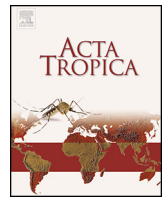




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# The emergence of arthropod-borne viral diseases: A global prospective on dengue, chikungunya and zika fevers



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## ARTICLE INFO

### Article history:

Received 25 August 2016

Received in revised form 27 October 2016

Accepted 16 November 2016

Available online 19 November 2016

### Keywords:

Arboviruses

Dengue

Zika

Chikungunya

Human transmission

Emergence

## ABSTRACT

Arthropod-borne viruses (arboviruses) present a substantial threat to human and animal health worldwide. Arboviruses can cause a variety of clinical presentations that range from mild to life threatening symptoms. Many arboviruses are present in nature through two distinct cycles, the urban and sylvatic cycle that are maintained in complex biological cycles. In this review we briefly discuss the factors driving the emergence of arboviruses, such as the anthropogenic aspects of unrestrained human population growth, economic expansion and globalization. Also the important aspects of viruses and vectors in the occurrence of arboviruses epidemics. The focus of this review will be on dengue, zika and chikungunya viruses, particularly because these viruses are currently causing a negative impact on public health and economic damage around the world.

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## 1. Introduction

Emerging infectious diseases (EID) are defined as infections that have recently appeared in a population, and are quickly increasing in frequency or geographic range (Morse, 1995). For a disease to emerge, several factors are required, including the introduction

of a pathogen and its spread into the human population, followed by its ability to be maintained in nature. Many pathogens require adaptation to emerge into a new environment, while for others adaptation is not necessary. Human behavior and ecology are two other factors that play a role in the emergence of diseases (Schrag and Wiener, 1995; Hahn et al., 2000; May et al., 2001). For example, the geographical expansion of human populations has facilitated the appearance of some emerging viruses, as well as the intensification of agriculture and the disturbance of habitats due to climate change or deforestation (Taylor et al., 2001; Jones et al., 2008).

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Actually, only a few infectious agents are restricted to humans. The majority of emergent pathogens that affect humans are zoonotic agents that are maintained in enzootic cycles (Lloyd-Smith et al., 2009). During the past 70 years, emerging zoonoses have made up most of the emerging infectious diseases affecting people, and they have caused economic damage exceeding hundreds of billions of U.S. dollars (Jones et al., 2008; Newcomb et al., 2011; Karesh et al., 2012). Zoonotic diseases account for billions of cases of human illness and millions of deaths every year and constitute long-lasting health problems worldwide (I.L.R. Institute, 2012).

The host range expansion of the zoonotic agents requires multiple factors to establish transmission into the human population. Anthropogenic changes related to agriculture practices and deforestation are two factors that may bring humans in close contact with zoonotic reservoirs. Many wildlife species have been identified as reservoirs of pathogens that can be transmitted to humans (Levins et al., 1993; Morse, 1994). For example, bats represent a major source of zoonotic viruses (Calisher et al., 2006), including rabies, Nipah (NiV), SARS (SARS-CoV) and Ebola (EBOV) viruses (Taylor et al., 2001; Woolhouse et al., 2005).

Many other zoonotic viruses are transmitted to humans by hematophagous insects (mosquitoes, sandflies, biting midges and ticks) and are designated arthropod-borne viruses (arboviruses) (Higgs and Beaty, 2005). In recent years, the prevalence of vector-borne diseases has expanded considerably, due to intensification of human travel and transcontinental commerce. The number of cases has increased in endemic regions, but cases have also spread into new regions where the viruses never existed before (Gubler, 2002; Weaver and Reisen, 2010; Weaver, 2013, 2014). Additionally, the development of mosquito resistance to insecticides has further complicated the control and eventual elimination of vector-borne diseases from specific areas (Saavedra-Rodriguez et al., 2012; Bisset et al., 2013).

