Chapter 2

Emerging and Re-emerging Arboviral Diseases as a Global Health Problem

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Additional information is available at the end of the chapter

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Abstract

Newly emerging or re-emerging infections continue to pose significant global public health threats. This chapter provides an overview of the combinations of factors that led to the emergence of arthropod-borne viruses as human and veterinary health threats, in order to understand the risk associated and how this can be mitigated. Considering the history of emergence of some arboviruses, these epidemics have occurred globally as a result of climate and socioeconomic changes that have allowed the spread to new geographical areas of viruses previously confined to specific ecological niches such as West Nile and Chikungunya, or viruses considered under control such as Dengue, Japanese encephalitis, and Yellow fever. Moreover, the greatest risk for humans derives from the ability of these viruses to adopt transmission cycles involving highly anthropophilic mosquito species. Finally, many other arboviruses are largely ignored despite their potential to emerge globally. The recent epidemic spread of Zika virus throughout the Americas is the evidence that arboviruses are likely to continually emerge and re-emerge and that improved scientific technologies and knowledge is essential to deal with future vector-borne epidemics. Research priorities should therefore focus on surveillance systems and vector control tools, as well as on the development of antiviral molecules or candidate vaccine.

Keywords: arbovirus, emerging infectious diseases, dengue, Chikungunya, yellow fever, West Nile, Zika virus

1. Introduction to arboviruses

Arthropod-borne viruses (arboviruses) are important cause of animal and human disease worldwide, infecting millions of individuals and causing a large social and economic burden.

These viruses are generally transmitted by arthropod vectors to their vertebrate host and circulate among wild animals serving as reservoir in sylvatic life cycle. Through spillover transmission from enzootic amplification cycles, humans can be infected as incidental and dead-end hosts. By contrast, some arboviruses undergo urban cycle involving humans as amplifying hosts and causing several epidemics in urban areas [1–3].

By definition, arboviruses require an arthropod vector in the transmission cycle, in which they must replicate prior to transmission [1]. Most common arthropods include mosquitoes, flies, and ticks along with others hematophagous arthropods [2, 3]. *Aedes* mosquitoes are the most important arboviral vectors; the two main species, *Ae. aegypti* and *Ae. albopictus*, allow the transmission of medically important viruses such as chikungunya virus (CHIKV), dengue virus (DENV), and yellow fever virus (YFV) [2]. Other prevalent vectors are *Culex* mosquitoes, ticks, sandflies, and *Culicoides* [4, 5]. Arboviral maintenance and amplification cycles involve horizontal, vertical, and venereal transmission. In horizontal transmission, the virus is transmitted from an infected vector to a vertebrate host, during blood feeding. Following a viremic bloodmeal, virus enters midgut and disseminates through the alimentary tract in the vector and replicates in the salivary glands. During the following blood feeding, injection of infectious saliva allows the transmission to a new host, initiating a new transmission cycle [1, 2, 4]. Many arboviruses are also maintained in nature through a secondary cycle that involves vertical transmission from an infected female to the offspring. In this case, disseminated virus infects the developing eggs, persisting in larval and pupal stages and subsequently into adults. Moreover, venereal transmission allows the transfer of virus from a vertically infected male directly to a female during copulation [2]. The long-term survival is also enhanced by non-viremic transmission, during which infected and noninfected mosquitoes or ticks co-feed on a non-viremic host and the virus is transmitted directly between them, without necessarily infecting the vertebrate host [2, 4].

Most of the arboviruses that cause human/animal diseases belong to four virus families, *Togaviridae* (genus *Alphavirus*), *Flaviviridae* (genus *Flavivirus*), *Bunyaviridae* (genera *Orthobunyavirus*, *Phlebovirus*, and *Nairovirus*), and *Reoviridae* (genera *Coltivirus* and *Orbivirus*) [2, 5]. Infections in humans and animals could range from subclinical or mild to encephalic or hemorrhagic with a significant proportion of fatalities. In contrast, arthropods infected by arboviruses do not show detectable signs of infection, even though the virus may remain in the arthropod for life [4].

A high proportion of arboviruses associated with human and animal disease circulate in tropical and subtropical regions, where arthropods tend to be abundant. However, many arboviruses also circulate among wildlife species in temperate regions of the world. Despite the global distribution of viruses such as West Nile virus (WNV), DENV and now CHIKV, most other arboviruses are generally endemic but limited to specific regions of the world. Nevertheless, even within this relatively localized distribution, dispersion to distant locations can occur via animal or vector migration [4]. Global warming, deforestation, and urbanization have led to rapid expansion of the habitats of the vectors and caused enormous increase in vector-borne diseases throughout the world. Increase in international travel, shipping, and industrialization can lead to transport of infected mosquito and eggs to different new

ecological niches facilitating the contact with naïve individuals causing outbreaks of high magnitude due to lower herd immunity [2]. The greatest health risk of arboviral emergence comes from extensive tropical urbanization and the colonization of this expanding habitat by the highly anthropophilic mosquito, *Ae. aegypti*, together with the recent invasion into the Americas, Europe and Africa of *Ae. albopictus* that could enhance transmission of these viruses in temperate regions [1].

