly targeted interventions can adversely affect an entire ecosystem.

Global warming, unusual rain and increased rate and volume of globalisation are likely to lead to higher incidence of MBDs both in endemic areas and in geographical areas previously non-endemic (Laaksonen *et al.* 2010; Waldock *et al.* 2013; Simon-Oke & Olofintoye 2015). Indiscriminate use of insecticides has been applied in an attempt to control mosquitoes, however, this strategy has become outdated not only due to insecticide toxicity but also because this favoured the selection of resistant mosquitoes. In this article, we reviewed current developments in MBDs control strategies and how it affects MBDs.

Methods:

We searched articles in PubMed and Google Scholar using keyword “Mosquito-borne diseases” or “MBDs”, AND “MBDs control”, OR “*Wolbachia*”, OR “Insecticide resistance”, OR “Molecular techniques” OR “Aedes”. Altogether, we reviewed 110 articles meeting the search criteria.

Results and discussion: The subject is “... mosquito-borne diseases..” All of a sudden, the whole of the following section is focusing of *Aedes* mosquitoes!!! What about *Culex*? *Anopheles*? May be the subject should change to also focus on *Aedes* mosquitoes!

Aedes mosquitoes and Aedes-borne diseases

Aedes albopictus was first described in 1894 in India and is endemic to Southeast Asia (Kraemer *et al.* 2015). In 2007, this mosquito species was limited to 28 countries (Benedict *et al.* 2007), 12 years later it was confirmed in over 64 countries (Vairo *et al.* 2019b) and considered to be the most invasive mosquito in the world currently (Benedict *et al.* 2007). The invasion of *Ae. albopictus* was effective due to its ecological plasticity, ability of adapt to cold temperatures and the increase in global trade and travel (Paupy *et al.* 2009). It has successfully spread due to its ability to exploit the growing human population, domestic animals and anthropic environment, as well as thriving in both arid, cold conditions and warm and wet climates, undergoing periods of adult diapause, and overwintering by laying desiccation-resistant eggs (Vairo *et al.* 2019a).

Ae. aegypti originated from West Africa, introduced through the slave trade to the New World and is now domesticated and established in much of the tropical and subtropical regions (Kraemer *et al.* 2015). This process of invasion and domestication started with the beginning of intercontinental travel, with sailing ships as early as the 16th Century (Powell & Tabachnick 2013) and has continued with the shift in the scale of trade by air, sea and road providing a route for spread of these species. *Ae. aegypti* breed indoors and the indoor habitat is less susceptible to climatic variations and increases the mosquitoes longevity (WHO 2019). *Ae. Aegypti* originally known as “Yellow Fever mosquitoes” cause a disease that is endemic in at least 47 countries in Africa and Central & South America, a concern due to its mortality rate (~50%) (WHO 2020b). Despite an extremely effective vaccine being available for yellow fever, an estimated 84,000-170,000 severe cases and 29,000-60,000 deaths occur in Africa annually (WHO, 2018; <https://www.afro.who.int/health-topics/yellow-fever>).

The global distribution of *Ae. aegypti* and *Ae. albopictus* has been shown to be influenced primarily by climatic variables (Kraemer *et al.* 2015; Kamal *et al.* 2018). Under the current and future predicted climatic conditions, the distribution patterns of both species is concentrated in the tropical and subtropical countries with extension into some temperate regions, with a dominant distribution of *Ae. albopictus* over the temperate regions whereas *Ae. aegypti* shows wider distribution over the tropical and subtropical regions (Kamal *et al.* 2018). Although they have considerable differences in their ecology (Table 2), *Ae. aegypti* and *Ae. albopictus* will be the primary challenge for future global control of dengue, chikungunya, Zika, West Nile, and yellow fever viruses (Kraemer *et al.* 2015).

Table 2: The comparison of *Ae. aegypti* and *Ae. albopictus* mosquito based on ecology and behaviour (WHO, 2016)(WHO 2016b)

<i>Ae. Aegypti</i>	<i>Ae. albopictus</i>
Bites primarily humans (Anthrophophilic)	Bites primarily wild and domestic animals (Zoophilic) but also humans
Tends to bites indoors (endophagic)	Tends to bites outdoors (exophagic)
Feeds multiple times per cycle of egg production	Feeds once per cycle of egg production
Adapts well to human urban settlements	Inhabits rural and urban areas

