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REVIEW

Emerging Mosquito-Borne Viruses Linked to *Aedes aegypti* and *Aedes albopictus*: Global Status and Preventive Strategies

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Abstract

Emerging mosquito-borne viruses continue to cause serious health problems and economic burden among billions of people living in and near the tropical belt of the world. The highly invasive mosquito species *Aedes aegypti* and *Aedes albopictus* have successively invaded and expanded their presence as key vectors of Chikungunya virus, dengue virus, yellow fever virus, and Zika virus, and that has consecutively led to frequent outbreaks of the corresponding viral diseases. Of note, these two mosquito species have gradually adapted to the changing weather and environmental conditions leading to a shift in the epidemiology of the viral diseases, and facilitated their establishment in new ecozones inhabited by immunologically naive human populations. Many abilities of *Ae. aegypti* and *Ae. albopictus*, as vectors of significant arbovirus pathogens, may affect the infection and transmission rates after a bloodmeal, and may influence the vector competence for either virus. We highlight that many collaborating risk factors, for example, the global transportation systems may result in sporadic and more local outbreaks caused by mosquito-borne viruses related to *Ae. aegypti* and/or *Ae. albopictus*. Those local outbreaks could in synergy grow and produce larger epidemics with pandemic characters. There is an urgent need for improved surveillance of vector populations, human cases, and reliable prediction models. In summary, we recommend new and innovative strategies for the prevention of these types of infections.

Keywords: arboviruses, *Aedes*, vector control, vectorial capacity and pandemic

Background

Since 1940s more than 60% of the ~400 emerging infectious diseases have been identified as zoonotic (Rohr et al. 2019). Specific geographical regions and interfaces between people, wildlife, livestock, and the environment have been identified as the origin of zoonotic infectious diseases, and should be targets for a more intense surveillance. There is a general agreement that vector-borne diseases are susceptible to weather and environmental changes, for instance, increased temperatures, excessive rainfall, and high humidity that allows diseases to be spread to regions where new vectors may act as carriers. Of interest, novel pathogens most likely to emerge are: (1) RNA viruses from nonhuman reservoirs; (2) viruses capable to exploiting a range of different hosts, and (3) viruses able to increase their transmission potential.

By calculating the universe of viruses yet to be found, it is speculated that each of the known 5,486 mammal species host an average 58 unique viruses unshared with other

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species. However, viruses pathogenic to humans represent only a small proportion. From this constantly evolving universe of vertebrate viruses, perhaps two or three are recognized every year to have crossed the species barrier (Rosenberg 2015).

Even with the current advances in diagnostic technology, there is still a likelihood that some pathogens (novel, emerging, and re-emerging) remain undetected with some being misdiagnosed. For example, the initial emergence of Chikungunya virus (CHIKV) in the Western Hemisphere in infecting a population of 1 million (Staples and Fischer 2014), the discovery of Lujo virus undescribed arenavirus belonging to the Old World group in Zambia (Briese et al. 2009), and the detection of Middle East respiratory syndrome coronavirus (MERS-CoV) in the Middle East (Zaki et al. 2012, World Health Organization 2014a).

Aedes aegypti and *Aedes albopictus* are considered as the most notable vectors of arthropod-borne viruses of public health importance (Lwande et al. 2020). These mosquito species play significant roles in the propagation and spread of emerging and re-emerging infections such as dengue and yellow fever, which are annually contributing to an estimated 25,000 and 30,000 deaths, respectively (Gubler 1998, Mutebi and Barrett 2002, Chiu et al. 2005, Lang 2012).

CHIKV, dengue virus (DENV), yellow fever virus (YFV), and Zika virus (ZIKV) are four important mosquito-borne viruses with nearly global presence, all vectored primarily by *Ae. aegypti* and *Ae. albopictus*. They are known to cause considerable disease burden and significant cost for health care, and they contribute to numerous hospital admissions. For many years these arboviruses have been restricted to particular regions, but currently spreading and establishing in new ecological zones causing outbreaks in many continents (Lwande et al. 2020).

Since the 1950s CHIKV has been observed to circulate in developing countries causing occasional outbreaks in Asia and Africa (Zeller et al. 2016). The disease is now spreading to additional areas causing local transmission in countries of the Americas with millions of infections (Burt et al. 2012, Seppa and Hirshfeld 2015). The introduction of CHIKV from tropical to more temperate regions, such as the United States and Europe, has been facilitated primarily by the highly invasive *Ae. albopictus* that has colonized many new regions recently (Rezza et al. 2007, Lara et al. 2014, Delisle et al. 2015, Kraemer et al. 2015, Venturi et al. 2017, Calba et al. 2018).

