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CHAPTER 1

THE SPREAD OF MOSQUITO-BORNE DISEASES: A MAJOR AND GLOBAL PUBLIC HEALTH PROBLEM

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Abstract

Despite centuries of control efforts, the past three decades have witnessed a dramatic spread of many mosquito-borne diseases worldwide. The acceleration of urbanization, global warming, the intensification of intercontinental trade and travel, the co-evolution and adaptation between pathogens and mosquito vectors, and the development of insecticide resistance, have greatly contributed to the mosquito borne diseases worldwide. This chapter presents the current situation regarding the expansion of mosquito-borne diseases and theirs vectors worldwide, highlighting the factors that have contributed to these dramatic expansions. Furthermore, this chapter addresses the main difficulties encountered for vector control implementation using traditional approaches.

1. Introduction

Vector-borne diseases (VBD) stand as a major public health problem. They account for more than 1.5 million of deaths per year and for 17% of the estimated global burden of all infectious diseases (WHO 2014). After HIV/AIDS and tuberculosis, they are the most important cause of death worldwide (Hill et al. 2005). The VBD have in common the need of an intermediate host, usually a blood-feeding arthropod, to be transmitted between humans. Indeed, vector borne diseases are defined as infections caused by a large variety of pathogens (i.e. parasites, bacteria, viruses) that are actively transmitted to vertebrates by infected arthropods vectors such as triatomine bugs, sandflies, blackflies, ticks and mosquitoes, with mosquitoes being the most important vectors of human pathogens. They are able to transmit pathogens such as *Plasmodium falciparum*, which is responsible for human malaria, and more than 500 arboviruses (arthropod-borne viruses) among which more than a hundred are known to be human pathogens (Saluzzo & Dodet 1997; Gubler 2002).

Unfortunately, the available strategies for alleviating the impact of such vector-borne diseases are insufficient. Despite centuries of control efforts, the burden of vector borne diseases,

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particularly mosquito-borne diseases, have been constantly increasing over the last three decades (Gubler 2002; WHO 2014; Hill et al. 2005; Kilpatrick & Randolp 2012). Several conditions are required for the emergence of a mosquito borne disease: first, the pathogen (i.e. arbovirus, parasite) must be present or be imported into a region inhabited by a susceptible mosquito population. Then, the mosquito must ingest the pathogen via a blood meal taken on a viraemic or parasitemic host. In addition, the susceptible mosquito has to be "competent" to transmit the pathogen, which means that the mosquito should be able to disseminate, replicate and transmit the pathogen to a new vertebrate host during the blood feeding process (Hardy et al. 1983). Finally, the pathogen must be successfully transmitted to a new vertebrate host where the quantity of pathogen delivered is enough to trigger a new infection in an individual that in general, would be immunologically naïve to that kind of infection. Moreover, the environmental conditions (i.e. temperature, photoperiod, rainfall) are constantly modulating each one of the cited vectorial transmission steps. For instance, as the insects are ectothermic animals, the temperature conditions will importantly shape the distribution of the potential mosquito vectors (Caminade et al. 2012; Rogers et al. 2014). Furthermore, temperature modulates the vector competence (Zouache et al. 2014) and the replication efficiency of the pathogens themselves (Dohm and Turell, 2001; Salazar et al. 2007), whereas rainfall plays an important role regarding the probabilities of contact between the virus and the vector. Indeed, the higher mosquito densities are generally recorded after important rain episodes (Roiz et al. 2011; WHO 2012), as they contribute to creating breeding-sites for the mosquitoes.

Which factors have contributed to the rise of the incidence and the global range of these diseases?

The global spread of mosquito-borne pathogens has undoubtedly been a consequence of the increasing global connectedness (Kilpatrick and Randolph 2012). Indeed, the globalization of the trade and travel have greatly contributed to the spread of many mosquito vector species worldwide and the pathogen importation by infected humans into new localities has been on the rise, increasing the probability of contact between the pathogens and their potential vectors. Furthermore, urbanization has enhanced probabilities of contact between the pathogens, the mosquitoes and the humans, as high densities of people are concentrated in relatively small areas

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that can become transmission “hot spots” with high epidemic potential. The environmental conditions that are constantly evolving in a context of climate change, have also modified the transmission dynamics, by in some cases, shortening the time lapse between the pathogen ingestion and transmission by the mosquito (Hardy et al. 1983; Vega-Rúa et al. 2015). In addition, the extensive use of pesticides in agriculture and for vector control has led to the development of insecticide resistance, which constitutes a real problem for vector borne disease control (Marcombe et al. 2009; Bisset et al. 2011; Karunamoorthi and Sabesan 2013). Finally, co-adaptation between certain pathogens and their vectors have also contributed to some of these dramatic expansions (Schuffenecker et al. 2006; Tsetsarkin et al. 2014). In this chapter, we will review the current status of dengue, chikungunya, zika and malaria and some of their respective vectors by analyzing (i) the history of their expansions, (ii) the role of the factors cited above on these expansions, and (iii) the vector control strategies that have been implemented to fight against these emergences. As the global expansion of these diseases was preceded by the global spread of their vectors (Charrel et al. 2014), we will start by reviewing the distribution range and the multiple invasions of the mosquito vectors *Aedes aegypti* and *Aedes albopictus.*

2. The Global Spread of Mosquito Vectors

2.1 Aedes albopictus

Ae. albopictus (Skuse 1894) also known as Asian "tiger mosquito" (Smith 1956) was described for the first time in Calcutta, India. This mosquito has a tremendous medical importance as it has been involved in the transmission of several important diseases including Chikungunya and Dengue (Gratz 2004). *Ae. albopictus* was a principal vector for CHIKV in a large number of outbreaks since La Reunion epidemic in 2005 (Gratz 2004; Schuffenecker et al. 2006; Rezza et al. 2007; Grandadam et al. 2011). In addition, *Ae. albopictus* has been a DENV vector in several outbreaks in Asia (reviewed in Gratz 2004), and in countries where *Ae. aegypti* is absent (Gjenero-Margan et al. 2011). This mosquito is also suspected of maintaining the circulation of DENV in some rural areas (i.e. Bangkok) (Gratz 2004). Furthermore, vector competence experiments have shown that *Ae. albopictus* is able to experimentally transmit at least 26 other arboviruses belonging to different families such as *Flaviviridae* (genus *Flavivirus*), *Togaviridae* (genus *Alphavirus*), *Bunyaviridae* (genus *Bunyavirus* and *Phlebovirus*), *Reoviridae* (genus *Orbivirus*) and *Nodaviridae* (genus *Picornavirus*) (reviewed in Paupy et al. 2009).

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Ae. albopictus is listed as one of the top 100 invasive species by the Invasive Species Specialist Group (ISSG 2009) and is considered the most invasive mosquito species in the world (Medlock et al. 2015). The ecological plasticity of *Ae. albopictus* together with the increasing human activities and intercontinental trade, have greatly contributed to the rapid global expansion of this mosquito species (Paupy et al. 2009). Indeed, *Ae. albopictus* can colonize both natural and artificial breeding sites (Paupy et al. 2009) which explains the abundance of this species in both rural and suburban sites. Studies on the biology of *Ae. albopictus* have also highlighted the existence of tropical and temperate forms (Hawley et al. 1987). Unlike *Ae. aegypti*, some populations of *Ae. albopictus* in temperate regions are able to adapt to cold temperatures and their eggs remain viable at low temperatures around 5°C (Hawley et al. 1987). Eggs can also get in facultative diapause generally during winter that can hatch with the arrival of the first spring rains (Mori and Oda 1981; Hanson and Craig 1994; Bonizzoni et al. 2013).

