Introductory Chapter: The Globalization of Mosquito-Borne Diseases and Their Ecofriendly Control

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1. Introduction

Mosquitoes are the most common bloodsucking arthropods and important insect vectors of human disease affecting the course of human events and continue to do so. The world’s mosquito fauna include approximately 3500 species, but the main important species are *Anopheles*, *Aedes*, and *Culex* [1]. Mosquito-borne diseases (MBD) hit across new regions worldwide as people and goods are moving around the planet at ever-increasing rates and speed. The rapid spread of highly aggressive pathogens along with the development of resistance in their vectors represents fairly overwhelming epidemics and a huge challenge in modern parasitology and tropical medicine [2, 3]. Coming out of MBD may perhaps involve simple overflow from enzootic, i.e., wildlife, cycles like that West Nile virus reaching into the Americas; secondary amplification in domesticated animals as those of Japanese encephalitis, Venezuelan equine encephalitis, and Rift Valley fever viruses; and urbanization where humans suit the amplification hosts and peri-domestic mosquitoes, *primarily Aedes aegypti*, act as a go-between human-to-human transmission in case of dengue, yellow fever, chikungunya, and Zika viruses. Chikungunya and Zika viruses are the newly arrived arboviruses in the Western Hemisphere [4].

*Aedes aegypti* is originated in Africa, from where it was widely distributed by the slave trade to much of the world via water barrels in ships transmitting several devastating viral diseases. In spite of its name, *Ae. aegypti* disappeared from Egypt for decades [5], but it recently remerged again transmitting a small outbreak of dengue in Red Sea Governorate in 2017 [6].

Vector management is facing significant challenges, due to the peculiar traits and the rapid spread of invasive *Aedes* vectors, especially the Asian tiger mosquito, *Aedes albopictus* (Skuse), showing a huge ecological and physiological plasticity and adaptability to a wide variety of habitats worldwide, including cold climates typical of Northern Europe [8, 9]. Furthermore,
A. albopictus has the ability to vector a wide number of viruses, including dengue, La Crosse encephalitis, West Nile, and chikungunya [10]. Zika virus might adapt to exploit A. albopictus as a vector represents a worth mentioning concern [3]. The estimated potential range of Ae. aegypti and Ae. albopictus in the United States is shown in Figure 1 [7]. The annoyance of mosquitoes is devastating enough to affect real estate values, tourist industries, and outdoor activities. More than a million people die every year from malaria, and other mosquito-borne diseases cause incalculable misery, poverty, and debilitation; Plasmodium falciparum takes more lives and causes more suffering than the other MBD put together. Despite the dramatic reductions in malaria incidence since 2000, malaria elimination from high-transmission settings still challenging and the increased arbovirus outbreaks in frequency and impact would worsen the situation. Zika virus epidemics (2015–2016) hit many countries representing an urgent need for united global action [2]. Mosquito-borne distress also includes significant agricultural losses occurring as a result of attacks on domestic animals [1]. Even with international resolve to prevent future epidemics, current practices in MBD control are mostly reactive and of limited efficacy [2]. Therefore, global approach for fighting MBDs needs precarious reevaluation and the aims of the chapter are to highlight the global impact of MBD along with their future epidemics and biorational control.

2. Global burden of mosquito-borne diseases

2.1. Malaria

Malaria is an ancient disease caused by Plasmodium parasites vectored by Anopheles mosquitoes. Five species cause malaria in humans, but P. falciparum and P. vivax throw up the greatest threat. Infectious agents transmitted by mosquitoes may have a greater connection to cancer and the immune system struggles to recognize and fight some of these infectious agents; therefore, the International Agency for Research on Cancer (IARC) highlighted that P. falciparum infections in holoendemic areas are probably carcinogenic to humans and placed them in Group 2A [11]. At the beginning of the twentieth century, malaria was endemic worldwide.
and 90% of the global population at risk [12]. During the 1930s and the early 1940s, effective campaigns include using environmental management and regular larvicidal treatment of breeding sites for the eradication of *An. gambiae* from 54,000 km² in northeast Brazil [13]. Before World War II, the Global Malaria Eradication Program supported by the World Health Organization (WHO) [14] required elimination of malaria, and such efforts eliminated malaria by 1978 from 37 countries, 27 of which were in the Americas and Europe [12], but malaria is, yet, a health burden in the tropics throughout the world and is a major cause of mortality in sub-Saharan Africa [2]. Malaria-endemic countries in the Eastern Hemisphere are shown in *Figure 2* [15].