DENV is presently considered one of the most important arbovirus since more than half of the world's population live in risk areas of contracting DENV (Gubler 2002, 2011, World Health Organization 2012). A 30-fold increase of DENV cases over the past three decades have been reported with ~390 million infections annually (World Health Organization 2009a, Bhatt et al. 2013). YFV was originally discovered in Africa and introduced to South America through the slave trade in the 15th century (Chippaux and Chippaux 2018). According to World Health Organization (WHO), ~200,000 yellow fever cases and 30,000 deaths occur annually with a majority (90%) originating from Africa (Mutebi and Barrett 2002). ZIKV is continuously endemic in Africa. The first isolation was made from Rhesus monkeys in Uganda more than 70 years ago, which was followed by human isolation in Tanzania 1952 (Dick et al. 1952, Smithburn 1952).

The virus gained attention during the 2015–2016 outbreak in the Americas prompting a public health emergency with >200,000 reported cases in Brazil and 8000 babies with congenital malformations linked to this virus infection (Tambo et al. 2016). In 2016–2017 local transmission of ZIKV was also reported from the United States, India (2018), and France in October 2019 (Giron et al. 2019). Like CHIKV, DENV, and YFV, ZIKV is transmitted by *Ae. aegypti* and *Ae. albopictus* (Leta et al. 2018).

Multiple factors working in concert are driving the geographic expansion of the mosquito vectors and their accompanying viruses. Arboviruses circulate constantly between mosquitoes and human hosts through the almost unlimited access of reservoirs. Given that many of these viruses cocirculate in many urban areas/regions, and the capability of individual mosquitoes to transmit more than one virus has influenced the infection rates and the impact on the epidemiology of the corresponding diseases. Such factors concurrently imply scenarios, often with serious public health consequences, that may lead to mosquito-driven pandemics characterized by synchronous infections, sometimes including more than one arbovirus.

Globalization has increased the risk for exposure of the world to emerging infectious diseases because more people are being exposed. In recent years we have seen transmission of traditional tropical diseases to temperate zones. Some examples are the introduction of CHIKV and DENV to the Americas, CHIKV in Italy (2007), and local transmission of dengue fever (DF) in France and Croatia (2010). An autochthonous case of ZIKV was reported in France (2019) as the first ZIKV case in Europe. Other observations are the increased number of imported YF cases in areas of southern Europe, probably through unvaccinated travelers from South America, specifically during the 2017–2018 outbreak in Brazil (Gossner et al. 2018). These occasional introductions increase the likelihood of local transmission if competent virus vectors are present (Gossner et al. 2018).

In 2016 it was reported that YFV was exported from Africa to Asia where ~2 billion immunologically naive people live in areas inhabited by *Ae. aegypti* (Wilder-Smith and Leong 2017). Why YF has not (yet) become endemic in Asia remains a mystery (Wilder-Smith et al. 2019). With the geographic expansion of *Ae. aegypti* and *Ae. albopictus* to new areas, including southern Europe, North America, Oceania, and Asia, the risk for local transmission of accompanying arboviruses increases (Monath and Vasconcelos 2015). It is likely that *Ae. albopictus*, a widely distributed vector, will become more involved in the transmission of these viruses, and perhaps play a more important virus vector in the future.

''Our previous review deals with the entomological perspective of vector ecology including types of habitat exploited by *Ae. aegypti* and *Ae. albopictus*, and expose the potential risk to global health including some recommendations for vector control and risk minimization'' (Lwande et al. 2020). This review focuses on CHIKV, DENV, YFV, and ZIKV transmitted by *Ae. aegypti* and *Ae. albopictus*. The four viruses are known to cause considerable disease burden and cost to health care and contribute to numerous hospital admissions. Having an in-depth understanding of the arbovirus transmission dynamics coupled with vector ecology and evolution will foster improvement of mitigation toward emerging infections. Strengthening the public health surveillance worldwide and providing cross-border early

warning systems has been the prime recommendation by many expert groups, but the emergence of novel pandemic agents is unpredictable.

Technological advances in modeling, diagnostics, communication, and informatics enable more focused global surveillance of emerging and previously unknown infections in human beings and other species. In this article, we discuss some global consequences of important emerging mosquito-borne viruses vectored by *Ae. albopictus* and *Ae. aegypti.*

Global Disease Status of Emerging Mosquito-Borne Viruses Transmitted by *Ae. aegypti* and *Ae. albopictus*

Chikungunya virus

CHIKV was first isolated in 1953 from the blood of a patient during an outbreak in Tanzania (Ross 1956). Since then, multiple outbreaks of CHIKV, and isolations of CHIKV have been documented in many continents (Table 1 and Supplementary Table S1).