More than 500 species of viruses are registered in the International Catalog of Arboviruses and this estimate is continuously increasing. While many current arboviruses do not appear to be human or animal pathogens, this large number of widely different and highly adaptable arboviruses provides an immense resource for the emergence of new pathogens in the future [4].

2. Emerging and re-emerging arboviral infections

2.1. Factors associated with arbovirus emergence or invasion

Recent global changes in climate and human behavior are important determinants of arbovirus emergence. The viral transmission can be limited by the ecology of the host or of the virus itself; arboviruses frequently persist at low maintenance levels until changes in single or multiple factors disrupt the transmission cycle, facilitating rapid and widespread amplification [1, 6]. Arboviruses can therefore emerge at epidemic levels due to changes in viral genetics, in the composition or dynamics of the host or vector population and/or in the environmental structure that often are of anthropogenic origin [1].

As arboviruses are virtually all RNA viruses lacking proofreading functions, a high frequency of mutations associated with fast replication allows them to rapidly adapt to different environments. The high rate of genetic mutations could lead to changes in virulence, epidemiology or competence of vectors, which can occur via simple point mutations [3, 5]. Often, outbreaks of emerging arboviruses may be related to relatively small changes in viral genetics or to the introduction of new strains that have increased virulence and viremia levels in vertebrate, thereby expanding the host range and increasing amplification potential. Alternatively, genetic changes can improve vector competence and therefore transmission rates [1].

Zoonoses exploiting complex rural or suburban ecosystems may have multiple vectors and infect a variety of vertebrate host species. Arboviral amplification can progress rapidly to epidemic levels when competent vector and vertebrate host populations meet repeatedly within a permissive environment for viral transmission and replication. Moreover, humans may be exposed to arboviruses when they invade rural environments or when bridge vectors bring viruses into peridomestic environments [1]. Deforestation associated with urbanization process has contributed to increase the contact between humans and vectors [7]. Furthermore, the expansion of urbanization has led to high concentrations of susceptible human hosts, often living in socioeconomic conditions favorable to the expansion of the vector population, facilitating viral transmission and outbreaks of epidemics [1]. Furthermore, the feeding

preferences (anthropophilic and/or ornithophilic) of arthropod vectors are of fundamental importance [8–10]. Arthropods frequently exposed to the human environment, domestic animals, and livestock can undertake an adaptive process defined as domestication [8, 11]. Moreover, many of the epidemic vectors are peridomestic, naturally existing in close association with humans. The vectors of CHIKV, YFV, and Zika virus (ZIKV) all use human habitat to maintain their populations [12, 13]; thus, general living conditions along with ineffective vector control programs, can contribute to providing one component necessary for arboviral transmission [5, 7].

Changes in the composition of vertebrate or vector host species may be related to environmental changes that expand old or create new ecological niches. Extensions of the vector range into permissive environments are often followed by invasion of the arboviruses they transmit. These invasions are generally facilitated by travel and commerce [1], constantly introducing new species of viruses and their arthropod vectors into new geographic areas. Most of these introductions are not detected until they cause an epidemic, when they are already well established and it is not possible to eliminate them from the new area [7]. An additional factor that plays a role in the generation of arboviral outbreaks is the immunity status of vertebrate hosts in the affected areas. Outbreaks registered for the first time in a new area usually involve immunologically naïve populations, exhibiting extremely high rates of attack. Even in areas where epidemics have previously occurred, rare epidemic events interspersed with significant interepidemic periods may render the younger generation susceptible to infection [5].

Following their recent local and global emergence, some arboviruses have acquired great importance in terms of public and veterinary health. The combinations of factors that led to their emergence are of fundamental importance to understand the risk associated and how this can be mitigated. Moreover, many other arboviruses are largely ignored despite their potential to emerge globally [1].

2.2. Emerging and re-emerging arboviruses

2.2.1. Dengue virus

DENV (*Flaviviridae*: *Flavivirus*) is the only arbovirus that has completely evolved and adapted to the human host and its environment, eliminating the need of other animal reservoirs. There are four DENV strains, referred to as DENV1–4 serotypes, antigenically distinct but with the same epidemiology and symptomatology in humans. Generally, DENV is associated with mild clinical manifestations during interepidemic periods, but it can cause epidemics associated with a more severe disease every 3–5 years. Co-circulation of multiple serotypes (hyperendemia) is the most common risk factor associated with the emergence of the severe form of the disease, dengue hemorrhagic fever/shock syndrome (DHF/DSS), in an area [7]. Relying exclusively on humans as reservoir and amplification hosts, the maintenance of DENV is based on transmission by mosquito vectors living in close association with humans [1]. The main vector in urban environments is *Ae. aegypti*, however DENV can also be transmitted by *Ae. albopictus* in suburban, rural, and forest areas in tropical, subtropical, and temperate regions of the world where it is widely present [8, 13]. DENV is the geographically most widespread arbovirus and the most serious arboviral threat, showing high levels of endemic transmission in the Americas, south-east Asia and the western Pacific, with about 4 billion people