Ae. albopictus is the vector of a wide range of human and animal pathogens including flaviviruses (dengue, Japanese Encephalitis, West Nile and Yellow fever), alphaviruses (Chikungunya, Eastern Equine Encephalitis, Ross River virus,) and bunya viruses (Rift valley fever, LaCrosse virus) (Benedict *et al.* 2007). During 2005-06, the French island of Reunion in the Indian Ocean experienced a large Chikungunya virus (CHIKV) outbreak. The outbreak was driven by a replacement of *Ae. aegypti* by *Ae. albopictus* as the main vector species of CHIKV transmission (Tsetsarkin *et al.* 2007). A mutation at A226V in the E1 gene of Chikungunya was responsible for CHIKV adaptation to *Ae. albopictus* mosquitoes, resulting in increased CHIKV transmission, viral infectivity and efficient viral dissemination into mosquito secondary organs, however, without affecting the pathogenicity of CHIKV (Tsetsarkin *et al.* 2007; Vairo *et al.* 2019a). This mutation enabled *Ae. albopictus* to cause an epidemic in a region lacking the typical vector (*Ae. aegypti*) (Tsetsarkin *et al.* 2007). After this mutation event, CHIKV has spread to more than 100 countries in the 10 years between 2008 and 2018 (Vairo *et al.* 2019a) and like *Ae. aegypti*, *Ae. albopictus* can now be described as fully domesticated. More outbreaks of Chikungunya mediated by *Ae. albopictus* especially in temperate countries are expected (Solimini *et al.* 2018), especially in countries where the long absence of malaria has generated some complacency on MBDs as a public health issue (De Zulueta 1998).

Insecticide resistance and alternatives: Separate into two Section: (i) Insecticide resistance; (ii) Alternative mosquito control methods. Note that Insecticide Resistance is ONLY one of the challenges in mosquito control!

Insecticide-based vector control has played a key role in reducing malaria and other MBDs since the beginning of the 20th century (Coleman *et al.* 2017). The main focus of malaria vector control is on insecticide-impregnated nets (ITNs) or indoor residual spraying (IRS) (Coleman *et al.* 2017). The 2010–2016 WHO Global report on insecticide resistance in malaria vectors showed that resistance to the four commonly used insecticide classes – pyrethroids, organochlorines, carbamates and organophosphates – is widespread among all major malaria vectors across the WHO regions (WHO 2019). By 2016, resistance to at least one insecticide has been reported from over 80% of malaria endemic countries (WHO 2017). Currently, the only insecticide recommended for use on ITNs by the WHO is based on pyrethroids, as they are relatively less toxic in mammals while having high insecticidal activity (Zaim *et al.* 2000). In 2013, two thirds of the IRS programs around the world relied on pyrethroids (Coleman *et al.* 2017). Furthermore, pyrethroids are widely used globally as a reliable insecticide in agricultural crop production (Coleman *et al.* 2017). Thus this combination of uses of pyrethroids resulted in a selective pressure for insecticide resistance (Ranson *et al.* 2011) and after 2015, the more expensive organophosphate Pirmiphos-methyls have widely replaced pyrethroids especially for IRS (Coleman *et al.* 2017). No promising new insecticides are in the pipeline which is likely to lead to widespread use of indiscriminate pesticides in the future, leading to a rapid decline of non-target insect populations and inducing growing resistance to

insecticides. This increases risk of resurgence of malaria and other MBDs along with ecological catastrophes.

An interesting observation is that insecticide repellents sprayed on human skin were shown to be less effective against infected mosquitoes (with a range pathogen, e.g. Sindbis, Zika), compared to uninfected counterparts, with an average of 62% reduction in protective efficacy (pooled odds ratio = 0.38, 95% confidence interval = 0.22–0.66). The reasons for this are unclear but might be related to the alteration of the physiology and behaviour of mosquitoes (Lajeunesse *et al.* 2019). Conflicting findings were observed between infected older adults and younger aged mosquitoes (Lajeunesse *et al.* 2019).

Multair *et al.* (2018) used multiple mosquito species and found that uninfected older adults are likely to be more sensitive to repellents (e.g. DEET) than uninfected younger ones. Meta-analysis by Lajeunesse *et al.* (2019) found older infected mosquitoes could be less sensitive to repellents than younger infected mosquitoes (Lajeunesse *et al.* 2019). Thus, the status of infection in mosquito can counterbalance age-dependent effects on repellency, which is in agreement with the effects of parasitism on host-seeking and host-feeding behaviours (Moore 1993). The information in these 2 paragraphs have no connection with the preceding or the following paragraphs!