In the early twentieth century, the distribution of *Ae. albopictus* was limited to the Indian subcontinent, Asia and the Indian Ocean islands (Madagascar, Mayotte, Reunion Island) (Gratz 2004). Over the past three decades, this species has spread over the five continents in temperate and tropical areas (Figure 1) (reviewed in Kraemer et al. 2015). *Ae. albopictus* was detected for the first time in the Americas in 1983 (Reiter and Darsie 1984), in Europe (Albania) in 1979 (Adhami and Reiter 1998), in Africa in 1989 (reviewed in Paupy et al. 2009), and in Oceania in 1990 (Kay et al. 1990).

The intensification of trade and notably, the transportation of used tires, was responsible for the arrival of *Ae. albopictus* in the Americas (Reiter 1998). *Ae. albopictus* was first reported in the New World in 1983, in Tennessee (United states) (Reiter and Darsie 1984). Then, in 1985, the first *Ae. albopictus* breeding-site was discovered in Houston (Texas) (Sprenger and Wuithiranyagool 1986). The biological characteristics of *Ae. albopictus* populations found in the United States (i.e. cold hardiness, sensitivity to changes in photoperiod, ability to diapause), and the intensity of tires trade with Japan, suggest strongly the introduction of the species from this latter country (Hawley et al. 1987). In the coming years after its discovery in the US, *Ae. albopictus* rapidly spread to the north of Illinois and eastward to Jacksonville (Florida) taking advantage of the commercial exchanges and the road networks. Within two years, the species had

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already colonized around 113 United States counties (Urbanski et al. 2010). Then *Ae. albopictus* reached Mexico, where the first mosquitoes were found in 1988 in used tires (again) (CDC 1989). In South America, *Ae. albopictus* was first reported in Brazil in 1986 (Forattini 1986) and after, the mosquito considerably expanded its distribution range in the region. *Ae. albopictus* has been reported in Argentina (1998), Colombia (1998), Paraguay (1999), Uruguay (2003) and Venezuela (2009) (Cuéllar-jiménez et al. 2007; Navarro et al. 2013; Schweigmann et al. 2004). In Uruguay, the presence of *Ae. albopictus* has been detected near the Brazilian border, but the colonization of the country by this species is not yet confirmed (Lourenço-de-Oliveira et al. 2013). Similarly, the presence of *Ae. albopictus* in Bolivia was reported by Benedict and collaborators in 2007 (Benedict et al. 2007), but this was not subsequently confirmed (Carvalho et al. 2014). In the Caribbean, the presence d'*Ae. albopictus* has been reported in Barbados (reviewed in Medlock et al. 2015), in Dominican Republic in 1993 (Pena et al. 2003), in Cuba in 1995 (Broche and Borja 1999), in the Cayman Islands in 1997 (Reiter 1998), in Trinidad in 2002 (Chadee et al. 2003), and in Haïti in 2010 (Marquetti Fernández et al. 2012). In continental central America, this mosquito has been reported in Honduras (Woodall 1995) and Guatemala (Ogata and Lopez Samayoa 1996) in 1995, in Salvador in 1996, in Panamá in 2002 (Cuéllar-jiménez et al. 2007) and Nicaragua in 2003 (Lugo et al. 2005). *In fine*, *Ae. albopictus* is now present in at least 19 countries of the Americas (Figure 1).

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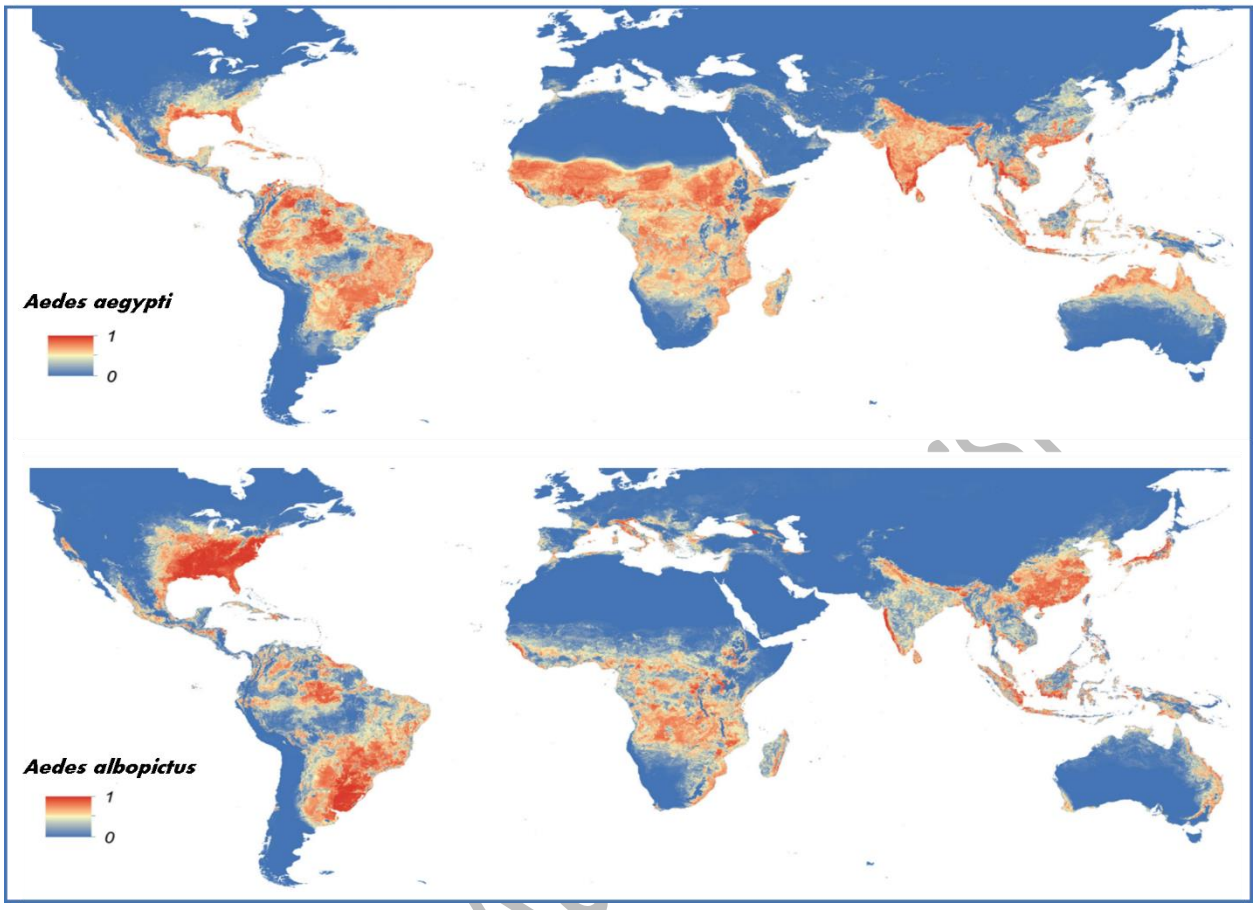

Figure 1. Global predicted distribution of *Ae. aegypti* (top) and *Ae. albopictus* (bottom) in 2015. The map depicts the probability of occurrence (from 0 blue to 1 red). Modified from Kraemer *et al* 2015.