at risk of infection [14]. Moreover, DENV is hyperendemic in many Asian tropical regions, where two or more serotypes circulate both endemically and epidemically [1]. A total of 390 million infections, of which about 100 million symptomatic, are estimated each year, with several hundred thousand cases of DHF and thousands of deaths [15, 16]. The resurgence of DENV has been stimulated by population growth and density, urbanization and international travels, as well as changes in environmental conditions, prevalence of vectors and virus genetics. The resulting geographic expansion has been accompanied by exponential increases in cases, epidemics, and co-circulation of different serotypes. In particular, hyperendemicity in many areas of tropics and subtropics is due to serotype dispersal derived from large-scale human movements, which together with levels of preexisting immunity of the herd to specific viral serotypes have led to an increase of DHF epidemics [17, 18]. Moreover, introduction of DENV has occurred several times in temperate or subtropical climate zones in recent years. By 2010, autochthonous cases of DENV infection were identified in Europe, and in October 2012, Madeira recorded a major DENV outbreak, with over 2100 cases by March 2013 [19–21]. Furthermore, the repeated episodes of DENV local transmission (Hawaii in 2001–2002, Texas in 2005, and Florida in 2009–2011) and the wide distribution of *Ae. aegypti* and *Ae. albopictus* in the USA underscores the importance of surveillance and vector control in areas at risk of DENV introduction [22–24].

2.2.2. Chikungunya virus

CHIKV is an *Alphavirus* of the *Togaviridae* family that circulates in enzootic cycles among nonhuman primates with multiple *Aedes* mosquitoes implicated as vectors, with *Ae. aegypti* identified as the main human vector [25]. Historically, CHIKV has been considered a highly debilitating but not life-threatening pathogen, whose infection is associated with fever, headache, myalgia, rash, and severe arthralgia. Because these symptoms often mimic those of DENV and because CHIKV circulates in DENV-endemic regions, CHIKV has long been underdiagnosed and underestimated as an important arboviral disease [1]. In Southeast Asia, CHIKV was recognized as the etiologic cause of febrile disease epidemics in the 1950s and continues to be an important pathogen [26]. Unlike in Africa, where there is evidence of a sylvatic cycle involving arboreal mosquitoes and nonhuman primates, CHIKV appears to be maintained in Asia in a strictly human-peridomestic cycle of mosquitoes [1]. CHIKV has re-emerged in 2005 in a succession of massive outbreaks in East Africa and the Southern Indian Ocean Islands [5]. The first major outbreak occurred in Kenya during 2004, followed by a large outbreak on La Réunion Island in 2005–2006 [6]. The genetic characterization indicated that the epidemic strain originated from the East/Central/South African (ECSA) lineage, but the outbreak of La Réunion was associated with a mutation on the viral envelope glycoproteins enabling more effective transmission by *Ae. albopictus* [6, 27, 28]. This new lineage, called Indian Ocean Lineage (IOL), spread quickly across the Indian Ocean Basin, India, and Southeast Asia. Moreover, infected travelers imported it into Europe, with two small outbreaks occurring in northern Italy and southern France [29–31]. Between late 2013 and beginning of 2014, autochthonous cases of CHIKV were reported in the Caribbean. The strain implicated belonged to the Asian strain, identified in the late 1950s in Southeast Asian countries [32]. Finally, a distinct East/Central/south African strain (ECSA) spread directly to Brazil in 2014 [33]. During these massive outbreaks of CHIKV, also the clinical presentation appeared to be evolving as well, with neurological manifestations and mortality. Moreover,

maternal infection was observed to be vertically transmitted, most commonly during birth, leading to severe disease and encephalopathy in half of neonates and resulting in long-term neurologic sequelae [34].