There is only one serotype of CHIKV, and the patients usually recover after a short period of illness while joint pains may last over a long period of time (Pialoux et al. 2007). Characteristic symptoms occur typically 3–7 days postinfection and include acute febrile illness with striking fever, headache, muscle and joint pain, swellings, and rash. A proportion of the cases, ∼15%, progress into a chronic disease that may persist for longer periods of time (Taubitz et al. 2007, Manimunda et al. 2010, Dupuis-Maguiraga et al. 2012, Makhani et al. 2019). CHIKV has also been associated with long-term chronic arthralgia that can persist for years (Schilte et al. 2013). In rare circumstances, the virus may cause complications in the eye, heart, and nervous system (Robin et al. 2008).

CHIKV epidemics in affected regions are associated with considerable high infection rates. Of note, one third of the people on the Réunion Island, ∼775,000 inhabitants, were infected during the outbreaks in 2005–2006. Subsequently, also other countries adjacent to the Réunion Island became affected as a result of the first outbreak (Renault et al. 2007). Of interest, *Ae. aegypti* was known to be the principal vector for CHIKV before an amino acid substitution in the envelope gene occurred and abruptly changed the adaptation and transmission from *Ae. aegypti* to *Ae. albopictus* (Tsetsarkin et al. 2007). By the year 2005 the combined vector competence by the two *Aedes* species elevated the number of CHIKF cases across South East Asia to ∼2 million (Bhatia et al. 2014, Leo et al. 2009, World Health Organization 2014b).

In 2007, the disease suddenly appeared in Ravenna, north east of Italy, where 205 cases were confirmed positive for CHIKV (Rezza et al. 2007). Later, in the past decade, the world has witnessed the spread of CHIKV into the western hemisphere, especially to the Caribbean islands where >440,000 cases of CHIKF were recorded (Morrison 2014). Transportation systems of humans and goods are known to enhance the incursion of the virus into new areas mainly, through viremic travelers and trade of used tires (Lanciotti et al. 2007, Gibney et al. 2011, Bennett et al. 2019). As of 2015, >1.3 million cases have been documented in the Americas (Weaver and Lecuit 2015). Worldwide, >100 countries have been affected by CHIKV.

To date no efficacious vaccines against CHIKV have been approved. At present, vaccine development and trails include live attenuated virus vaccines (Weiss et al. 2020) as well a substitute-based virus-like particles and subunit vaccines. Many of those have yielded promising results (Chen et al. 2020, Stapleford and Mulligan 2020).

Dengue virus

Dengue infections are mostly asymptomatic but some patients' present milder forms of the illness referred as DF. More severe cases are denoted dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) (George 1997).

DENV like most arboviruses is not transmitted directly between humans, except for a few occasional cases such as mother to unborn child, tissue transplantations, or by blood transfusions. Of interest, during the large epidemic of DENV-4 in Brazil (2012) ∼0.5% of blood donations were found DENV RNA positive and approximately one third thereof resulted in transfusion-transmitted DF (Sabino et al. 2016). However, viremic donations are rare relative to other clinical cases (Busch et al. 2016). Possible sexual transmission of DF has also been reported (Liew 2020).

Dengue is considered the most rapidly spreading mosquito-borne disease in the world (Table 1 and Supplementary Table S2). DENV is a considerable problem in Africa, Americas including the Caribbean islands, Southeast Asia, Australia, and the Pacific islands, all together involving >100 endemic countries (Gubler 1998). According to estimates by WHO, ∼2.5 billion people are at risk of contracting DF, and between 50 and 528 million people are infected each year, including ∼10,000–20,000 mortalities (Henchal and Putnak 1990, Bhatt et al. 2013, Carabali et al. 2015, Stanaway et al. 2016).

Of all human cases, ∼2.5% succumb to the disease and half a million (mainly children) develop severe forms of the disease, for example, DHF or DHS. In 2010, autochthonous DENV infections were detected in Croatia and France (La Ruche et al. 2010, Gjenero-Margan et al. 2011). In addition, a large outbreak of DF counting >2,000 cases occurred in 2012 on the island of Madeira, Portugal (Wilder-Smith et al. 2014). It was assessed that up to half of DENV-infected people showed no symptoms but contributed to DENV transmissions.