In continental Africa, *Ae. albopictus* was first detected in South Africa (where it has been controlled) and later in Nigeria (1991), Cameroon (1999), Equatorial Guinea (2003), Gabon (2006), Central African Republic (2009), and Algeria in 2010 (Savage et al. 1992; Krueger and Hagen 2007; Paupy et al. 2009; Izri et al. 2011; reviewed in Diallo et al. 2012; Ngoagouni et al. 2015). Furthermore, the presence of the species in Brazzaville (Congo) has been confirmed during the 2011 chikungunya outbreak (Mombouli et al. 2013). Regarding Europe, *Ae. albopictus* has so far been reported in 25 countries, where this species has mainly been introduced via passive transport of eggs in used tires or lucky bamboo (Medlock et al. 2015). After its first report in Albania, the mosquito has been progressively reported: Italy in 1991(Dalla Pozza and Majori 1992), France in 1999 (Schaffner and Karch, 2000), Belgium in 2000

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(Schaffner et al. 2004), Switzerland in 2003 (Wymann et al. 2008), Croatia in 2004 (Klobucar et al. 2006), Spain in 2004 (Aranda et al. 2006), and the Netherlands in 2005 (Scholte et al. 2008). Although the species was identified for the first time in France in Normandy in 1999 (Schaffner and Karch 2000), it is only since 2004 (Delaunay et al. 2009) that the species is implanted permanently in the southeast of France and began a gradual colonization of the country up to 20 departments currently (Paty et al. 2014). *Ae. albopictus* has also been established in Greece, Malta, Monaco, Montenegro, Romania, Turkey, and has been reported but no established so far in Germany, Czech Republic and Serbia. Italy is now the most heavily *Ae. albopictus*-infested country in Europe (reviewed in Medlock et al. 2015).

2. 2. Aedes aegypti

Ae. aegypti (Linnaeus 1762), the main vector of yellow fever, dengue, chikungunya, zika and many other arboviruses is thought to have an African origin (Christophers 1960; Gubler 1998; Powers and Logue, 2007). In Africa, two *Ae. aegypti* forms differentiated by morphological and eco-ethological criteria are present: (i) *Ae. aegypti formosus*, dark ancestral form of various trophic preferences that lives in sylvatic and urban areas, where the larvae can breed in natural deposits (i.e. hollow rocks, tree holes, leaf axils) and in artificial containers (i.e. water storage, flower pot); and (ii) *Ae. aegypti aegypti*, lighter form known to be domestic and strictly anthropophilic that lives in urban areas, and whose larvae develop in artificial breeding-sites in and around the human habitations (reviewed in Paupy et al. 2010). This latter form is the most medically important in terms of pathogens transmission throughout the tropical and subtropical areas worldwide.

As global trade increased over the centuries, highly human-adapted *Ae. aegypti aegypti* were spread across the world (Brown et al. 2013). The species was likely introduced to the Americas, the Mediterranean basin, and into Eastern and Western Africa at multiple occasions by slave trade ships between the 15th and 18th centuries (Tabachnick 1991). Then, the species spread to Asia probably during the late 19th century, when the first urban dengue emergences were observed in the region (Smith 1956; Tabachnick 1991; Powell and Tabachnick 2013). The transportation of humans and material during the World War have also contributed to the expansion of *Ae. aegypti*, especially in the Pacific Islands (Gubler 1998). After all these

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introductions, *Ae. aegypti* spread very rapidly in each region. Indeed, in the Americas, between the 16th and 18th centuries, the species has spread throughout the continent and already in 1950, all countries except Canada had reported the presence of *Ae. aegypti* (Tabachnick 1991; Bracco et al. 2007). In Europe, by the first half of 20th century, *Ae. aegypti* is reported in Spain, Portugal, Italy and Turkey (reviewed in Medlock et al. 2015). In Asian and Africa the species is found in most of the main urbanized cities at that time.

The increase of mosquito-borne diseases burden that followed the rise of infestation by *Ae. aegypti* and other medically important mosquito vectors (i.e. *Anopheles* sp) worldwide, promoted the implementation of mosquito eradication campaigns. Indeed, during 1950-1960, a mosquito eradication campaign based on the use of dichloro-diphenyl-trichloro-ethane insecticide (DDT) and aiming to decrease the burden of malaria as the final goal was conducted. This campaign along with the improvement of sanitation (i.e. expansion of piped water systems) and local vector control programs, lead to the eradication of *Ae. aegypti* populations from the Mediterranean basin (Gubler 1998). Also in the fifties, the Pan American Health Organization (PAHO) undertook a campaign to eradicate yellow fever in the Americas. By the sixties, this campaign led to the decline of *Ae. aegypti* populations in almost the whole continent except Suriname, Guyana, Venezuela, some Caribbean Islands and the United States, where eradication was not achieved because local mosquitoes were particularly resistant to DDT (Soper 1963; Schatzmayr 2000). Unfortunately, due to the lack of funds and the discovery of a prophylactic mean to fight against yellow fever, the eradication campaign was stopped in 1970. Then, the explosion of intercontinental sea and air transportation have led to a re-infestation of areas where *Ae. aegypti* was previously established as well as the importation of the species into new areas (Gubler 1998; Bracco et al. 2007). Since the re-introduction of *Ae. aegypti* in Brazil in 1975 (Schatzmayr 2000), all the South American countries were re-infested: Bolivia in 1980 (Paupy et al. 2012), Peru in 1984 (Urdaneta-Marquez and Failloux 2011), the North of Argentina in 1986 (Vezzani and Carbajo 2008), Uruguay in 1997 (Salvatella Agrello 1997) and Chile in the 2000s (Bracco et al. 2007). Genetic studies based on mitochondrial and microsatellites markers have revealed the existence of multiple haplotypes and two major genetic lineages of *Ae. aegypti* in Argentina (Dueñas et al. 2009), Brazil (Bracco et al. 2007), Peru (Costa-da-Silva et al. 2005), Venezuela (Herrera et al. 2006), Bolivia (Paupy et al. 2012), Mexico and Central America

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(Gorrochotegui-Escalante et al. 2002), confirming the occurrence of multiple *Ae. aegypti* reintroductions in the Americas from various sources before and after the eradication program. In this sense, two possible scenarios of re-colonization of the Americas by 1970 are generally considered: (i) the spread of mosquitoes from countries where eradication has never been reached (i.e. Venezuela, Suriname, Caribbean, USA) and (ii) the dispersal of *Ae. aegypti* that survived the intensive vector control in countries where the vector was believed "eradicated" (Bracco et al. 2007). In any case, the distribution of *Ae. aegypti* in the Americas by 1995 has reached the same level as before the eradication campaign (Gubler 1998).