2.2.3. Zika virus

ZIKV (*Flaviviridae*: *Flavivirus*) is primarily transmitted by mosquitoes of *Aedes* genus, including not only *Ae. aegypti* for urban transmission but also *Ae. albopictus*, *Ae. poliniensis*, and *Ae. hensilli.* Recently, transmission of the virus has also been reported via sexual, neonatal, and blood transfusion. ZIKV infection can be asymptomatic or cause a mild febrile illness characterized by headaches, myalgia, fever, rash, and conjunctivitis [35]. ZIKV was isolated and associated with human disease more than 60 years ago, but remained poorly studied until an association with neurological involvement was observed. In fact, an increase in the incidence of cases of Guillain-Barré syndrome and microcephaly in neonates was observed in regions with an ongoing ZIKV epidemic [35, 36]. The first major outbreak of ZIKV was reported outside Africa in 2007 in Micronesia [37, 38], followed by a second major outbreak in French Polynesia in 2013 [39]. The largest ZIKV outbreak began in Brazil at the end of 2014 with 1.3 million cases estimated by the end of 2015. In May 2016, 47 countries and territories in the Americas, including the USA, reported autochthonous cases of ZIKV [6]. The impact of ZIKV infections on the development of the central nervous system will be defined only in the years to come; at present, the degree of developmental delay or other neurological sequelae that could have babies born to mothers affected by ZIKV is not known. Another important aspect of the future epidemiology of ZIKV infections is the possibility of blood transmission and the consequent need for blood testing in high-incidence areas [35]. In 2017, the number of reported cases that decreased dramatically in Brazil and other American countries, maybe due to the high number of infected people who have acquired protective immunity to reinfection and improved vector control strategies in countries where an epidemic has been reported. However, now the epidemic is no longer considered an international medical emergency and there may be a sharp decline in investment in research and control related to ZIKV. Although the number of ZIKV cases has declined, the risk of another major epidemic in Brazil and other tropical and subtropical countries is still significant and its intensity is difficult to predict. It is therefore essential to develop systems that allow a more accurate diagnosis of ZIKV infections to differentiate it from other flavivirus infections, in particular by using serological tests that can be performed in any developing country. Furthermore, the development of a safe vaccine is of paramount importance for the containment of ZIKV infection, in particular for immunocompromised and pregnant women, but the adverse effects in the development of Guillain-Barré syndrome and the enhancement of other flavivirus diseases by antibodies produced against ZIKV, in particular, toward a future DENV infection must be considered [35].

2.2.4. Yellow fever virus

YFV is the type of species in the *Flavivirus* genus of the family *Flaviviridae*. The primary transmission cycle occurs between nonhuman primates and a range of arboreal mosquito species mainly belonging to the genera *Aedes* and *Haemagogus*, in Africa and South America, respectively. Transmission to humans occurs as the result of frequent spillover events in the so-called zone of emergence, where the presence of *Ae. aegypti* as primary peridomestic vector

can initiate an urban cycle characterized by rapid human-mosquito transmission that leads to explosive outbreaks [40, 41]. The epidemiology of YFV in Africa often involves both sylvatic and urban cycles increasing the force of infection during human epidemics, that result larger than in South America [40]. In humans, YF is a severe acute illness with fever, nausea, hepatitis with jaundice, renal failure, hemorrhage, and shock with case fatality lower in Africa (20%) than in south America (40–60%) [42], suggesting a correlation between genetic factors and lethality of the infection. In Africa as well as in South America, high YF case rates likely occur due to low vaccination coverage in area of endemic transmission. According to WHO and the United Nations Children's Emergency Fund (UNICEF) estimates, only 41% of the target population had received YF vaccination in 2014, well below the recommended 80% threshold for the prevention of an epidemic [41]. However, the underlying reasons for virus amplification could be multifactorial, including the possibility of a new virus lineage emerging correlating with the expansion of YFV activity [43]. In endemic areas, deforestation has been associated with emergence of YF outbreaks due to the higher biting activity of vectors, especially in new settlements inside or near the forest frequently colonized by unvaccinated migrant populations. Moreover, perturbation in environmental conditions, such as increase in rainfall and temperatures, has been associated with an abundance of vectors enhancing YFV circulation with increased outbreaks in Africa and South America [40]. YFV could potentially emerge and disperse in a similar manner to DENV, CHIKV, and ZIKV in South America. The recent outbreak of YF in Brazil and multiple reports of cases outside endemic regions highlight the possibility of urban YF arising [8]. In fact, many cases were reported in areas considered free of virus circulation, where routine YF vaccination is not performed. A molecular study showed implicated a new YFV lineage which evolved from the lineage circulating in Brazil in the 1990s, and moved toward the Atlantic coast, the most populated area in Brazil [40]. Moreover, YFV could become the next arbovirus to emerge as a public health emergency if swift to international spread occurs. Since December 2015, YF epidemic has been reported in Angola, spreading to Kenya and the Democratic Republic of the Congo. Moreover, in April 2016, YFV was exported to China via unvaccinated workers, representing the first laboratory-documented cases of YFV in Asia [41]. This risk is particularly acute in the Asia-Pacific region, where systems for YFV surveillance and detection are largely untested and YF vaccination is limited to travelers [44]. If introduction of YFV occurs in areas with a high density of *Ae. aegypti*, it is possible that local transmission could occur and potentially spread to Southeast Asia, putting approximately 2 billion people at risk without there being sufficient vaccine stockpiles [41].