Attempts to develop efficacious and potent vaccines against DENV have yielded five types of vaccines against DENV including live attenuated vaccine, inactivated vaccine, recombinant subunit vaccine, viral vectored vaccine, and DNA vaccine (Edelman and Hombach 2008, Webster et al. 2009, Deng et al. 2020). One commercially available vaccine version, chimeric yellow fever 17D—tetravalent dengue vaccine (CYD-TDV)—sold under the brand name Dengvaxia (Guy et al. 2010), is registered in 20 dengue endemic countries, and more recently also by the regulatory authorities of the European Union (EU) and United States. However, the immunization implementation has been limited to subnational public health programs only in two countries, Brazil and the Philippines (Alkaff et al. 2020).

In 2017 a DENV vaccine controversy occurred in the Philippines involving a vaccination program with the CYD-TDV vaccine for school children. The vaccine was found to increase dengue virulence and deaths in seronegative children. In the age group less than 9 years, hospitalization from

Table 1. Global Trend of Outbreaks of Viruses Linked to *Aedes aegypti* and *Aedes albopictus*, Chikungunya, Zika, Yellow Fever, and Dengue, Across Continents (2007–2020)

Year	*Dengue fever Locations*	*Yellow fever Locations*	*Zika fever Locations*	*Chikungunya fever Locations*
2007	Thailand, Myanmar, Paraguay	Togo	Micronesia	
2008		Brazil, Paraguay, Burkina Faso, Liberia, Guinea, Cote d'Ivoire, Central African Republic		
2009	Cambodia, Malaysia, Vietnam, American Samoa, Cook Islands, French Polynesia, New Caledonia, Tonga, Cape Verde, Bolivia	Brazil, Democratic Republic of Congo, Cameroon, Liberia, Guinea, Cote d'Ivoire, Sierra Leone, Central African Republic		
2010	Guadeloupe, Martinique (Americas)	Senegal, Democratic Republic of Congo, Guinea, Cameroon, Uganda (Africa)	Cambodia (Asia)	Gabon (Africa)
2011		Senegal, Ghana, Cameroon, Cote d'Ivoire	Senegal	Congo
2012	Portugal (Europe)	Sudan, Democratic Republic of Congo (Africa)	Thailand, Senegal (Asia and Africa)	Papua New Guinea (Asia/Oceania)
2013		Sudan, Ethiopia, Cameroon, Democratic Republic of Congo	French Polynesia, Thailand	French Polynesia, Carribean
2014		Democratic Republic of Congo	Vanautu, New Caledonia, Easter Island, Easter Island, New Caledonia, French Polynesia, Thailand	French Polynesia, Caribbean, Brazil, Puerto Rico, Colombia United States, Venezuela, Mexico
2015			Australia, Brazil, Colombia, Maldives, United States, Venezuela, Suriname, El- Salvador, Guatemala, Mexico, Paraguay, Panama, Honduras, French Guiana, Martinique, Puerto Rico, American Samoa, Fiji, Marshall Islands, Micronesia, Palau, Samoa, Tonga	Puerto Rico
2016	Uruguay (Americas)	Democratic Republic of Congo, Uganda, Angola (Africa)	Guyana, Ecuador, Barbados, Haiti, Saint Martin, Bolivia, Dominican Republic, St. Croix, Nicaragua, Jamaica, Bonaire, Aruba, Trinidad and Tobago, Saint Martin, Saint Vincent, Argentina, Dominica, Cuba (Americas)	Puerto Rico (Americas)
2017	China, Seychelles, Myanmar, India, Burkina Faso, Vietnam, Côte d'Ivoire, Sri Lanka, Pakistan	Bolivia, Brazil, Nigeria, French Guiana, Peru (South America and Africa)	Thailand	Bangladesh, Italy, China, Indonesia (Asia, Europe and Africa)
2018	Spain, Oman, Bangladesh, China (Europe, Middle East, Asia)	French Guiana, Peru, Brazil, Nigeria, Ethiopia (South America and Africa)	India	Indonesia, Sudan, Ethiopia, Thailand (Asia and Africa)
2019	Sudan, French Polynesia, Guam, Honduras, Nepal, India, Indonesia (Africa, Oceania, Central America and Asia)	Brazil (South America)		Taiwan, Democratic Republic of the Congo, Thailand, Myanmar (Asia and Africa)
2020	Indonesia and Singapore (Asia)			

Data extracted from Supplementary Tables S1–S4.

DENV infection was higher in vaccinated children compared with the nonvaccinated control group. This may represent antibody-dependent enhancement in children who were DENV naive at the entry to the study trials, and have been primed but not protected by the vaccine.