Today, *Ae. aegypti* occurs in tropical and subtropical areas (from 45°N to 35°S) of Africa, the Americas, Asia and Oceania (Slosek, 1986; Bracco et al., 2007; Capinha et al., 2014) (Figure 1). In Europe, *Ae. aegypti* is present in Madeira island since 2004 (Portugal), and in the South-East of Russia and Georgia (reviewed in Medlock et al. 2015). In Australia, the distribution of *Ae. aegypti* is confined to Queensland (Barker-Hudson et al. 1988; Muir & Kay 1998). This distribution range is explained by the intolerance of *Ae. agypti* to temperate winters. Indeed, unlike *Ae. albopictus*, *Ae. aegypti* eggs do not enter into diapause during the unfavorable season, restricting the ability for this latter species to establish in more temperate regions (Hawley et al. 1987). Nevertheless, the current global climate change can contribute to an expansion of the distribution range of this species to higher latitudes and this can have important implications regarding *Ae. aegypti*-borne diseases transmission. Already, *Ae. aegypti* populations from temperate localities from Argentina and Uruguay have shown to transmit dengue virus as efficiently as the populations from tropical localities of the same region (Lourenço-de-Oliveira et al. 2013).

3. The globalization of pathogens

3.1. Dengue virus

Dengue virus (DENV) is a positive-sense, single-stranded RNA virus that belongs to the genus *Flavivirus* (family *Flaviviridae*) and is mainly transmitted to humans by the mosquitoes *Ae. aegypti* and *Ae. albopictus* (Figure 2). DENV is responsible for the highest incidence of human morbidity and mortality among all of the flaviviruses, with 50–100 million people becoming infected every year and death rates ranging between 0.03 and 1.4% (Guzman et al. 2010). There

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are four dengue viruses (DENV-1, DENV-2, DENV-3, DENV-4) that are antigenically distinct but have the same epidemiology and cause similar illness in humans (Gubler 2002). Most DENV infections are asymptomatic (Duong et al. 2015) or result in mild dengue fever, which is characterized by the followings symptoms: fever, muscle, joint pain, and rash. However, approximately 0.5% of infections result in the most severe manifestation of the disease, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which can be fatal in 5% of cases (reviewed in Guzmán et al. 2008; Guzman et al. 2010; Vasilakis et al. 2011). In nature, DENV is maintained in two distinct transmission cycles: (i) a sylvatic cycle, with transmission occurring between arboreal *Aedes* mosquitoes and non-human primates in Africa and South east Asia forests, and (ii) an urban cycle, with transmission occurring between domestic and peridomestic *Aedes* mosquitoes (i.e. *Ae. aegypti aegypti* and *Ae. albopictus*) and humans (Vasilakis and Weaver 2008; Vasilakis et al. 2011). The increasing urbanization of Asian and African regions where sylvatic DENV circulates contributed to the spillover of sylvatic DENV into human populations. The DENV emergence from the sylvatic cycle (ancestral) into the evolutionarily and ecologically independent urban cycles occurred independently for each serotype from hundreds to a few thousand years ago (Weaver et al. 2010).

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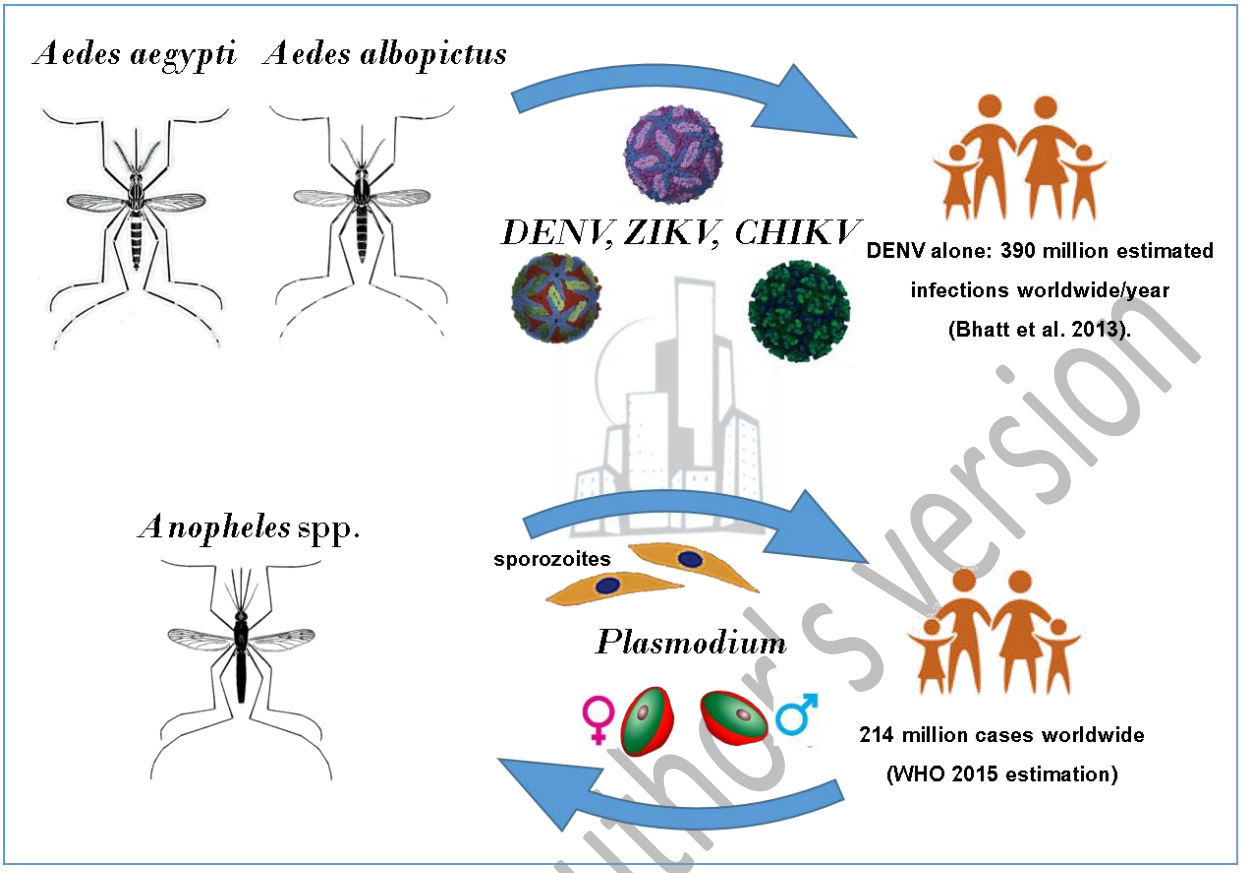

Figure 2. Dengue (DENV), chikungunya (CHIKV), Zika (ZIKV) and *Plasmodium* spp. vector-borne transmission in urban environments. Source for mosquito images: Vichai Malikul/Department of Entomology/Smithsonian Institution.