### 1.1. Factors associated with the emergence of arboviruses

Arboviral diseases are caused by viruses that are maintained in transmission cycles between vertebrate hosts and blood-sucking arthropods such as mosquitoes, sandflies, midges and ticks. In order to complete the transmission cycle, the virus must produce a sufficiently high level of viremia in the vertebrate host for a susceptible arthropod to become infected while taking a blood meal (Karabatsos, 2001). There are at least 135 arboviruses that have been known to cause human disease. Arboviral infections can range from asymptomatic to fulminant fatal disease. The clinical symptoms are generally categorized as systemic febrile illness, hemorrhagic fever and invasive neurological disease (Gubler and Vasilakis, 2016). The vast majority of arboviruses are RNA viruses, belonging to the genera *Alphavirus*, *Flavivirus*, *Orthobunyavirus*, *Nairovirus*, *Phlebovirus*, *Orbivirus*, *Vesiculovirus* and *Thogotovirus*. Among DNA viruses, African swine fever virus (*Asfivirus* genus) represents the only DNA arbovirus (Calisher and Karabatsos, 1988; King et al., 2011).

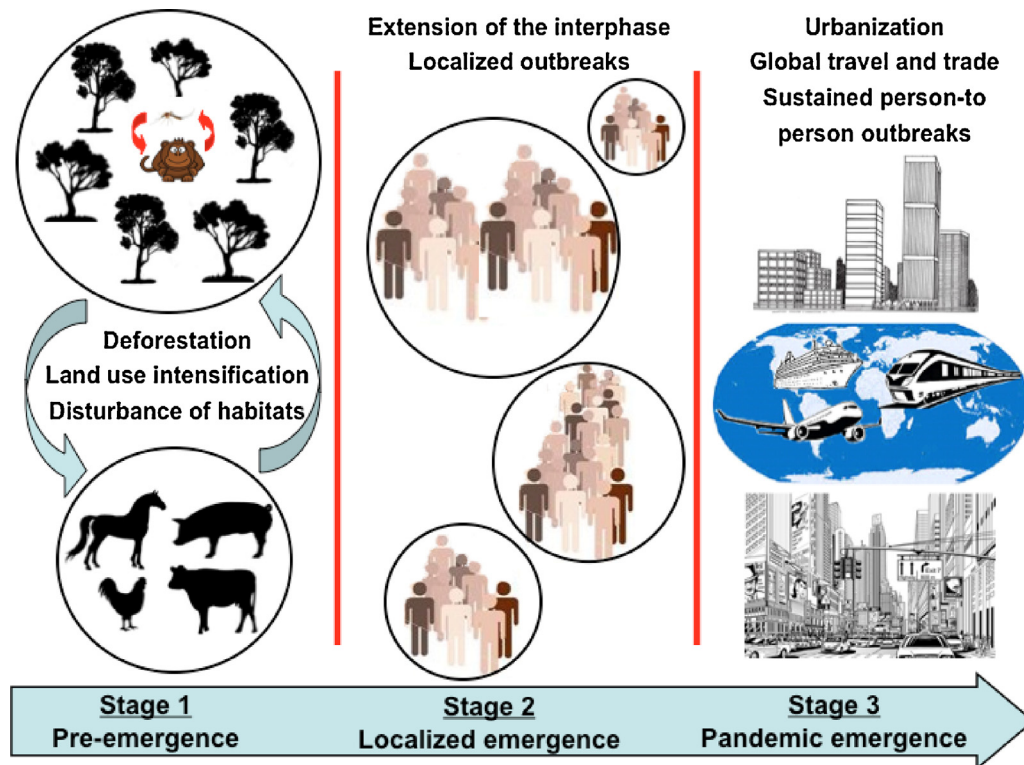
In the past few decades, the total number of arboviral epidemics has significantly increased (Gubler and Vasilakis, 2016). In most cases, the emerging arboviral diseases were caused by viruses previously considered to be controlled or of little public health importance (Gubler and Vasilakis, 2016). Introduction of viruses into new geographic areas (i.e. WNV into the Americas), where naïve vertebrate and arthropod hosts were susceptible and able to sustain infection, also contributed to the occurrence of major outbreaks. In other cases, epidemics were associated with the regional spread of viruses previously considered restricted to a specific geographic area, e.g. Rift Valley fever, Ross River and chikungunya fevers, Japanese encephalitis and Venezuelan equine encephalitis.