Dengvaxia seems to give protection to individuals who have previously been infected with DENV but efficacy is less when given to DENV-naive vaccines (Dejnirattisai et al. 2016). The program was stopped when Sanofi Pasteur advised the government that the vaccine could put previously uninfected people at higher risk of developing severe forms of DENV infection in the future (Guy et al. 2015, Wilder-Smith et al. 2016, Dayrit et al. 2020). Another novel tetravalent dengue vaccine candidate developed by Takeda Pharmaceutical Company (TAK-003) is based on a live attenuated DENV-2 virus. This virus provides the genetic backbone for the other three serotypes that are represented as chimeric strains in TAK-003. As expected, the vaccine efficacy was highest against DENV-2 (97.7%) and modest (62.6–73.7%) against the other three serotypes (Biswal et al. 2019).

Yellow fever virus

Yellow fever is an acute febrile illness characterized by jaundice together with fever, chills, loss of appetite, nausea, muscle pain, and headache (Monath 2001). In severe cases, the virus may cause liver damage, bleeding, and kidney problems. Twenty-nine countries in Africa and 13 in Central and South America are endemic or contain regions that are endemic for YF. A study based on African data sources estimated in 2013 the disease burden of YF to 84,000–170,000 severe cases and 29,000–60,000 deaths (Table 1 and Supplementary Table S3) (Staples et al. 2010, World Health Organization 2018).

A large proportion of the African cases occurs in Angola, Democratic Republic of Congo, Cameroon, Kenya, Sudan and Uganda (Mutebi and Barrett 2002). The case fatality rate in Angola and the Democratic Republic of Congo was estimated to 9.7% and 21.6%, respectively (Barrett 2016, Chan 2016). Furthermore, between July 1, 2017 and April 24, 2018, a total of 1,218 confirmed human cases of YF were observed in Brazil and 364 of those died (Makhani et al. 2019). In February 2020, an outbreak of YF was reported by the Ministry of Health in the Central equatorial state of South Sudan (World Health Organization 2020). However, plans to conduct an emergency yellow fever vaccine campaign were delayed after South Sudan confirmed the first COVID-19 cases in early April 2020.

At present, one of the most successful examples in the history of vaccine development is the attenuated vaccine strain of YFV (the 17D vaccine), a safe and effective vaccine that has been available for more than 80 years. A single dose provides lifelong protection to most people (Barrett 2017). The demand for the yellow fever vaccine has continued to increase owing to the growing number of countries implementing yellow fever vaccination. As an emergency measure, experts have suggested using a fractional dose (1/5 or 1/10 of the usual dose) to extend existing supplies of vaccine (Barrett 2016, Monath et al. 2016).

Despite vaccination campaigns, just over half of the population in the affected areas are vaccinated, meaning that there is significant potential for ongoing transmission.

Zika virus

Like DENV, ZIKV infections are typically associated with mild and asymptomatic symptoms, although more severe forms of the disease exist (Olson and Ksiazek 1981). Of note, ZIKV infection has been associated with Guillain–Barré syndrome in adults and serious fetal brain malformations resulting in microcephaly in newborns (Mlakar et al. 2016, Parra et al. 2016). Brazil has reported >200,000 ZIKV cases and 8,000 babies with congenital malformations linked to this virus infection (Tambo et al. 2016).

ZIKV, which is related to DENV and YFV, was first isolated in 1947 from a monkey in the Zika forest of Uganda (Dick et al. 1952, Hayes 2009). Early research noticed that ZIKV was circulating in the equatorial belt of Africa and Asia, but more recently the occurrence of the virus has shifted also to other geographical regions. In 2007, ZIKV outbreaks occurred in nine municipalities of Yap islands and in Federal States of Micronesia (Duffy et al. 2009, Ioos et al. 2014). During 2015 and 2016, ZIKV caused large epidemics in South America, North America, Caribbean islands (Table 1 and Supplementary Table S4) (Musso et al. 2014b, Nereida 2015, Lazear and Diamond 2016, Petersen et al. 2016, Younger 2016). More recently autochthonous cases of ZIKV have been confirmed to occur in France (Giron et al. 2019).

In many areas affected by ZIKV the seropositivity to DENV is very high, and in such areas, there is great difficulty in distinguishing ZIKV and DENV infections serologically. An interesting question arises, does the DENV immunity influence ZIKV infection and disease? Recent studies indicate that DENV immunity is protective against ZIKV (Rodriguez-Barraquer et al. 2019). But, the widespread circulation of ZIKV in DENV endemic regions raises another question concerning the possible contribution of DENV antibodies to ZIKV replication. Some data indicate that dengue immunity may drive higher ZIKV replication, and have clear implications for disease pathogenesis, and ZIKV and dengue vaccine programs in the future (Dejnirattisai et al. 2016, Langerak et al. 2019).