DENV was spread around the world via navigation and increased trade between the 18th and 19th centuries (Gubler 1998). Dengue was first documented in the Americas, where the first outbreaks of clinical "dengue-like" syndrome were reported in 1635 in Martinique and Guadeloupe, and in 1699 in Panama (Brathwaite et al. 2012). In Asia and Africa, the first reports of major epidemics of an illness thought to possibly be dengue date from 1779 and 1780 (reviewed in Gubler 1998). By the twentieth century, epidemics caused by dengue virus were extensive and took place periodically in most of tropical areas from the world (Gubler 2002; Weaver et al. 2010). The ecologic disruption in the Southeast Asia and Pacific during and following World War II created ideal conditions for increased transmission of mosquito-borne diseases in that region, and it was precisely in this setting that a global pandemic of dengue began: increased epidemic transmission, co-circulation of multiple dengue virus serotypes (hyperendemicity) and the appearance of severe dengue forms DHF and DSS. The first known

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epidemic of DHF occurred in Manila (Philippines) in 1953-1954, and in approximately 20 years the disease spread throughout Southeast Asia and the Pacific Islands becoming a leading cause of hospitalization and death among children in the region (reviewed in Gubler 1998).

In the Americas, the development of air transport has led to the re-settlement and re-introduction of *Ae. aegypti* into new areas following the eradication program conducted during the fifties, and to a subsequent emergence of DENV outbreaks in Brazil (Schatzmayr, 2000), Bolivia, Paraguay, Chile, Argentina (Vezzani and Carbajo 2008), Cuba, Puerto Rico, French Guiana and other localities (reviewed in Urdaneta-Marquez and Failloux 2010). During these epidemics, the four serotypes described for DENV invaded the Americas leading to an increased periodicity of outbreaks and the aggravation of patient clinical symptoms. In 1981, a new DENV-2 strain belonging to the South East Asia genotype (SEA) was introduced into Cuba and responsible of the first severe dengue hemorrhagic fever (DHF) outbreak and dengue shock syndrome (DSS) reported in western hemisphere causing 158 deaths (Kouri et al. 1987). Since its introduction in the Americas, the SEA genotype of DENV has been responsible for severe outbreaks involving high numbers of DHF cases in several countries, and has displaced the American genotype of DENV which previously circulated in the continent (Rico-Hesse et al. 1997; Guzman and Kouri 2008). This displacement seems associated to an enhanced replication and dissemination in *Ae. aegypti* mosquitoes of DENV-2 strains belonging to the SEA genotype in comparison with those of the American genotype (Anderson and Rico-Hesse 2006), highlithing *in senso lato* the role of arboviruses genetic variability on the vector-pathogen interactions and its potential epidemiological implications.

The current situation regarding dengue is compelling (Figure 3). Before 1970, only 9 countries had experienced severe dengue epidemics and today the disease is endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. One recent estimate indicates 390 million dengue infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease) (Bhatt et al. 2013). The Americas, South-East Asia and Western Pacific regions are the most seriously affected with more than 3 million cases reported in 2013. In 2015 the number of cases in these regions increased, with 2.35 million of DENV cases

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reported in the Americas alone of which 10 200 cases were diagnosed as severe dengue causing 1181 deaths (WHO 2016a). The threat of a possible outbreak of dengue fever in Europe is more real than ever as local transmission was reported for the first time in France and Croatia in 2010 (Gjenero-Margan et al. 2011; La Ruche et al. 2010), an outbreak took place in Madeira Island (Portugal) in 2012 and since, at least 10 European countries have reported imported dengue cases (WHO 2016a). These numbers witnessed the weakness of vector control activities in the region, as well as the receptiveness of local mosquitoes to this arbovirus.

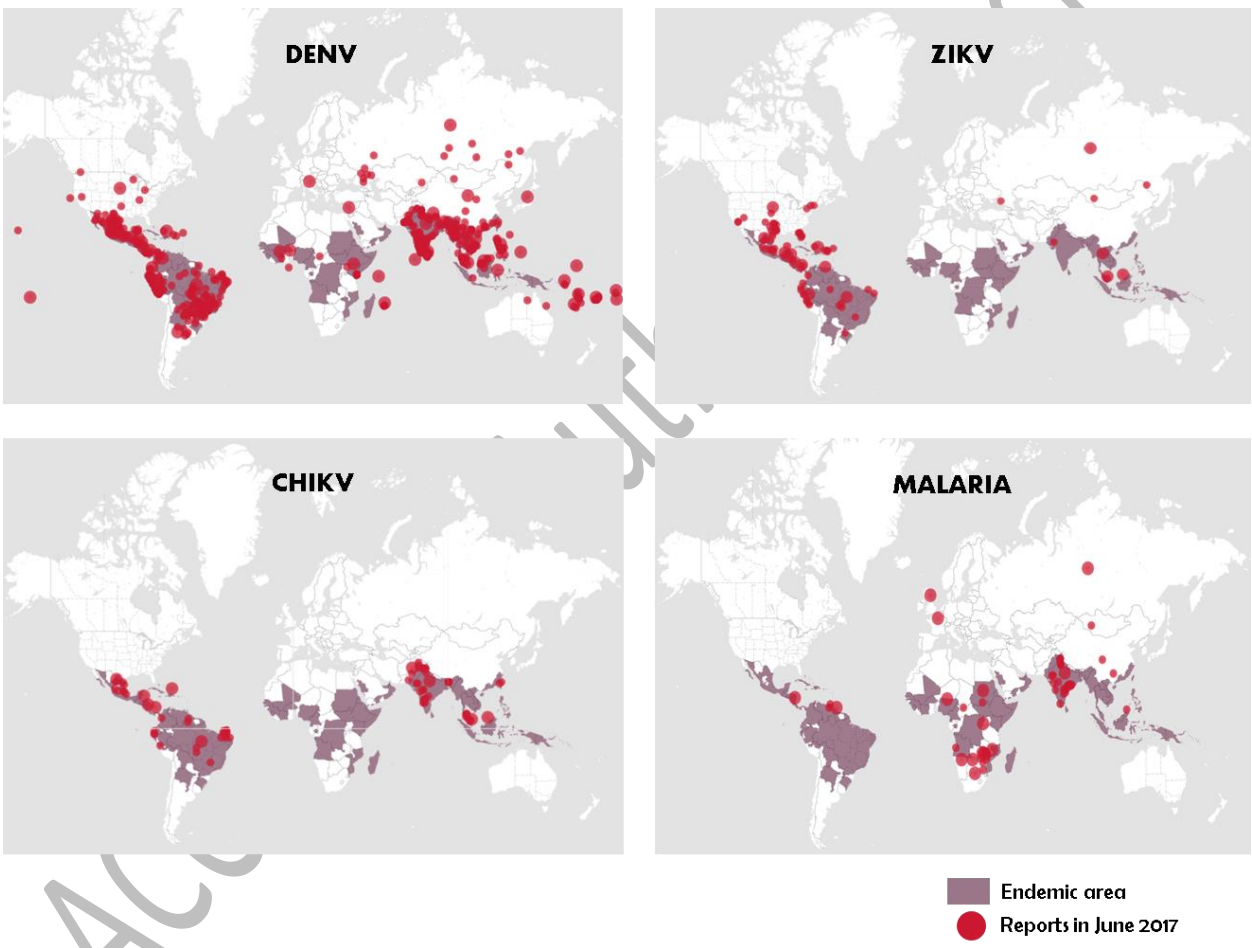

Figure 3. Current global distribution and recent reports (June 2017) of dengue virus (DENV), zika virus (ZIKV), chikungunya virus (CHIKV) and malaria. Based on Health Maps statistics (http://www.healthmap.org).