One example of an arbovirus that has significantly expanded its geographic range and moved into new territories is chikungunya virus (CHIKV). CHIKV is a member of the genus *Alphavirus*, family *Togaviridae*; historically it was restricted to the Old World (Jupp and McIntosh, 1988). There are indications that the virus was originated in sub-Saharan Africa, where it is believed that CHIKV was maintained in an enzootic transmission cycle between non-human primates (NHP) and arboreal *Aedes* mosquitoes (Powers et al., 2000; Volk et al., 2010). Spillover transmission to nearby human populations probably occurred multiple times, resulting a continuous transmission cycle between humans and anthropophilic mosquitoes, such as *Ae. aegypti* (Diallo et al., 1999, 2012; Volk et al., 2010). In 2004, CHIKV emergence was reported in the coastal area of Kenya (Chretien et al., 2007) following a global expansion to different regions of Africa, Asia, several islands in the Indian Ocean (Hochedez et al., 2006; Lanciotti et al., 2007; Taubitz et al., 2007) and temperate areas in Europe (Rezza et al., 2007; Grandadam et al., 2011). The contributing factor for the emergence of CHIKV was presumably via travelers who became infected in endemic/epidemic areas and returned home contributing to the establishment of autochthonous transmission (Hochedez et al., 2006; Lanciotti et al., 2007; Taubitz et al., 2007).

Four genotypes of CHIKV have been identified since its discovery in 1952: East-Central-South African (ECSA), West African, Asian, and the Indian Ocean Lineage (IOL) (Powers et al., 2000; Volk et al., 2010). The different CHIKV lineages can exhibit distinct patterns of infectivity and transmissibility in the mosquito vectors (Arias-Goeta et al., 2013; Vega-Rua et al., 2013). The acquisition of specific mutations in the E1 (Tsetsarkin et al., 2007; Vazeille et al., 2007) and E2 (Tsetsarkin and Weaver, 2011; Tsetsarkin et al., 2014) envelope glycoprotein of emerging IOL strains allowed virus adaptation and consequent increased transmission in the peridomestic mosquito *Ae. albopictus*. This adaptation may have contributed to the spread and continuous transmission of CHIKV in tropical urban areas where *Ae. aegypti* is abundant and also to peridomestic and/or temperate habitats where *Ae. albopictus* is more adapted (Leisnham et al., 2014).

Despite the presence of both *Ae. aegypti* and *Ae. albopictus* mosquito vectors and reports of imported cases from the 2006–2009 period (Lanciotti et al., 2007) in the Americas, local transmission of CHIKV was only been reported recently. In 2013, an Asian lineage of CHIKV was introduced into the Caribbean island of Saint Martin and established the first mosquito-human cycle in the Americas (Leparc-Goffart et al., 2014). Subsequently, cases of autochthonous transmission of CHIKV were reported throughout the Caribbean and Central America, South America and Florida (Weaver and Forrester, 2015). In Brazil, two different CHIKV lineages were detected (Nunes et al., 2015). The Asian lineage reported in North Brazil possibly originated from travelers coming from the Caribbean, while the index case for the ECSA lineage reported in the northeast region (Bahia state) probably was introduced from a resident returning from Angola (Nunes et al., 2015).

Zika virus (ZIKV) is another arbovirus of the *Flaviviridae* family, genus *Flavivirus*, that is rapidly expanding its geographic distribution and has been recently introduced into areas not previously reported. The disease is characterized by a broad range of clinical symptoms, including fever, rash, headache, retro-orbital pain, myalgia, arthritis or arthralgia, conjunctivitis and vomiting, which are clinical signs similar to dengue disease and many other diseases of viral (e.g. chikungunya and Mayaro fevers) and parasitic (e.g. scrub typhus and leptospirosis) aetiologies (Macnamara, 1954; Olson et al., 1981; Duffy et al., 2009; Foy et al., 2011; Kutsuna et al., 2014). ZIKV was first isolated in 1947 from the blood of a sentinel rhesus monkey exposed in the canopy of Ziika Forest in Uganda during epidemiologic studies of yellow fever (Dick et al., 1952). Subsequent isolations of the virus were made from *Aedes*



**Fig. 1.** The emergence of arboviral diseases from sylvan or rural habitats into urban areas. Distinct stages are involved in the introduction of arboviral diseases into human environments.