Considerable efforts have been allocated for diagnosis, treatment, and vaccine development against ZIKV infections, but so far, no vaccine has been approved for public use. To our knowledge several vaccine candidates are currently under development, including, a purified vaccine comprising inactivated ZIKV particles (ZPIV); a DNA vaccine encoding the envelope and premembrane protein (E and PrM), a live vaccine generated from a genetically attenuated virus strain and messenger RNA (mRNA) vaccines encoding the E and PrM proteins. Finally, also chimeric viral vector-based vaccines as genetic carriers of immunogenic ZIKV proteins (*e.g.*, adenovirus and measles virus back bone) (Dowd et al. 2016, Lin et al. 2018).

Economic Burden of Mosquito-Borne Viruses Transmitted by *Ae. aegypti and Ae. albopictus*

There are no comprehensive reports on the combined economic burden from vector-borne infections worldwide, except for single diseases. According to the WHO, vector-borne diseases represent 17% of all infectious diseases and cause >700,000 deaths annually, with 80% of the world's population at risk of being infected by one or more vector-borne diseases.

Of all known vector-borne diseases, mosquito-borne infectious diseases account for the highest number of reported cases, mortality, and disability-adjusted life-years (DALYs). As an example, the global cost of DF was estimated in 2013 to 8.9 billion US$ (95% uncertainty interval [UI] 3.7–19.7 billion) (Shepard et al. 2016). However, the economic costs from medical care, surveillance, vector control, and lost productivity associated with DF and CHIK is much higher, and accounts annually for ~39 billion USD (Fredericks and Fernandez-Sesma 2014). In that view, pandemics could be economically devastating, particularly for developing countries where the disease is endemic.

For ZIKV, report estimates calculate the cost for the outbreaks in six states of the Americas (at an attack rate of 1%) to ~1.2 billion US$ (Lee et al. 2017). Of interest, another parallel estimate by the United Nations Development Programme (UNDP) suggests that the costs could reach 18 billion US$ (Gray and Mishtal 2019). When using data-driven computational simulation models for the CHIK infections in the Americas (for acute and long-term health conditions, and accounting underreporting of cases), the health burden for the 2013–2015 epidemic was estimated to >39.9 million cases. Moreover, the economic cost for the estimated 23.8 million DALYs was assessed from a societal perspective to ~185 billion US$ (Bloch 2016).

These estimates clearly demonstrate how these epidemics are burdening the public health sector. It is expected, if the goals from the WHO's Global Technical Strategy for Malaria 2016–2030 becomes true then 10 million lives, and >4 trillion US$ could be saved (World Health Organization 2015). But, presently there are no valid estimates. In addition, YF is still a considerable burden to South America and Africa. The fatality rate for YF is estimated to ~15% regardless of the availability of a safe and efficacious long-term vaccine. Of the 200,000 persons infected annually by YF, 30,000 die (Tomori 1999).

Risk Factors to Emerging Mosquito-Borne Virus Pandemics

It is evident that arboviruses are present in most parts of the world, and continue to expand their territories while leaving tracks from epidemics in urban areas and cities. Moreover, recent demonstrations show that infections in vertebrates (humans) may occur from bites of mosquitoes infected with multiple arboviruses. Of interest, it has been shown that *Ae. albopictus* and *Ae. aegypti* can be coinfected by DENV and CHIKV. Another example is that a single bite of *Ae. aegypti* may transmit both ZIKV and CHIKV.

It is interesting to notice that mosquitoes have the capability to replicate and disseminate multiple viruses simultaneously (Vazeille et al. 2010, Nuckols et al. 2015). Of note, such coexisting infections do not affect the infection or transmission rates of the two coexisting viruses (Norman et al. 2016). This implies that *Ae. aegypti* can accelerate the transmission of ZIKV, DENV, and CHIKV concurrently because a single bite of *Ae. aegypti* may include more than one virus (Table 1 and Supplementary Tables S1–S4). During the last 15 years, simultaneous outbreaks of arboviruses involving DENV, ZIKV, YFV, and CHIKV have occurred in different parts of the world (Table 1 and Supplementary Tables S1–S4). In summary, individuals with dual or triple infections (ZIKV, DENV, and CHIKV) have become more frequent as demonstrated in South America (Sardi et al. 2016, Zambrano et al. 2016).