2.2.5. West Nile virus

WNV belongs to the Japanese encephalitis virus (JEV) serocomplex in the genus *Flavivirus.* It is maintained in nature within an enzootic transmission cycle among birds and *Culex* mosquitoes, with outbreaks caused by spillover transmission to equids and humans, which are dead-end hosts [1]. Based on serological evidences, WNV circulates in the absence of clinical disease in the majority of humans and a wide variety of different animal species, but in abundancy of *Culex* species mosquitoes WNV, may also cause epidemics with disease symptoms ranging from subclinical or mild febrile to encephalic with or without flaccid paralysis and fatality [8, 10]. WNV is distributed globally, with two main genetic lineages: Lineage 1 is widely distributed and highly invasive, whereas Lineage 2 appears to have remained

enzootic in Africa. Lineage 3 and 4 have been described from single isolates in Central Europe, whereas Lineage 5 appears to be confined to India [45]. International dispersal of *Cx. pipiens* mosquitoes that appear to be closely associated with human infection and urban outbreaks, and the introduction of the house sparrow (*Passer domesticus*) as a highly competent host for most WNV strains, has provided the availability of maintenance and amplification cycle of the virus almost circumglobally. Moreover, climate changes at northern temperate latitudes, recently, have made these areas more conducive to WNV invasion [1]. Outbreaks of WNV were recorded throughout the Mediterranean basin, Central Europe, and Russia, where *Cx. pipiens* appeared to be the primary vector. In the Americas, WNV was introduced into New York during the summer of 1999. Phylogenetic evidence suggest that the invading strain was closely related to a 1998 isolate from Israel that contained a mutation causing high viremia and mortality in American crows and higher transmission competence of *Culex* mosquito species. Once the virus had been introduced in the USA, migratory birds played a major role in the dispersal of WNV throughout North America [1, 10]. WNV is now one of the most broadly distributed arboviruses in the world, as well as the most common cause of arboviral neuroinvasive disease in the USA [1, 5]. Currently, WNV vaccines are only available for equids, although human vaccines are under development [6]. However, the motivation for human vaccine development may be limited by the low attack rate that the virus exhibits in humans following epidemics. Therefore, in the near term, protection for public health will continue to rely on mosquito control [1].

2.2.6. Japanese encephalitis virus

JEV is the most frequent cause of mosquito-borne encephalitis globally. The public health significance and the global distribution of JEV have been progressively expanding; currently, more than 3 billion people in Asia reside in areas at risk of JE, with an estimated 50,000 symptomatic cases and 10,000 deaths occurring annually [46]. Taxonomically, JEV is placed within the genus *Flavivirus* and is the type of virus for the JEV serocomplex. JEV is maintained within an aquatic bird-*Culex* mosquito transmission cycle and is amplified within a domestic swine-*Culex* cycle. Moreover, *Culex* mosquitoes can transmit JEV to equids and humans, which are dead-end hosts for the virus. JEV is endemic in large parts of Asia and the Pacific, where mosquito vectors are present in association with rice and other irrigated crops [1, 46]. Of the five major genetic lineages, lineages 1 and 3 have been found co-circulating in subtropical and temperate latitudes and are associated with outbreaks of neuroinvasive disease. However, lineage 5 now appears to be emerging as the predominant genotype. The epidemiological significance is bounded to the fact that lineage 5 is antigenically the most diverse genotype and the current JEV vaccine shows limited efficacy against this genotype [8, 47]. Moreover, the primary mosquito vector, *Culex tritaeniorhynchus,* has been recently identified in north western Greece [48] and JEV RNA was detected in *Cx. Pipiens* mosquitoes in Italy [49], thus potentially increasing the risk of JEV emergence in Europe. In addition, the even more recent detection of autochthonous JEV co-infection during the YF outbreak in Angola [50] supports the idea that JEV may have already expanded its Asian boundaries [8]. The rapid and widespread expansion of JEV in the Asian continent was associated closely with increases in human populations, in acreage of irrigated rice and pig farming. In endemic areas of Japan, the avian-*Culex* maintenance cycle may be bypassed when vertically infected *Cx. tritaeniorhynchus* directly initiate the amplification cycle

in pigs [1]. The risk that JEV becomes a greater threat in the near future is quite high, given the genetic diversity of the virus and several *Aedes* species as marginal competent vectors [6]. Air transport of mosquitoes was the probable cause of JEV outbreaks on isolated Pacific Islands, demonstrating the potential of this virus to invade new areas such as the west coast of the USA. Moreover, with the spread of JEV into much of the Indian subcontinent, other destinations served by frequent routes of commerce or passenger air travel, such as Africa and Europe, also could be at risk [1].