*africanus*, *Ae. luteocephalus* and *Ae. fuscifer* (all tree-hole breeding mosquitoes implicated in the sylvan cycle of yellow fever virus) in Uganda, Senegal, Nigeria, Burkina Faso, Ivory Coast and the Central African Republic (Haddow et al., 2012). These reports were interpreted as evidence that ZIKV is maintained in forested areas of tropical Africa in a cycle similar to that of sylvan yellow fever (i.e. arboreal mosquitoes and non-human primates). ZIKV was first isolated from humans in 1954 from a 10 year old Nigerian female (Macnamara 1954). The virus was isolated from mice inoculated with the patient's serum sample; two other human cases were also confirmed from the same country. In 1969, ZIKV was isolated for the first time outside the African continent from *Ae. aegypti* mosquitoes collected in Malaya (Marchette et al., 1969); and in 1977, the first human case was described in Indonesia (Olson et al., 1981). The factors associated with the emergence of ZIKV are not understood. On the island of Yap, in Micronesia, where the first large outbreak was reported in 2007, ZIKV was speculated to have been introduced by either viremic travelers or infected mosquitoes originating from the Philippines, since travel exchange between Yap state and Philippines is very frequent.

In 2013 a major epidemic of ZIKV was reported in French Polynesia, where human subjects were presenting dengue-like symptoms and rash. Interestingly, few of the affected patients presented severe neurological complications and non-vector borne transmission (sexual and transfusion-associated cases) were also described (Laigret et al., 1967; Cao-Lormeau et al., 2011; Musso et al. 2015). Although the total number of confirmed cases remains unknown, the number of patient consultations presenting symptoms of Zika fever was estimated to be about 28,000. A retrospective serosurvey, estimated the overall infection rate at 50–66% of the total population (Aubry et al., 2015). The virus strain involved in French Polynesia outbreak was phylogenetically closely related to strains isolated in Yap and in Cambodia, suggesting that ZIKV could have been introduced from these regions (Cao-Lormeau et al., 2014;

Musso et al., 2014). In 2014, ZIKV cases were reported in New Caledonia in the South Pacific; unlike other Pacific regions where the virus source was unknown, in this outbreak the majority of the cases originated from individuals who have been in French Polynesia (ProMEDmail, 2014a; Dupont-Rouzeyrol et al. 2015). In Easter Island, a local festivity that happens every year may have facilitated the introduction of ZIKV through people who came from several Pacific regions including French Polynesia (ProMEDmail, 2014b; Musso, 2015). Following the introduction of imported cases from French Polynesia, other human infections were described and the presence of autochthonous cases of ZIKV was confirmed in the Cook Islands and on Easter Island in 2014 (ECDC, 2014; ProMEDmail, 2014b; WHO, 2015).

In 2015, ZIKV reached the Americas. The first country to report the virus was Brazil, where an outbreak of exanthematic disease was described and affected more than 6000 people in North-east region of that country (ECDC, 2015b; ProMEDmail, 2015; Zanluca et al. 2015). The state of Bahia was the first state to report autochthonous transmission of ZIKV; however, the virus easily spread across the country, where 14 states described autochthonous transmission (PAHO, 2015; WHO, 2015). Several factors may have played a role in the emergence of ZIKV in Brazil. The abundance of *Ae. aegypti* and *Ae. albopictus* vectors probably facilitated the virus emergence. There is speculation that ZIKV was introduced in Brazil through people attending in the 2014 World Cup, although many countries with reported cases of ZIKV did not participate in the competition (Salvador and Fujita, 2015). Similarly athletes attending the World canoe championship, which took place in Rio de Janeiro, may also have been responsible for ZIKV's introduction, as many represented countries had major epidemics at the time (e.g. French Polynesia, New Caledonia, Cook Island and Chile). Concurrent phylogenetic analysis identified the Brazilian ZIKV as an Asian strain, suggesting that the virus may indeed have been entered Brazil through Asia or the South Pacific (Musso,

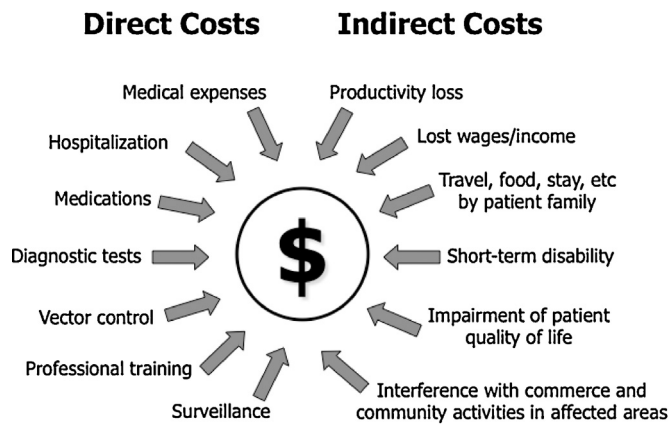


Fig. 2. Economic impact of emerging infectious diseases. Representation of direct and indirect costs accounted for the total expenses of infectious diseases.