In 2010 and 2012 many countries of the world have suffered from outbreaks involving some of the four distinguished arboviruses, and some countries have in successive years faced re-emerging outbreaks (Table 1 and Supplementary Tables S1–S4).

A combination of risk factors increases the likelihood for epidemics, or even pandemics in the near future. These factors include the following: urbanization, endemic circulation of viruses in competent vector populations, transportation of goods and people that results in introduction of vectors and viruses. As a consequence, it results in an increased number of cases.

Future Challenges for Arbovirus Mitigation

Most arboviruses circulate frequently in sylvatic transmission cycles, between nonhuman primate hosts and forest-dwelling mosquitoes. The relocation of rural mosquito vectors, and their accompanying viruses, into urban environments allow transmission and amplification cycles in close proximity to humans. The greatest threat comes from the extensive urbanization and expanding habitats of anthropophilic mosquitoes, for example, *Ae. albopictus* and *Ae. aegypti*.

The expanding urbanization has resulted in close contact between mosquito vectors and susceptible human hosts often living under poor conditions. Emerging and invading arboviruses may successively amplify to epidemic levels because natural environmental structures have been disturbed by changes in host or vector populations or combinations thereof. Outbreaks of emerging arboviruses are sometimes related to relatively small changes in viral genetics through an introduction of new genotypes that may have improved fitness in some geographical areas, increased virulence, increased amplification potential, high viremia levels in vertebrates, and/or expanding host range (Weaver and Reisen 2010).

DENV originates from an ancestor virus infecting nonhuman primates. These strains are still circulating in the forests of West Africa and Southeast Asia. Of interest, arboviruses such as DENV and CHIKV viruses of today have lost their requirement for enzootic amplification. Consequently, DENV that cause most human diseases is no longer dependent on animal reservoirs because DENV may utilize humans as reservoir and amplification hosts exclusively, and rely on viral transmission by mosquito vectors that live in close association with people.

YFV, known to be endemic and cause infections in Africa and South America was exported to Asia in 2016 by international travelers (Monath et al. 2016). The introduction of YFV to China came from imported cases of 11 unvaccinated Chinese citizens who acquired the virus during their work in Angola (Woodall and Yuill 2016, Wilder-Smith and Leong 2017). In addition, during the 2016 YFV epidemic in Angola, ~884 laboratory YFV were confirmed with 373 deaths (Wilder-Smith and Massad 2018).

At present, the population in China alone is ~1.3 billion people and the entire Asian population is 4.5 billion. This population is immunologically naive, and most of the people are susceptible to YFV infection. Billions of people are at risk because of the already present mosquito vectors (*Ae. aegypti* and *Ae. albopictus*). As we bear in mind, ZIKV infections

moved rapidly from anonymity to Public Health Emergency of International Concern in 2016, YFV may become the next arbovirus to reach this level, perhaps in Asia.

In the past, arboviral diseases were considered as minor contributors to global morbidity and mortality. As a consequence, arbovirus research, investment, and related public health infrastructure were given low priority. Accordingly, we have seen an exceptional increase in the incidence of epidemic arboviral during the past decades.

Insufficient preparedness comes from the lack of awareness and results in unsatisfactory political determination including ineffective application of existing strategies against expanding mosquito populations in urban centers. Such problems are often associated with wastewater and water puddles that serve as dwelling sites for mosquitoes. In addition to urbanization, and the lack of sustained mosquito control programs, we have seen an increased use of disposable containers, plastics, cans, and tires that may contain small amounts of water. Those are good breeding sites for mosquitoes. Furthermore, trade with open containers have undoubtedly facilitated the spread of arbovirus strains and enhanced worldwide distribution of mosquito vectors and their accompanying viruses.

The basic understanding is that no single intervention is sufficient to reduce the consequences from arbovirus diseases. Critical assessment of present vector control tools, improve and invest in new technology should guide the research agenda toward novel tools together with state-of-the-art vector control programs.

Vaccines are cost-effective tools to prevent infectious diseases, but it takes time and money to develop them. Advances in clinical care have tremendously decreased case fatality rates for many arbovirus diseases, but still there is no effective antiviral therapy to most arbovirus diseases. However, intensive research gives good hope for preventive vaccines and antiviral treatments (Wilder-Smith et al. 2017). The most cost-effective and sustainable strategy for disease reduction is a combination of vector interventions, effective cross-border reporting systems, and effective treatments of arboviral diseases.