Significant advances in vector control include initiatives such as The World Mosquito Program (WMP), using the naturally occurring intracellular bacterium *Wolbachia*, to control *Aedes*-borne diseases including dengue, Zika, chikungunya and yellow fever (World Mosquito Program 2019). *Wolbachia* occurs naturally in up to 60% of all insect species (World Mosquito Program 2019). Although it is not found in the *Ae. aegypti* mosquitoes, the WMP has successfully transferred *Wolbachia* from other insects into *Ae. aegypti* mosquitoes (Hoffmann *et al.* 2011). When mosquitoes are infected with *Wolbachia* they have a reduced ability to transmit viruses due to the reduction in insect lifespan or reduction of the ability of viruses and other pathogens to replicate within the insect (Hoffmann *et al.* 2011). *Wolbachia* can spread rapidly into uninfected host populations inducing the death of embryos from *Wolbachia*-uninfected females and infected males (Riegler *et al.* 2005). In addition, *Wolbachia* can affect pathogen transmission. A study using *Wolbachia*-infected mosquitoes that were orally infected with dengue showed a near complete disruption of dengue transmission (Moreira *et al.* 2009). In Australia, nearly 100% of *Aedes* mosquitoes were infected with *Wolbachia* one year after release of *Wolbachia*-infected mosquitoes in nature, which was responsible for the reduction of 90% of dengue cases over 44 months (Callaway 2018). In Brazil, the introduction of *Wolbachia*-infected mosquitoes resulted in a 71% reduction of dengue (Pacidônio *et al.* 2017) and 75% reduction of chikungunya incidence in a year (Kelly Sevick 2019). In Indonesia it has resulted in a 76% drop in dengue infection (Hellen Branswell 2019). In the Nha Trang region of Viet Nam, the release of *Wolbachia* infected mosquitoes in 2018 resulted in an 86% reduction in dengue cases in 2019 (Simmons 2019).

The removal of mosquito species will cause fundamental ecological shifts and it is not clear what the consequences will be but without doubt will contribute to biodiversity decline and may perversely increase other pest species through loss of predatory mammals such as bats dependent on mosquitoes for food. Moreover, this removal will result in the loss of pollinators. Contributing to the loss of insects in some regions would be unwise (Lindblade *et al.* 2000; Lafferty *et al.* 2018) because of potential critical consequences on human health and well-being. To eradicate globally the *Anopheles* mosquitoes (around 45 species) responsible for human malaria transmission, without removing many other species, would be difficult (Massey

et al. 2016). This may not even be necessary, as it has been shown that malaria can be eliminated on a national scale (Europe and North America, the Caribbean and parts of Asia and South-Central America (Carter & Mendis 2002)) as a side effect of land transformation and hydrological engineering. In some places, the eradication was achieved using more localised measures such as impregnated bed nets and targeted spraying and mosquito breeding control around water (Wakabi 2007). The biggest challenge is the zoophilic species that escape chemical control around households (Killeen *et al.* 2017). However, some alternatives such as zooprophyllaxis strategy have been developed and there is much to be gained in a One Health approach in this research field (Kemibala *et al.* 2020).

The use of molecular techniques in MBDs control

The development of a gene editor capable of collapsing a vector population to levels that cannot support the disease transmission is a long-sought scientific and technical goal (Curtis 1968). Current advances in gene editing are an important advance in biomedical research. A recent study showed successful gene editing of the malaria vector *Anopheles gambiae* that induced complete sterility and total generation collapse in 7-11 generations (Kyrou *et al.* 2018). Kyrou *et al.* used a clustered regularly interspaced short palindromic repeat DNA sequences CRISPR-Cas9 assay on the mosquito gene “double sex” which resulted in complete suppression among caged mosquitoes (Kyrou *et al.* 2018). Success still depends on proof-of-concept through field implementation of these technologies.

There is also a considerable advance of proteomics technology in controlling mosquitoes and MBDs. Dhawan *et al.* (2017) used high-resolution mass spectrometry to analyse *Ae. aegypti* salivary gland proteome and identified 15 proteins responsible for blood meal digestion and 29 proteins in immunity-related pathways in salivary glands. These findings opened the door for future design and development of virus blocking strategies and novel molecular targets in the control of the vector *Ae aegypti* (Dhawan *et al.* 2017).

A focus on single species such as *Ae. aegypti* and *Ae. albopictus* has several difficulties including finding methods that are effective and specific in all habitats. Perhaps advances on species targeting methods, such as the use of genetic sexing strains (GSS), may represent a sensitive approach worth exploring. For instance, a GSS approach applied to *Ae. aegypti* called Release of Insects carrying a Dominant Lethal (RIDL), involves the exploitation of the tTAV gene which interferes in the vector cell function by inactivating other genes and causing death (Alphey *et al.* 2013). Matthews *et al.* (REF, year) provided further insight into the genome of *Ae aegypti*, including the size and composition of the sex-determining M locus, revealed copy-number variation among glutathione S-transferase genes that are important for insecticide resistance and mapped new candidates for dengue vector competence and insecticide resistance (Matthews *et al.* 2018). Buchman *et al.* (2019) described the development of *Aedes aegypti* mosquitoes synthetically engineered to impede vector competence to all four serotypes of dengue virus. Therefore, gene-editing is an alternate tool to be explored for vector control, which may avoid extensive collateral damage to ecosystems.