2015). Since ZIKV introduction in Brazil, autochthonous transmission has been reported in 31 countries/territories in the Americas (PAHO/WHO, 2016).

### 1.2. Origin of dengue virus and dengue disease

The earliest evidence of dengue-like disease came from reports found in the Chinese medical encyclopedia dating back to AD 265–420 (further edited in AD 610 and AD 992) (Nobuchi, 1979). The disease was linked to the presence of water-associated flying insects and thus named ‘water poison’. Other reports of dengue-like disease were described in the West Indies in 1635 and in Panama in 1699 (Howe, 1977; McSherry, 1982). Following this period, numerous epidemics of disease resembling dengue were described in the continents of Asia, Africa and North America. Between 1779 and 1788, countries including Indonesia, Egypt, Spain and USA have reported dengue-like illness (Bylon, 1780; Christie, 1881; Hirsch, 1883; Pepper, 1941; Howe, 1977) characterizing the wide geographic distribution of the disease.

In Asia, dengue viruses probably first emerged into the human population during deforestation practices for the establishment of agricultural settlements in areas adjacent to the jungle. The peridomestic *Ae. albopictus* mosquito was likely the bridge vector in the transmission of DENV in these areas (Gubler, 2006). Consequently, human migration and trade facilitated introduction and establishment of DENV transmission into more populated areas of tropical Asia, where the *Ae. albopictus* and other peridomestic *Stegomyia* mosquito species were abundant (Gubler, 2006).

The introduction of the anthropophilic African mosquito *Ae. aegypti aegypti* in Asia, as well as in the New World, was facilitated by the sea-borne and slave trade. Beginning in the 17th century, a wide distribution of *Ae. aegypti* was present throughout the tropics, starting in port cities and expanding inwards into the continent as part of the human urbanization expansion. As a result, a favorable environment was established for the transmission of DENV and major dengue epidemics have occurred, which rapidly became pandemics following World War II and continuing until now (Leichtenstern, 1896; Halstead, 1992; Gubler, 1997). Also, following World War II, a new dengue-associated disease affecting predominantly children was described in endemic areas of Southeast Asia (Gubler, 1998). An initial outbreak in Manila in 1953/1954, followed by a larger outbreak in Bangkok in 1958, provided the first clinical description of dengue hemorrhagic fever (DHF) (Hammon et al., 1960).

In the Americas, DENV (and Yellow Fever virus) epidemics were restricted by a control campaign initiated in 1947 by the Pan American Health Organization (PAHO) aiming to eliminate *Ae. aegypti*

from Central and South America. However, with the suspension of the control campaign in the 1970s, the region was reinfested with *Ae. aegypti* and the incidence of dengue started to rise again, reaching the pre-campaign levels by 1995. Since then the geographic distribution of dengue have increased not only in the Americas, but also in other regions of the world, from non-endemic to, in some circumstances, hyperendemic levels (Gubler and Clark, 1995; Gubler, 2002; Shepard et al., 2011).

### 1.3. DENV transmission cycles

Dengue viruses are maintained in nature through two evolutionary and ecologically distinct transmission cycles: a sylvatic cycle, where the virus is transmitted among non-human primates by several arboreal *Aedes spp* mosquitoes, and the urban/human cycle, where virus transmission occurs between humans and mainly the domestic *Ae. aegypti* mosquito (Vasilakis et al., 2011).

The human transmission cycle is by far the most important cycle, considering its impact to public health and by the fact that it is occurring throughout the tropics. Although the *Ae. aegypti* mosquito is the major vector, the peridomestic *Ae. albopictus* and *Ae. polynesiensis* can play a role as secondary vectors of transmission (Gubler et al., 1979; Gubler and Trent, 1994). Human-to-mosquito DENV transmission depends on the magnitude of human viremia necessary to infect mosquitoes and their vector competence (Vazeille-Falcoz et al., 1999; Bennett et al., 2002). Previous studies demonstrated that none or little transmission was achieved when the blood meal titer was below  $10^3$  viral RNA copies/ml and the level of transmission reached close to 100% when a dose was above  $10^9$  viral RNA copies/ml (Nguyen et al., 2013).