2.3. Arboviruses with potential of emergence

2.3.1. Rift Valley fever virus

Rift Valley fever virus (RVFV) is classified within the genus *Phlebovirus* in the family *Bunyaviridae* and circulates in Central West, East and South Africa and in the Arabian Peninsula [8, 51]. Infection causes severe and often fatal illness in sheep, cattle, goats and camels, with occasional spillover to humans, in which the infection shows no symptoms or a mild illness associated with fever and liver abnormalities [1, 8]. However, during RVFV epizootics, up to 10% of affected humans may develop more severe disease, including encephalitis, retinitis, and hemorrhagic fever with case fatality rate approximately 10–20% [8, 52]. RVFV is maintained in an enzootic cycle among wildlife and a wide variety of mosquito species, including *Aedes*, *Culex*, *Anopheles*, and *Mansonia*. The virus is maintained by vertical transmission in eggs of *Aedes* species during dry season, with intermittent epizootic outbreaks occur during rainy season [1, 8]. Historically, RVFV was restricted to sub-Saharan eastern Africa, especially Rift Valley of the Kenya and Tanzania. Subsequent outbreaks with human involvement have been documented in South Africa, the Nile Valley, and the Saudi Arabian Peninsula. A large outbreak in Mauritania indicated dispersal of the virus in West Africa [53, 54], demonstrating the ability of RVFV to escape historical enzootic areas. Major irrigation projects and the El Nino effect are considered to be the important factors influencing the epidemiology of RVFV [4, 55] and the movement of viremic camels along trade routes that has been suspected to be the routes of dispersal. Moreover, before the onset of the disease, humans develop viremias suitable to infect susceptible mosquitoes; uncontrolled air travel therefore could introduce RVFV into North America or Europe where susceptible wild and domestic hosts and suitable vectors reside [1, 56]. RVFV is generally considered to be a candidate for emergence and global dispersion but, as the virus is transmissible by a wide variety of mosquitoes adapted to the local habitats in Africa and *Ae. Aegypti* is not a recognized primary vector, the likelihood of expansion outside Africa and Saudi Arabia appears to be low. However, RVFV could be inadvertently introduced via infected mosquitoes into a tropical region where competent domestic *Ae. aegypti* predominate in the urban environment [8]. Nevertheless, laboratory infection has highlighted the presence of competent *Cx. Pipiens* in Southern France and Tunisia with the potential for RVFV epizootics to occur in the virus, which was introduced into countries of the Mediterranean basin [57]. Several vaccines for RVFV have been developed and appear effective; however, their use is limited. Failure to contain these outbreaks provides a source of virus to seed outbreaks into other areas of Africa and the Middle East as well as the rest of the world. With a high potential impact on wildlife, domestic animal, and human health, failure to contain RVFV could seriously impact veterinary and human health in Asia, Europe, and the Americas [1, 51].

2.3.2. Mayaro virus

Mayaro virus (MAYV) is an emerging *alphavirus* with autochthonous transmission in central and south America with higher prevalence in amazon region; recently, it has been reported to circulate in the Caribbean [58, 59]. Infection produces indistinguishable symptoms to the closely related CHIKV; therefore, due to the high degree of co-circulation with CHIKV, DENV, and similar viruses, cases of MAYV infection are not reported frequently. An estimated 1% of all febrile dengue-like illness in northern South America is caused by MAYV, as evidenced by the high rates of detection during regional serosurveillance [6, 60, 61]. The transmission cycle of MAYV is similar to the sylvatic transmission of YFV, with nonhuman primates as main reservoirs. The primary vectors are likely mosquitoes from the genus *Haemagogus*; however, the virus has also been detected in other mosquitoes and mites [1]. A major concern is that MAYV has also been detected in two of the most abundant mosquito genera: *Culex* and *Aedes* [6, 62]. Experimental evidence suggests that the virus is highly infectious to *Ae. aegypti* [63] and can be transmitted at low rates by *Ae. albopictus*, making that species a potential secondary vector [6, 64]. Historically, MAYV outbreaks have been sporadic, however, spillover events have occurred following deforestation and urbanization in endemic areas, both of which bring the virus into closer proximity to larger human populations, and to their associated urban vectors [1, 6, 65]. Given the close genetic relationship with CHIKV, it is plausible that MAYV could also evolve to become more infectious to humans or anthropophilic mosquitoes, and experience similarly high levels of outbreaks.

2.3.3. Venezuelan equine encephalitis virus

Venezuelan equine encephalitis virus (VEEV) is an alphavirus (*Togaviridae: Alphavirus*) widely distributed in tropical and subtropical regions of the Americas, where it circulates endemically between mosquitoes of the genus *Culex* and rodents. The VEEV complex can be subdivided into six different subtypes (I to IV) with type I further divided into other antigenic variants; only VEEV subtypes IAB and IC are considered epizootic variants and are pathogenic for horses [66, 67]. Also humans infected with epidemic VEEV strains develop high titers viremia and may therefore play a role as maintenance and amplification hosts [67–69]. Main epidemics occur when VEEV epidemic strains spill over into competent mosquitoes of the genera *Aedes* and *Psorophora*, which have a peridomestic behavior and may transmit VEEV to equids. An equine-mosquito amplification cycle may induce an extensive virus circulation that may spill over to humans and cause outbreaks of VEEV. Epidemic VEEV infection in humans is a highly disabling dengue-like febrile disease, which can lead to severe encephalitis with fatality rates of between 1 and 3%, especially in children [67, 70]. Moreover, if infection occurs during pregnancy, it may lead to severe neurological birth defects and anomalies [66]. The emergence of VEEV epidemics is based on a combination of ecological and viral genetic factors. Enzootic VEEV strains are not able to achieve a sufficient viremia for equine amplification. However, a single mutation in the viral genome can lead to changes in the viral envelope improving equine amplification. Because alphaviruses replicate with low genetic fidelity, it is likely that mutations competent for equine amplification occur regularly within sylvatic cycles. Then, the transport of mutants strains competent for the equine amplification in areas with susceptible equids and mosquito vectors allows the emergence of epidemics [1]. The last major VEE epidemic, which involved ca. 100,000 persons with an estimated 300 deaths, occurred in