In agriculture, integrated pest management has become popular, with more precision and targeting, with attention to collateral damage to environment and health. However, regarding human health, there are legal protections on pharma development even if the product is toxic to the environment as long as it has proven benefits but this position may change. Similarly the use of pesticides which reduce health risks to people are largely accepted, bar a few under the

Stockholm convention e.g. DDT. Therefore, gene editing and *Wolbachia* technology might avoid many of the challenges of more crude, imprecise methods of controlling mosquitoes, rendering them sterile or impairing their competence as pathogen vector.

Other techniques in use

Gamma irradiation

Irradiation techniques offer cheaper and non-chemical solutions for mosquito control. Use of Gamma irradiation in *Culex pipiens* mosquito reduced fecundity and egg hatchability (Hasaballah 2018). Irradiation also affects the emergence of adult from pupae (Hasaballah 2018). Gamma irradiation for male sterilisation has shown limited success, the irradiated males have a shorter life span and face difficulties in competing with natural male mosquitoes in mating with females (Machi *et al.* 2019).

Use of Ivermectin

Large-scale use of ivermectin in the control of the malaria vector has received attention in recent years. Ivermectin is a broad-spectrum antihelminthic drug that is widely used to for control of onchocerciasis and lymphatic filariasis and is used as a strategy in mass drug administration (MDA) for controlling these diseases. Ivermectin also acts as an endectocide, causing the death of *Anopheles* mosquitoes that ingest a sufficient dose in a blood meal (Kobylinski *et al.* 2010). It also affects the fertility of surviving mosquitoes (WHO 2016a). Clinical studies confirmed similar findings using membrane and direct-feeding methods (Ouédraogo *et al.* 2015). Models using data from studies using Ivermectin in MDA showed that it has the potential to reduce malaria transmission, mainly by reducing parasite survival, fitness, fertility and potentially inhibiting sporogony (Slater *et al.* 2014; WHO 2016a). There are however concerns over environmental and species impacts of ivermectin drugs (Sommer *et al.* 1993).

Attract and Kill techniques:

ITNs and IRS can effectively control mosquitoes that rest and bite humans indoors (Coleman *et al.* 2017). However, a significant proportion of malaria transmission occurs outdoors. For controlling outdoor mosquitoes, mosquito landing boxes (MLB) have been applied to attract and kill outdoor mosquitoes, including major malaria mosquitoes *An. arabiensis* and *An. funestus*. In these MLBs, mosquitoes are attracted with synthetic human odours while electrocuting grids and automated sensors are used to kill them. MLBs close to humans have been shown to reduce the risk of mosquitoes attempting to feed on them. This is a non-chemical technology that is beneficial for the killing of mosquitoes resistant to chemical insecticides or with behavioural resistance (e.g., avoidance of contact with lethal insecticidal surfaces and/or the change of their biting time) (Matowo *et al.* 2016) .

Integrated vector Management (IVM):

IVM is a rational decision-making process for optimal use of resources for insect control. WHO recommend IVM as an important step of MBD control, irrespective of the species of mosquitoes and availability of resources (Stone *et al.* 2014). It includes five elements of i) advocacy, social mobilization, regulatory control of public health, ii) collaboration within the health sector and with other sectors, iii) integration of non-chemical and chemical vector control methods, iv) evidence-based decision making and v) development of adequate human resources and training (WHO 2020a). IVM is a universal approach for control of MBDs useful to especially endemic countries.

One Health Vaccine

Alternatives to vector control include prophylaxis. An example is a recent vaccine developed for Rift Valley fever, which provided 100% protection in multiple livestock species trials and is set to be tested in human clinical trials to develop the world's first One Health vaccine (Warimwe *et al.* 2016; Warimwe 2019) applicable to both humans and animals.

Conclusions The conclusion should reflect the objectives and major findings!

Wolbachia mediated vector control seems to be the current-best implementable non-invasive technology for *Aedes* related diseases control. Nevertheless, the success of gene editing and omics technologies provide some hope of achieving major gains in MBD control but until now there has been no “magic bullet” and consideration must be given to analysing the ecological consequences of these new technologies. For malaria and other MBDs, integrated vector management still seems to play the key role in combating the vectors and MBDs globally especially in endemic settings. The conclusion should be based on the findings of the synthesis and not from any other cited information!

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