In 2014 and despite the African problems, Egypt eliminated malaria and there have been no cases of locally transmitted malaria ever since then [16]. The year 2015 was an extraordinary year for malaria control, due to three major news: Youyou Tu had won the 2015 Nobel Prize, for developing the antimalarial drug artemisinin; the development of the first vaccine against *Plasmodium falciparum* malaria (i.e., RTS,S/AS01 (RTS,S)); and the fall of malaria infection rates worldwide, with special reference to sub-Saharan Africa [17]. In the past two decades, such efforts resulted in a 60% reduction in malaria mortality worldwide and a 66% reduction in Africa [18]. Regardless of everything and in 2016, there were almost 216 million cases of malaria reported in 91 countries, with a rise of 5 million cases over 2015; malaria deaths

![Figure 2](image-url). Malaria-endemic countries in the Eastern Hemisphere, adapted from CDC [15].
reached 445,000 in 2016 reaching a similar number (446,000) to that of 2015. In 2016, Africa was homewards to 90% of malaria cases and 91% of malaria deaths. For malaria elimination, total funding for malaria control and elimination reached an estimated US$ 2.7 billion in 2016 and contributions from governments of endemic countries reached US$ 800 million (31% of funding) [14].

2.2. Lymphatic filariasis

Lymphatic filariasis (LF, elephantiasis) is an ancient [16] and a neglected tropical disease caused by Filarioidea nematodes such as *Wuchereria bancrofti* (responsible for 90% of cases) and by *Brugia malayi* and *B. timori*. Globally, an estimated 25 million people suffer from genital disease, whereas over 15 million people are badly affected with lymphedema [19]. *Culex* species, primarily *Cx. quinquefasciatus* [20], are the most common vectors across urban and semiurban areas of Asia [19]. Egypt stands on the verge of eliminating LF in 2004 as a huge national elimination campaign has been under way for 5 years, supported by unique public-private partnerships developed with WHO through the framework of the Global Alliance to Eliminate Lymphatic Filariasis. The fifth annual mass drug administration to 2.5 million people serves as the final phase of the Egyptian hard work to eliminate such disfiguring disease [21].

2.3. Yellow fever

*Ae. aegypti* transmit Flavivirus causing yellow fever, a devastating disease that has wrought havoc wherever emerged. After establishing in the New World, *Ae. aegypti* caused many epidemics. For example, the British army lost 1741; the French lost 29,000 of 33,000 men trying to acquire Haiti and the Mississippi Valley. France was willing to negotiate the Louisiana Purchase chiefly because of the presence of yellow fever in Louisiana and parts north. Many outbreaks hit coastal cities in the United States, such as Charleston, New Orleans, and Philadelphia, and gold-rush settlements in California. Yellow fever and malaria forced France to abandon completion of the Panama Canal until William Gorgas developed a program of mosquito control in Havana and then applied it to Panama [1]. Before twentieth century, yellow fever affected the entire New World. The efforts of Dr. Fred Soper and the Pan-American Health Organization resulted in a successful mosquito-control campaign in the post-World War II years contained yellow fever to the Amazon basin until very recently [1]. Yellow fever virus has three transmission cycles: jungle (sylvatic), intermediate (savannah), and urban. Urban yellow fever is transmitted only by *Ae. aegypti*, but a sylvatic form existing in monkeys is transmitted by other *Aedes* spp. such as *Ae. africanus* in Africa and *Haemagogus* and *Sabethes* mosquitoes in South America [22]. There is no risk of yellow fever in Egypt, and the government of Egypt requires proof of yellow fever vaccination only if visitors are arriving from a country with risk of yellow fever [23].

Dengue (breakbone fever, epidemic hemorrhagic fever) is a Flavivirus disease transmitted by *Ae. aegypti*. The annual number of dengue fever cases worldwide has more than doubled since 2000, and over 100 countries are now endemic and the spread of arboviruses was
Thailand had high incidences of dengue in 2001, 2002, and 2010 as the incidence during these years was 50% higher than the average throughout the 10-year period. On the other hand, Laos experienced over 800,000 cases of dengue during 2000 and 2001 [24]. In 2015, Delhi, India, recorded its most terrible outbreak since 2006 with more than 15,000 cases. The Island of Hawaii, United States of America, was affected by an outbreak with 181. The Pacific island countries of Fiji, Tonga, and French Polynesia have continued to record cases [25]. During 2016, large dengue outbreaks worldwide occurred as the Americas region reported more than 2.38 million cases, while Brazil alone recorded slightly less than 1.5 million cases, about 3 times higher than those recorded in 2014, and 1032 dengue deaths were also reported in the region; the Western Pacific Region gives an account of more than 375,000 suspected cases of dengue in 2016 mainly in Philippines and Malaysia. The Solomon Islands stated an outbreak with more than 7000 suspected. In the African Region, Burkina Faso reported a localized outbreak of dengue with 1061 probable cases. In 2017, the Region of Americas have reported 50,172 cases of dengue fever, a reduction as compared with corresponding periods in previous years [25].