Venezuela and Colombia in 1995 [71, 72]. In these areas, natural emergence will occur periodically, as long as equine herd immunity is not maintained at adequate levels by vaccination or natural acquisition of immunity from enzootic exposure. The risk of epidemic emergence may be increasing by the conversion of large areas of tropical forest to ranching and other forms of agriculture, increasing opportunities for infection of bridge vectors competent to the generation of an equine amplified cycle. Furthermore, urban peridomestic mosquito vectors such as *Ae. aegypti* [73] and *Ae. albopictus* [74] are capable of transmission after oral doses comparable to human viremia titers, making an *Ae. aegypti*-borne epidemic VEEV cycle possible [1]. Prevention and control of epizootic/epidemic VEEV depends on effective use of veterinary vaccines, but equine vaccination in many countries is not widespread. Therefore, during epizootic/epidemic transmission, mosquito control is an important adjunct to vaccination [7].

3. Strategies for arbovirus control

Because they are not an essential part in the zoonotic arbovirus life cycle, arbovirus disease control based on humans and domestic animals cannot eradicate the arbovirus. Consequently, the reservoir in wild species places a limitation in the control disease emergence, and only understanding the interactions involved in the biology of the virus, hosts, and ecology will lead to effective control and prevention strategies [4, 5]. With effective vaccination and sustainable vector control programs, it is possible to control or even eliminate human transmission cycles. In fact, vaccination can increase herd immunity, making it easier to sustain reduced virus transmission with vector control. On the other hand, vector control can complement a vaccine by lowering the risk of infection, making vaccine delivery goals easier to achieve [75].

The YF vaccine has been used extensively in West Africa and has been instrumental in eliminating the urban transmission cycle in South America. However, despite its efficacy and low-cost production, epidemics continue to occur due to inadequate vaccination coverage, as demonstrated by the recent YF outbreak in Angola and Democratic Republic of Congo [76]. Adequate and continuous vaccination programs along with high levels of herd immunity are of paramount importance for the control of YF. In Africa, together with childhood immunization, mass preventive vaccination campaigns to protect elderly people need to be implemented [77]. Moreover, in South America, people of coastal areas are largely unvaccinated and therefore exposed to the risk of YFV coming from the near enzootic regions [75]. Finally, YF cases reported from travelers from Angola to China highlight the need to implement the WHO International Health Regulations in order to protect travelers and to avoid the introduction of YFV in naïve areas of Asia where the vector is widely present [76]. Japanese encephalitis was controlled in Japan, Taiwan, and Korea using inactivated vaccines, which also contributed to control infection in China [10, 78]. A live attenuated JEV vaccine was used to reduce the risk of infection in children in China, as well as being part of the large children immunization campaign in India [10]. At the end of 2015, the first dengue vaccine was licensed (CYD-TDV vaccine Dengvaxia). The results of a large phase III study in 10 endemic countries in Asia and South America showed a complex performance of the vaccine with efficacy dependent on serotype, as well as previous immunity and age of the subject [79, 80]. Two other live dengue virus vaccines are in phase III trials and many other dengue vaccines are in phase I and II trials [75]. Research on vaccines against CHIKV has been slow, as CHIKV causes

major epidemics only every 10–30 years, limiting the interest of the pharmaceutical industry for a financial return [75]. However, two vaccines against CHIKV have recently completed phase I clinical trials, both are strongly immunogenic after 2–3 doses and are currently in phase II trials [81, 82]. Among more than 40 Zika vaccines developed, DNA, RNA, and inactivated virus [83–85] versions started clinical trials and the first live-attenuated vaccine has been demonstrated to be safe and efficacious after a single dose in mice [86]. However, there are some concerns about potential interactions with immunity generated by other flavivirus natural infections or vaccines leading to more severe manifestations of the disease, as well as the immune trigger in the development of Guillain-Barre syndrome [87]. Currently, there is no specific licensed anti-arbovirus agent, and patient management is therefore mainly supportive. Passive immunotherapy is a promising approach for the management of newborns exposed to CHIKV. The anti-CHIKV human immunoglobulins purified from convalescent donors exhibit strong anti-CHIKV effects in vitro and animal models [88], and are now evaluated in the prevention of mother-to-child CHIKV transmission in newborns born to viremic mothers [87]. Novel antiviral therapies are also being investigated. Drug repurposing strategies have identified potential inhibitors of *Flaviviridae* replication. Ivermectin strongly inhibits the replication of YFV, DENV, and WNV [89], while azithromycin inhibits the cytopathic effects induced by ZIKV in glial lines and in human astrocytes and is also considered safe for use during pregnancy [90]. Further new approaches aim to identify host factors and pathways that are critical for viral replication and to identify the putative inhibitors of these pathways as host-targeting antivirals [87].