3.2. Zika virus

Zika virus (ZIKV) is a positive-sense, single-stranded RNA *Flavirirus* (family *Flaviviridae*) of

10,794nt (Kuno and Chang, 2007) that was first isolated from a rhesus monkey in 1947 in the Zika forest near Kampala, Uganda (Dick 1952). Some reports indicates that ZIKV can occasionally be sexually transmitted between humans (Frank et al. 2016; WHO 2016b), but the most important transmission mode remains the vectorial transmission via the bite of infected mosquito vectors (Figure 2). The primary vectors of ZIKV in Africa are thought to be *Aedes* mosquitoes, which is supported by viral isolations from field-caught mosquitoes such as *Aedes africanus*, *Aedes apicoargenteus* (McCrae and Kirya, 1982), *Aedes luteocephalus* (Fagbami 1979), *Aedes furcifer*, *Aedes taylori*, and *Aedes vittatus* (Diallo et al. 2014). The human-biting mosquitoes *Ae. aegypti* and *Ae. albopictus* have been proven to be laboratory-competent vectors of ZIKV (Li et al. 2012; Wong et al. 2013; Chouin-Carneiro et al. 2016), and viral isolations were reported from both species in the wild highlighting their possible major role on the transmission of this virus (Marchette et al. 1969; Grard et al. 2014; Diallo et al. 2014). As for DENV, ~80% of ZIKV infections are asymptomatic and when symptoms occurs, they are mild including fever, itchy maculopapular rash, conjunctivitis, joints arthralgia, myalgia and headache with retro-orbital pain (reviewed in Sampathkumar and Sanchez, 2016). However, recent ZIKV infections have been associated with more severe disease outcomes with neurological or auto-immune complications such as Guillain-Barre syndrome (GBS) (Oehler et al. 2014; Cao-Lormeau et al. 2016) and microcephaly (ECDC 2015; Oliveira-Melo et al. 2016).

Since its isolation, only sporadic ZIKV cases were reported in Africa and Southeast Asia until 2007, when the first large outbreak occurred in the Yap State (Micronesia), involving approximately three quarters of Yap residents (Duffy et al. 2009). Then the virus spread to French Polynesia, where it caused an outbreak from October 2013 to April 2014 involving approximately 32 000 suspected cases. During this outbreak, the virus was associated with GBS for the first time, as an unusual and unprecedented increase (20-fold more than expected) of this pathology was recorded in that period (Cao-Lormeau et al. 2016). Furthermore, an increase of new-born microcephaly cases also occurred during this ZIKV outbreak (Cauchemez et al. 2016). Subsequently, the virus spread to New Caledonia, Easter Island and the Cook Islands in 2014 (Dupont-rouzeyrol et al. 2015; Musso et al. 2016; Tognarelli et al. 2016). In May 2015, the virus was first reported in Brazil (Campos et al. 2015), where an unprecedented outbreak began and the first association between ZIKV and microcephaly arose (ECDC 2015). Indeed, around 150

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confirmed microcephaly cases were reported in Brazil between 2013 and 2014 prior to ZIKV arrival in the country, whereas from 22 October 2015 to 9 July 2016 (during the ZIKV outbreak), the number of cases dramatically increased up to 1687 (PAHO / WHO 2016). Since then, ZIKV has explosively spread throughout the Americas and today 84 countries, territories or subnational areas have reported evidence of vector-borne Zika virus transmission worldwide (WHO 2017).

As for dengue, chikungunya, and other mosquito-borne pathogens, the intercontinental travel, as well as the high densities and susceptibility of local human and mosquito populations to ZIKV, have importantly contributed to the spread of this virus that has now reached pandemic proportions (Figure 3). The organization of supranational events such as the World Cup soccer games and the World Sprint Championships, involving several thousands of visitors from different countries, may have also contributed to the transcontinental movement of ZIKV from the Pacific Island to Brazil (Weaver et al. 2016). In addition, some authors pointed out that climatic conditions may have played a role in the recent explosive spread of Zika virus in South America, as it seems that El Niño caused exceptional climatic conditions in northeastern South America. Indeed, certain regions from Southern Brazil and Uruguay had an unusually wet winter followed by a warm summer (Paz and Semenza, 2016). Finally, when ZIKV evolves it creates new molecular relationships with factors of the mosquito vector and/or the human host (Weaver et al. 2016). Thus, it is also possible than factors linked to these evolution and the interactions with the encountered mosquito vectors and vertebrate hosts, may have played an important role on ZIKV expansions since 2007. Nevertheless, knowledge about this issues are still scarce for ZIKV, and deserve therefore to be more deeply investigated in order to better understand and perhaps predict the epidemiology of this intriguing virus.

3.3. Chikungunya

Chikungunya (CHIK) is one of the major emerging diseases of the past 50 years, with a global distribution (Figure 3) and the ability to rapidly move into new regions and cause epidemic disease with high attack rates. Chikungunya is an acute viral disease that has been identified in more than 103 countries in Asia, Africa, Europe - and now the Americas (Centers for Disease Control and Prevention (CDC) 2016). Phylogenetic studies suggest that the virus originated in West Africa, potentially within a zoonotic cycle that included monkeys, and/or rodents, squirrels,

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and birds (Chevillon et al. 2008). From this source, it appears to have spread to Central, Southern, and East Africa (ECSA clade), and from there moved to Asia (Asian clade) and to the Indian Ocean Islands. In contrast to the ecologic picture seen in West Africa, illness in Asia and the Indian Ocean region has generally appeared in the setting of large, sporadic outbreaks. In 2005-2006, approximately 272,000 people were infected on the Islands of Reunion and Mauritius, followed, in the same year by an outbreak in India where close to 1.5 million people were infected (WHO 2007). In 2007, the first European CHIK outbreak took place in Italy (Rezza et al. 2007), and subsequently, autochthonous cases have been reported in France in 2010 and 2014 (Grandadam et al. 2011; Delisle et al. 2015). In December 2013, CHIK arrives to the Americas and rapidly spread throughout the continent reaching more than 46 countries and/or territories (http://www.cdc.gov/chikungunya/geo/index.html; Figure 3). Today, estimates indicate that close to 39% of the global population live in areas with a high risk of CHIK transmission and between 33,000 to 93,000 clinical cases occur *per annum* with case fatality rates between 0.1 and 2.8% (Labeaud et al. 2011). It is also believed that the reported cases of CHIK represent just a fraction of the cases which actually occur, due both to underreporting and a relatively high rate of asymptomatic infection (Nakkhara et al. 2013; Appassakij et al. 2013). Although the fatality rates associated with CHIK infections are low, morbidity is high and the DALY's associated with CHIKV infections make it of significant concern for public health agencies.