Advances and Innovative Strategies for Prevention and Control of Emerging Viruses Transmitted by *Ae. aegypti* and *Ae. albopictus*

As stated previously, no single strategy is sufficient to control mosquito vectors and prevent infections from accompanying emerging mosquito-borne viruses. Studies have encouraged community-based control programs such as citizen science, which requires involving the public to participate in scientific research, focused and effective surveillance programs associated to vector control and prevention/therapeutic strategies against viral infections (Lwande et al. 2020). Such examples include GIS mapping of risk areas shown to be prone to virus outbreaks, use of insecticides that aims at mosquito vectors known to be competent for emerging viruses, genetic alteration of vector species and development of effective vaccines and useful antiviral therapeutics that have been suggested in our previous review (Lwande et al. 2020).

Many strategies are already existing; nevertheless, there is an urgent need for new innovative tools that could be used in combination with the existing ones.

Prediction models based on surveillance data of patients with confirmed virus infections may serve as good indicators for unrecognized and/or on-going arboviral infections. A good example is the development of the Severity Index for Suspected Arbovirus (SISA) model that was recently applied in Ecuador (Sippy et al. 2020). However, such assessment tools need to be further developed and evaluated.

Models built on predisposing factors to acquisition of emerging viruses, that is, living in mosquito-infested areas, climatic and weather conditions that favor thriving of virus vectors like rainfall, humidity, and the presence of reservoir hosts could also provide information when mapping potential outbreak areas. Mobile clinics that randomly screen individuals presenting febrile illnesses could be valuable, especially in remote settings. Surveillance and clinical assessment should be an important and integrated part of the health system, especially in rural areas.

The advancement of next-generation sequencing platforms, for example, metagenomic arbovirus detection using the pocket-size MinION nanopore sequencing, has provided a unique possibility to discover viral pathogens in field settings during an ongoing epidemic (Batovska et al. 2017). The sequencing technology is able to detect viruses through the sequence of viral genomes, and provide greater insights into the virus, the vector, and host dynamics over time. Mobile genetics laboratory can provide expeditious results and allow scientists to conduct genetic analyses, support risk planning and priority setting, and allow rapid interventions under emergency conditions *in situ*.

Conclusions

This review highlights the extreme importance of being aware and prepared to meet epidemic challenges and consequences generated from arboviruses in high-risk areas. The two invasive species *Ae. aegypti* and *Ae. albopictus* have colonized large parts of the world, and vector competence experiments conducted on *Ae. aegypti* and *Ae. albopictus* ascertain their vector competence to CHIKV, DENV, YFV, and ZIKV. These mosquito vectors are also able to harbor, replicate, and transmit more than one arbovirus, and the capacity to transmit these viruses is highly dependent on the virus titer in the saliva, the infectious dose, and the density of the vector and naive human populations.

The presence of autochthonous cases of CHIKV and ZIKV viruses in Europe and elsewhere underlines the need for effective prevention and treatments with an aim of avoiding virus transmission to immunologically naive regions. Beside the exception of the notable YFV vaccine, there is a great lack of efficacious and safe human vaccines approved against arboviruses, for example, CHIKV, DENV, and ZIKV. In addition, there are no effective antiviral therapy to most arbovirus diseases. Development of effective antivirals could be used in the management of patients already presenting with disease symptoms.

We advise new priorities and innovative strategies for the prevention and control of these viruses and need effective prediction models and more focused surveillance. The surveillance should be an organized as monitoring the level of virus activity, vector populations, infections in vertebrate hosts and human cases including other factors that is able to detect and predict changes in the transmission dynamics of

arboviruses. We propose a dedicated and focused education of decision makers in endemic areas to create an awareness and engagement by local authorities. We also need training of first responders in sampling, transportations, and reporting manifestations that may be connected to virus transmission. Moreover, the establishment of mobile applications could enable channeling incident data as well as tracking geographic locations and risk management.

Emphasis on capacity building with regard to surveillance and rapid detection of viruses will provide reliable data that is useful in assessing the risk of large-scale epidemic. Inclusion of the virus detection will enable early detection of disease cases that can be controlled before they spill over to larger populations and cause outbreaks. Allocation of funds for prevention and management of emerging mosquito-borne viruses is vital for any economy, especially, in developing countries.

Authors' Contributions

O.W.L., G.B., and J.N. conceived the study and wrote the draft of the article. C.A., K.I., and M.E. participated in discussions affecting the contents and further improvements of the article. All authors have read and approved the final version of the article.

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Author Disclosure Statement

The authors declare no conflict of interest.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4

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