The continued outbreaks of YFV and JEV demonstrate that even with a widely available and effective vaccine, it is difficult to control a vector-borne disease using only vaccination [6]. Overall, the best current perspectives for controlling the majority of vector-borne diseases rely on reducing the contact between the vector and susceptible humans and the most effective approach for this goal remains the elimination or reduction of mosquito populations [87]. Nowadays, many of the insecticides used in the mid-twentieth century eradication campaign are considered environmentally unacceptable, as well as being economically prohibitive and at risk of developing resistance in mosquito populations [87, 91]. Several alternative approaches are focused on reducing the abundance of mosquitoes or preventing the transmission of pathogens by the mosquito. Environmental management includes modification of the natural breeding habitat of mosquitoes and the adoption of human behaviors that reduce the incidence of the bite, such as the elimination of domestic oviposition and larval sites, the indoor residual spraying and fumigation, the use of insecticide-treated bed nets and screening windows together with lethal traps, which have been found to be effective in reducing *Ae. aegypti* populations and transmission of CHIKV and DENV [87, 91, 92]. Another approach involves genetic modification of vectors and the release of genetically modified male mosquitoes expressing a dominant lethal gene, determining the death of all progeny from mating with wild females (sterile insect technique, SIT) [87, 91, 93]. Moreover, also the vector competence can be reduced by limiting viral infection or transmission through the introduction of transgenic mosquito lines in the field [94, 95]. Biological control represents another possible intervention and includes the use of natural predators or pathogens against mosquitoes. The strategy that involves the release of mosquitoes infected by *Wolbachia pipientis*, an endosymbiont bacterium that is transmitted vertically, allows to suppress the viral transmission by interfering with the reproduction of the mosquitoes [6, 87, 91]. *Wolbachia* infection affects sperm

preventing successful reproduction between infected and uninfected males and between infected males and females harboring different strains of *Wolbachia*, similar in method and effect to SIT [91, 96]. *Wolbachia* can also be used as a population replacement strategy, which consists in the release of female mosquitoes infected by *Wolbachia*, relying on high levels of maternal transmission [97]. The introduction of *Wolbachia* in the naturally uninfected field *Ae. aegypti* populations is currently used to confer resistance to viral infection, making infected mosquitoes poor vectors of pathogens of medical importance including DENV and CHIKV [98, 99] with similar effects characterized recently against ZIKV [100, 101].

The implementation of localized arthropod control measures during epidemics, for example, in high-density urbanized areas, can play an important but transient role in reducing the impact on humans and animals of emerging arboviruses if these are supported from surveillance systems, which differ at regional level and in many areas are completely absent [4]. Furthermore, it is essential to characterize and understand viral genetics, antigenic properties, virulence patterns, vector associations, and maintenance mechanisms to identify and control future arboviral outbreaks. The next public health needs include communication to the population and physicians of vector-borne diseases, the guarantee of vector control programs, and the maintenance of adequate surveillance systems with trained personnel, together with the availability of drugs, vaccines, and rapid diagnostic testing [5].

4. Conclusions

Arboviruses already have a well-known history of emergence and will undoubtedly continue to emerge in the future. There are many unidentified arboviruses that, due to their high mutation rates, may emerge as pathogens even if they are not yet present as epidemic strains in the wild environment. Recent progress in sequencing offers new opportunities to identify them during surveillance activities, especially in the tropics, where viral diversity is higher [3]. The greatest risk for humans derives from the ability of some arboviruses to adopt urban transmission cycles involving highly efficient and anthropophilic vectors, such as *Ae. aegypti* and *Ae. albopictus*, or enzootic peridomestic cycles involving *Culex* urban populations [1]. The ability to urbanize and cause an epidemic, exemplified by DENV, CHIKV, and YFV, could be acquired by many other viruses, including VEEV and MAYV, which have the potential to infect these urban vectors and whose exposure to urban populations in the tropics is already known. A more complete understanding of the molecular interactions associated with the emergence will be particularly useful in predicting the likelihood of this happening [3]. The public health emergency of ZIKV, the threat of the YF, and the re-emergence of DENV and CHIKV should serve as a wake-up call for governments, academics, and WHO to strengthen the control and research programs on arboviral infections [75]. A continuous international and interdisciplinary response is needed to improve the ability to anticipate, control, and mitigate the risk of emerging and re-emerging arboviruses. Research priorities should focus on surveillance systems, knowledge of factors responsible for adaptation to other vectors, and other determinants of infection and transmission, as well as on the development of antiviral molecules or candidate vaccine. The shared characteristics of these viruses could stimulate common research themes for the development of antiviral therapies and vaccines, while the co-circulation of these viruses requires the development of differential diagnostic systems,

including more specific serological tests for seroprevalence studies. The socioeconomic and environmental factors driving the proliferation of vectors, particularly in cities of low-income countries, must be mitigated. An assessment of the available and developing vector control tools is needed to identify the most effective techniques and their combination with vaccination. Finally, new global alliances are needed, such as the global Dengue and the *Aedes*-related disease consortium, to enable the combination of the most effective and timely solutions against arboviral diseases [75].

Conflict of interest

The authors declare no conflict of interest.

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