Illness is characterized by acute onset of high fever, with potentially disabling polyarthralgias. In most instances symptoms of the disease resolve spontaneously within 7-10 days. However, depending on strain and host population, joint symptoms can persist for months to years. In a case series from Marseille (patients returning from the Indian Ocean region), 46% of patients reported persistence of joint symptoms for at least 6 months after acute illness (Simon et al. 2007); in a study from South Africa, 12% of patients reported arthralgias 3 years after acute illness (Brighton et al. 1983). There is also increasing recognition of more serious complications and deaths, particularly among children, including encephalitis, febrile seizures, and acute flaccid paralysis. It is unclear whether these more severe symptoms are the result of better reporting, in a setting where diagnostic tests are available; are a function of increasing virulence of the strain; and/or reflect changing host immunologic responses. The strain that has reached the

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Caribbean in December of 2013 belongs to the Asian clade (Lanciotti and Valadere, 2014; Leparc-Goffart et al. 2014).

The transmission of CHIK may be urban or sylvatic, especially in Africa where several arboreal *Aedes* species are involved in a sylvatic transmission cycle (Diallo et al. 1999). In the urban cycle (Figure 2), transmission is often sustained by the peri-domestic *Ae. aegypti* and *Ae. albopictus* (Reiter et al. 2006), although other local *Aedes* mosquito species may also play a role in CHIKV transmission (Diallo et al. 1999). However, in new areas to which CHIK spreads there is a need for detailed investigations to confirm the role of other local mosquito species in CHIK transmission dynamics. Both mosquito species are known to co-occur in rural and urban environments (Juliano et al. 2004) although *Ae. aegypti* predominates in urban settings and *Ae. albopictus* in rural settings (Lourenco-de-Oliveira et al. 2004). There is also evidence that *Ae. albopictus* is predominant in many environments where they co-occur (Braks et al. 2004). The efficiency of viral transmission by either vector seems to be influenced by single point mutations in the viral envelope protein and it was shown in the Indian Ocean outbreak that a mutation in the viral envelope protein (A226V mutation) led to increased fitness of CHIKV in *Ae. albopictus* (Tsetsarkin et al. 2007; Vazeille et al. 2007) that enabled its rapid expansion. Other investigators have found that *Ae. aegypti* has a better transmission efficiency for the original CHIK viral strain (African strain) than the Asian genotype (Vega-Rua et al. 2014). As previously stated, the extensive distribution of *Ae. aegypti* and *Ae. albopictus* in many parts of the world has increased the risk associated with arbovirus transmission (Gratz 2004).

3.4 Malaria

Malaria, a mosquito-borne disease caused by a parasitic protozoan in the genus *Plasmodium*, continues to present a global public health threat with a presence in close to 100 countries around the world (Figure 3). There are more than 120 species of *Plasmodium*, but only five are infectious to humans. Four of these species cause widespread infections in humans including *P. falciparum* that is responsible for the most severe malaria, and *P. vivax* is the second important cause of malaria and is most prevalent in Asia, the Americas and the Pacific and *Plasmodium ovale* and *Plasmodium malariae*, both of which occur in Africa, particularly in Central and

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Western Africa. The little known *Plasmodium knowlesi*, is a zoonotic malaria infection commonly found in Gorillas and chimps, but also has the ability to infect humans (CDC 2015).

The public health importance of malaria can be surmised by the World Health Organization that estimates that 3.3 billion people are at risk of malaria infection world-wide (30% of which are at high risk) (WHO 2015b). Estimates available indicate that more than 200 million malaria infections occurred globally with approximately half a million deaths, most of which were in Africa. Of these deaths, most were children under 5 years old (WHO 2015a). In the Americas with a combined population of 895 million people, 61% of the population is at a high risk of malaria infection (WHO 2015b). More than 3 million cases of malaria occur in the Americas, of which 39% were reportedly due to *P. falciparum* (Hay et al. 2010).

Anopheles mosquitoes are the primary vectors of malaria (Figure 2) with at least 40 species of Anopheles mosquitoes having been identified to be capable of transmitting malaria. In Africa, the predominant mosquito vector is *Anopheles gambiae* and *Anopheles funestus*. The ranges of these mosquito vectors extend from South America to the Sahel in western and northern Africa. In the Americas and Asia, several species complexes are involved the transmission of malaria. The distribution range of *Anopheles albimanus* is expected to increase in the face of land cover changes in South America (Alimi et al. 2015). In Asia, *Anopheles stephensi* plays the critical role in malaria transmission. The distribution of malaria vectors is influenced in part by the availability of breeding sites, host blood mean sources, which in turn affects malaria transmission. The transmission dynamics of malaria varies depending on vector behavior. In most areas of sub-Saharan Africa, both indoor and outdoor biting malaria vectors sustain transmission. The fact that transmission occurs both indoors and outdoors has complicated the IRS program for malaria control, leading to the inclusion of outdoor spraying for malaria control. In many malaria endemic areas of the world, great strides have been made in the reducing malaria incidences, however measures that have been put in place must be sustained because historical evidence has shown that malaria cases can resurge even in places where it was previously brought under control. Some of the factors that are responsible for the resurgence of malaria include resistance to insecticides and to antimalarial medications. The classic example of where malaria was controlled and later resurged is Sri Lanka where in the 1970's malaria levels

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were brought to down to less than 1%, and due to the lack of sustainable control measures coupled with insecticide resistance, there was a resurgence of malaria (Dutt et al. 2010). In Zanzibar, the use of effective medications and widespread ownership of ITN's lead to significant reductions of malaria. The continued high coverage of malaria interventions should be continued to sustain the gains. However, as has been observed in many countries, resurgences in malaria has been most caused by a lack of resources (Cohen et al. 2012).

In recent years, increasing temperatures have resulted in the malaria vectors shifting from their traditional locations to invade new zones (Ngarakana-Gwasira et al. 2016). In fact, climate change is considered the most important factor that might influence malaria transmission in high elevation areas where malaria transmission could never be sustained. In other instances, the changes in land use patterns, including agricultural developments, deforestation and large scale infrastructural developments such as the development of dams and hydroelectric power plants have result in the creation of favorable habitats for malaria mosquitoes breeding, which in turn has led to an increase in malaria transmission (Tompkins and Caporaso 2016). In addition, such developments attract human settlements from people moving in search of jobs and livelihoods.

4. Mosquito Vector Control Strategies

Over the first half of the 20th century when organized mosquito control was started, there was heavy reliance on chemical insecticides (Simmons and Upholt 1951). One of the most controversial insecticides ever used in mosquito control was the chemical known as dichloro-diphenyl-trichloroethane or simply DDT. It was an environmentally safe chemical because of its persistence in the environment and was therefore taken up in the food chain. Yet it was able to reduce the burden of major vector borne diseases in large parts of the world. DDT was particularly effective in reducing the burden of malaria in the world during the global push by the WHO malaria elimination program of the 1960's (Najera et al. 2011). The side effect associated with DDT use (environmental side effects and persistence), sparked (spurred) the search for insecticides that were environmentally benign. Many classes of insecticides have been developed since that are very effective in controlling mosquitoes but with less environmental impact on non-target species and in contaminating soil and water. It is also very important to minimize the

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development of insecticide resistance to these chemicals. Therefore, strategies have been implemented to supplement, and in some cases, totally replace the use of insecticides that have been rendered ineffective due to resistance. The WHO panel of experts on mosquito control has recommended the use of Integrated vector management (IVM), which essentially provides guiding principles for the control of mosquito vectors with minimal impact to the environment (WHO 2004). Integrated Vector Management is an old concept that was first developed and applied by William Crawford Gorgas to eliminate Yellow Fever from Havana in the summer of 1901, and to control malaria transmission during construction of the Panama Canal. Its principal components are complementary keeping infected mosquitoes away from people with bed nets and spraying residual insecticides to kill infected mosquitoes, as well as environmental modification and larviciding that would reduce the sources of mosquitoes by removing stagnant water and other breeding sites (Figure 4).