2.4. Rift Valley fever

Rift Valley fever (RVF) is an emerging mosquito-borne zoonotic infectious viral disease caused by the RVF virus (RVFV) (Bunyaviridae: Phlebovirus) inducing noteworthy threats to global public health and agriculture in Africa and the Middle East. In the past 15 years, RVFV caused tens of thousands of human cases, hundreds of human deaths, and more than 100,000 domestic animal deaths. Animals as cattle, sheep, goats, and camels act as amplifying hosts for the virus [26]. The virus has a significant potential for international spread and use in bioterrorism; RVFV has caused large, devastating periodic epizootics and epidemics in Africa over the past ∼60 years, with severe economic and nutritional burden on humans from illness and livestock loss.

Figure 3. National and state maps of West Nile virus (including county-level data) from 2003—present, adapted from CDC [27].
2.5. West Nile virus

West Nile Virus (WNV) is transmitted by mosquitoes, mainly species of *Aedes*, *Ochlerotatus*, and *Culex*. WNV causes West Nile fever, a disease that rapidly spread across the United States following its introduction in the late 1990s. WNF is a serious disease in elderly people, and numerous deaths have been reported, especially in the west and upper Midwest. Current statistics are updated through the Centers for Disease Control and Prevention (Figure 3) [27].

2.6. Chikungunya

Prior to 2013, chikungunya virus cases and outbreaks had been identified in countries located in Africa, Asia, Europe, as well as the Indian and Pacific Oceans; during the late 2013, the first local transmission of chikungunya virus in the Americas was recorded in Caribbean countries and territories [28]. Countries and territories where chikungunya cases have been reported in 2018 are included in Figure 4.

![Figure 4. Countries and territories where chikungunya cases have been reported (as of May 29, 2018), adapted from CDC [28].](image)

2.7. Zika

Zika virus, a *Flavivirus virus*, was identified for the first time in Uganda in 1947 in *Rhesus* monkeys within a monitoring network of sylvatic yellow fever. In 1952, it has been identified in humans in Uganda and the United Republic of Tanzania [29]. Zika virus arises after dengue, West Nile virus (emerged in 1999), and chikungunya (emerged in 2013). The Zika epidemic in the 2015–2016 is the worst case scenario of MBD tragedies as the virus spread in 20 months to
67 countries and territories [30]. The recent outbreaks of Zika virus infection were mainly vectored by *Aedes* mosquitoes as *Aedes aegypti*, *Aedes albopictus*, and *Ochlerotatus japonicus* [31, 32].

### 3. Future epidemics and ecofriendly control

Since 2017, Zika cases, fortunately, have diminished, but Zika may be a harbinger of more MBD epidemics to come because human populations come into contact with mosquitoes, adapted to feed only on animals’ blood, as urbanization allowed new zoonotic pathogen transmission to immunologically naïve humans. Lately, yellow fever cases are climbing up in the Brazilian states, e.g., Minas Gerais, Espírito Santo, and São Paulo, urging rapid local and global public health authorities to consider the resurgence of urban yellow fever transmission for the first time in decade. Moreover, there were sporadic outbreaks of Mayaro virus in the Amazon and Caribbean regions. The players for future epidemics include Oropouche virus, Sindbis virus, and Venezuelan Equine Encephalitis virus [2]. Africa is not only the ancestral cradle of humankind but also, in our context, the spawning land of numerous zoonotic diseases, notably arboviruses; it is expected that Africa has the greatest potential for novel zoonoses and dormant pathogen to invade elsewhere at a global scale [8]. Despite the upcoming threats, we could see that there is no global surveillance system tracking the emergence and spreading of MBDs.

Social networks “VazaDengue” is an information system for preventing and combating MBD used to strengthen and classify the content of the entomological surveillance of mosquitoes transmitting dengue, Zika, and chikungunya automatically by providing geolocated reports, represented through dynamic maps, which could be directly included by the users or harvested from social networks such as Twitter and Instagram [33]. Because there is no reliable and specific treatment for arboviruses, avoidance of mosquito bites remains the best strategy [18]. Current prevention tools are represented by the employ of mosquito repellents as DEET (N,N-diethyl-m-toluamide). More information about commercial repellents and their safety concerns is reviewed [34]. Some strategies need to be integrated in regions with endemic mosquito-borne diseases for the reduction or removal of mosquito breeding sites, along with mosquitocidal treatments using chemical, botanical, or microbiological ovicides, larvicides, and pupicides [35–37]. Regarding application of synthetic pesticides, development of mosquito-resistant strains and some environmental and health concerns need to be considered. Overall, the major ecological and toxicological issues experienced with the overuse of chemical pesticides have boosted a renewed interest for the so-called “Biological control of mosquitoes covers a various range of predators and pathogens of mosquito young instars and adults [35]. The other control measures include the followings:

The behavior-based control tools are very effective for controlling mosquito populations. The “*lure and kill*” strategy and *Sound traps* are useful tools [38]. When applied in Cuba in 1949 against *Anopheles albimanus*, sound traps collected a high number of males [39]. Related approaches led to successful removal of *Culex tarsalis* males, reducing female insemination, [40] and diminishing *Culex tritaeniorhynchus paorus* females [41]. Despite their efficacy, traps work only for a limited distance [38]. There is a renewed interest in sterile insect technique
(SIT) for suppression of mosquito vectors, especially for *Anopheles* spp. Recently, SIT has been combined with autodissemination as adult females contaminated with dissemination stations of juvenile hormone for treating breeding habitats. Such technique controlled *Aedes* spp. efficiently, but cannot be used at large scales. Therefore, *boosted SIT* might enable the area-wide eradication of mosquitoes. Release of Insects carrying a Dominant Lethal (RIDL) is a useful tool. In anticipation of perfect sexing mechanisms, a combination of *Wolbachia*-induced phenotypes, like cytoplasmic incompatibility and pathogen interference, and irradiation may prove to be the safest solution for population suppression [17].

**Botanicals** as plant extracts, essential oils (EOs), and crushed plant parts have a long history of successful applications in traditional medicine and folk ethno-veterinary of many developing and developed countries [42, 43]. The emerging scenario highlights screening plants as rich source of antiparasitic materials [35, 44–51]. They are often effective at few parts per million against mosquito larvae [52–55]. Botanical pesticides and repellents are still used nowadays and have also stimulated natural product research; repellent products are extensively reviewed [34, 35, 52]. EOs and leaf extracts are effective larvicide against *Culex pipiens in low doses* [53–55]. Botanicals are cheap, easy to apply, and scarcely toxic to humans and other vertebrates; some of them are effective at very low doses, which are comparable to those of chemical pesticides currently marketed; aqueous plant extracts can be easily employed to threat mosquito breeding sites, without applying synthetic surfactants; finally, the development of resistance against them is extremely unlikely [36, 52]. Apart from the previous advantages of botanical-based pesticides and repellents, the number of currently marked products remains very low. In addition, both researchers and the industry are facing several challenges such as improving yield and efficacy, standardization, insufficient governmental support, and very slow and highly expensive way of registration of the developed products. Encapsulation and nanoparticles are useful for improving the persistence and efficacy of botanical insecticides [34, 36, 52]. Intestinally, *Aganosma cymosa* leaf extract used for nanosynthesis of Ag nanocrystals stimulates oviposition of *An. stephensi, Ae. aegypti*, and *Cx. quinquefasciatus* [56]. Botanicals could be used for the synthesis of mosquitocidal nanoformulations [57–60] as well as cheap repellents with low human toxicity [61].

### 4. Concluding remarks and future perspectives

The increased travel and trade accelerated trends toward the importation of exotic mosquito-borne diseases. In spite of the increase in frequency and intensity of arbovirus outbreaks, malaria mortality has been cut in half since 2000 due to successful mosquito control. Yet, major challenges still deserve attention in order to boost malaria prevention and control as development of artemisinin resistant strains, and inefficient RTS,S vaccine against *Plasmodium vivax* malaria predominant in many countries outside Africa. The carcinogenic infectious agents transmitted by mosquitoes may be undetected as either no one is looking for them, or they are looking in wrong anatomical locations and/or with inadequate tools [62]. More research is required to establish whether simian and avian forms of malaria play a part. If they do, such infectious agents could provide unique markers for early cancer detection [62]. Even though
the available MBD prevention and control tools are quite expensive and not affordable by poor and most populations in tropical and subtropical areas worldwide, several promising technologies for mosquito vector control are in the pipeline. Along with reduction or removal of mosquito breeding sites and employing personal mosquito repellents, integrated mosquito control strategies should be tailored in different geographical distribution including biological control tools in the presence of ultra-low quantities of nanoformulated botanicals to increase their performance and predation rates [60], SIT, boosted SIT [63], Wolbachia-based programs, RIDL, [64], and the repeated releases of genetically modified male mosquitoes. Innovative methods of identification of swarming sites are urgently necessary for the “lure and kill” approach and sound traps to work for long distances [38] as well as for the possibility to disrupt or enhance swarms, manipulating artificial markers. These efforts may lead to create “kill zones” within or in close proximity of villages where high numbers of mosquitoes would be attracted and killed [38]. The WHO and several funding agencies have sponsored that control efforts achieve more widespread MBD control and elimination initiating new ambitious global goals to reduce global malaria mortality by 90% by 2030 [65]. Fortunately, the current global approaches for fighting MBDs are heading toward such targets. We anticipated that when MBD control adopted globally, MBDs will hold back within the next two decades.

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