Figure 4. Surveillance and mechanical destruction of *Aedes aegypti* breeding sites in Saint Martin Island by workers from the Regional Agency of Health and the Institut Pasteur of Guadeloupe. Photo: Laboratory of Medical Entomology-Institut Pasteur of Guadeloupe.

4.1 Insecticides

Mosquito control in the pre-DDT era relied heavily on very toxic chemical products. In the US, as in other parts of the world, there was extensive use of Paris green and petroleum by-products (Simmons and Upholt 1951). With the discovery of DDT as pesticide and its widespread application, it enabled the eradication of many vector borne diseases, and most notably malaria (Simmons and Upholt 1951). After its introduction in 1946, the detrimental effects of DDT were made public leading to a re-evaluation of its use. The United States Environmental Protection Agency has classified DDT and its metabolites, DDE and DDD, as persistent chemicals in the environment because they do not biodegrade and can take nearly 15 years before they are no

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longer present (EPA Division Health and Ecological Criteria 2008). There is also the risk of bioaccumulation in the food chain, resulting in high exposure levels for humans leading to damage to the liver, nervous system, and reproductive system (EPA Division Health and Ecological Criteria 2008). In an effort to protect people and the environment, the Stockholm Convention on Persistent Organic Pollutants restricted the use of DDT in 1996, when they stated that as long as "locally safe, effective and affordable alternatives are available" then DDT should not be used. However, in 2004, DDT was restricted to malaria control in areas where local, safe and effective and affordable alternatives were unavailable. With many countries banning the use of DDT, safer chemical alternatives that were benign to the environment but equally effective and mosquito control were developed. Several insecticide classes have been developed including chemical such as pyrethroids, carbamates, organophosphates, insect growth regulators (IGR's) and biological such as *Bacillus thuringiensis* (var *israelensis*), RNAi, and other that are biological classes of insecticides. Many of these insecticides have been used very effectively in the control of mosquito vectors and vector borne disease, but their use has led to the appearance of insecticide resistance in many mosquito vector populations (Karunamoorthi and Sabesan 2013), which highlight the need to review the current vector control strategies regarding insecticides.

4.2 Environmental management

Environmental management for mosquito control according to the World Health Organization (WHO) is defined as the planning, organization, implementation and monitoring of activities that modify and/or manipulate environmental factors or their interaction with man with a view to preventing or minimizing insect vector propagation and reducing man-vector-pathogen contact (WHO 2004). It entails either or both of the following: a) environmental modification - permanent infrastructural changes of a capital-intensive nature, b) environmental manipulation - recurrent actions aimed at achieving unfavorable conditions for vector breeding. In the pre-DDT era, much of the major vector control activities consisted of both environmental modification and manipulation and changes to human habitations and behavior. Drainage of potential mosquitoes breeding sites (wetlands, marshes) was undertaken largely by digging of canals. However, since wetlands are recognized as ecosystems themselves that are needed to protect the biodiversity, changes have been made in how wetland ecosystems are managed for vector borne disease

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control. Proper management and implementation of major environmental manipulation projects is needed for protecting the environment while at the same time ridding the mosquito problem.

4.3 Genetic tools

The idea of genetic control of vector borne diseases was first used effectively to control the sleeping sickness in Tanzania when sterile hybrids were created by the interspecific mating of *Glossina swynnertoni* a vector of Trypanosomiasis with a non-vector *Glossina morstians centralis* (Vanderplank 1947; Vanderplank 1948). In these crosses, males were sterile and female hybrids were partially sterile with the idea that gradually, the entire population would be replaced by these sterile and non-vector species. This set the stage for the use of genetic strategies for vector borne disease control. Several methods have been tried that utilize genetic mutations or modifications to reduce mosquito reproduction including sterile insect technique, the release of Insects with Dominant Lethality (RIDL) (Thomas et al. 2000) and the use of the endosymbiotic bacteria *Wolbachia* (Slatko et al. 2014; Caragata et al. 2016) among others. The control of mosquito populations through population replacement with mosquitoes that are either refractory to the pathogens, or that do not produce viable offspring might help in the control of mosquito borne diseases (Wood 2005). The use of RIDL technique developed and tested by Oxitec© has been shown to induce premature death in progeny and to have very good results in mosquito population suppression (Atkinson et al. 2007). However, the use of genetic modified mosquitoes is a highly controversial issue that is hampered by different legislations depending on the region. In addition, as the RIDL approach is not self-sustainable (i.e. need to continuously produce and release RIDL mosquitoes), its application seem more suitable in small island rather than in large continental areas. *Wolbachia*, an endosymbiote rickettsia-like bacteria that naturally infects cytoplasmic vacuoles of insects including mosquitoes (Beard et al. 1998), has the ability to alter their reproduction, and has also shown great promise in the fight against arboviral diseases. The *Wolbachia* infection causes cytoplasmic incompatibility and therefore mosquitoes that are incompatible will not have viable offspring. For a detailed review of the *Wolbachia* and mechanisms of CI and how it has been used as a paratransgenesis tool, refer to (Beard et al. 1998). Many field trials with *Wolbachia*-infected mosquitoes for the control of dengue have been tried out and the evidence is strong that *Wolbachia* infected mosquito reduce the transmission potential of Dengue (Ye et al. 2015; Lambrechts et al. 2015). In addition, evidence from other

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studies indicate that *Wolbachia*-infected mosquitoes reduces or blocks Chikungunya and Zika transmission(Aliota et al. 2016a; Aliota et al. 2016b). However, other studies have shown that *Wolbachia* might enhance infection with WNV (Dodson et al. 2014) in *Wolbachia*-infected *Culex tarsalis*. Furthermore, as *Wolbachia*-infected mosquitoes are laboratory strains that are probably susceptible to insecticides, the success of this approach requires the suspension of insecticide treatments in concerned localities. Otherwise, *Wolbachia*-infected mosquitoes will be all killed after the first insecticide treatment and only the resistant wild-type local mosquitoes will survive.

4.4. Future of vector control

As vector borne disease spread across the globe and into new areas, it will be necessary to apply a multiplicity of control tools available but also to develop new tools of greater specificity and respectful of the environment. The idea of integrating several vector control tools is not a new one but the concept of rational decision-making process for optimal use of resources for vector control that forms the core of IVM is key to the sustainability of vector management approaches (WHO 2004). In the past, it has been difficult to implement the IVM strategy but the refining of the different components and the discovery of new tools should allow that many vector control programs adopt IVM. These components include collaboration, integrated approach, evidence based decision making, capacity building and advocacy, social mobilization and legislation.

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