### 1.4. Emergence of dengue virus

The emergence of all four DENV serotypes from a common sylvatic ancestor occurred thousand years ago, congruent with the establishment of early human settlements large enough to sustain transmission and was associated with vector changing from arboreal *Aedes* to peridomestic/domestic *Aedes spp.* and human reservoir hosts (Wang et al., 2000). Emergence of the serotypes occurred independently and repeatedly in allopatric regions prior to their expansion in sympatric regions, using similar non-human primate hosts (Vasilakis et al., 2010, 2011).

Phylogenetic studies demonstrated DENV was dispersed rapidly into new locations with the advent of air travel that enabled the movement of humans during the viremic phase of infection, resulting in the shift or extinction of local lineages (Rico-Hesse et al., 1997; Carrington et al., 2005; Myat Thu et al., 2005; Diaz et al., 2006). Ecological factors are also involved in the emergence of DENV. Deforestation is one of the major factors driving sylvatic DENV emergence. As people are exploring new resources deep into the forest, living in areas previously unexplored, the chances of sylvatic DENV emergence are also increasing (Patz et al., 2004). In regions of Asia and Africa, where rapid and uncontrolled urbanization takes place, the risk of sylvatic dengue emergence is high.

### 1.5. Antigenic relationship of dengue viruses

Historically, flaviviruses were classified into serocomplexes based on serologic relationships, such as the virus neutralization profile (Calisher et al., 1989). Following primary DENV infection, the monotypic immune response generates a full protection against homologous viruses, but partial and transient protection, lasting for only a few months, against heterologous DENV strains (Sabin, 1952). As a result, a single person can potentially be infected with all four DENV serotypes during her lifetime (Rothman, 2011).

**Table 1**  
Examples of important arboviruses affecting humans.

Virus	Family	Vector	Vertebrate hosts	Geographic distribution	References
Chikungunya	<i>Togaviridae</i>	Mosquitoes: <i>Aedes</i> and <i>Culex</i> spp.	Primates, birds, cattle, and rodents	Africa, Asia, Europe, Americas, Oceania	Busch and Erickson (2015), Staples et al. (2015), Vanlandingham et al. (2006)
Mayaro	<i>Togaviridae</i>	Mosquitoes: <i>Haemagogus</i> spp.	Primates, other mammals, birds	South and Central America	Stanton (1919), Tesh et al. (1999)
Ross River	<i>Togaviridae</i>	Mosquitoes: <i>Aedes</i> and <i>Culex</i> spp.	Marsupials, other mammals, birds	Oceania and Asia	Klapsing et al. (2005), PHAC (2014)
O'nyong-nyong	<i>Togaviridae</i>	Mosquitoes: <i>Anopheles</i> spp.	?	Africa	PHAC (2011), Vanlandingham et al. (2006)
Sindbis	<i>Togaviridae</i>	Mosquitoes: <i>Aedes</i> , <i>Culex</i> , and <i>Culiseta</i> spp.	Birds	Europe, Africa, Oceania, Asia	ECDC (2015a), Kurkela et al. (2008)
Barmah Forest	<i>Togaviridae</i>	Mosquitoes: <i>Aedes</i> and <i>Culex</i> spp.	Birds? Marsupials, Others?	Oceania	Ehlkes et al. (2012), Naish et al. (2011)
Eastern equine encephalitis	<i>Togaviridae</i>	Mosquitoes: <i>Culiseta</i> , <i>Aedes</i> , <i>Coquillettia</i> , and <i>Culex</i> spp.	Birds, horses, other mammals	Americas	CDC (2015a), CFSPH (2015), Weaver and Reisen (2010), Zacks and Paessler (2010)
Western equine encephalitis	<i>Togaviridae</i>	Mosquitoes: <i>Culex</i> , <i>Aedes</i> , <i>Ochlerotatus</i> , and <i>Coquillettia</i> spp.	Birds, horses, other mammals	Americas	CFSPH (2015), Weaver and Reisen (2010), Zacks and Paessler (2010)
Venezuelan equine encephalitis	<i>Togaviridae</i>	Mosquitoes: <i>Culex</i> , <i>Ochlerotatus</i> , <i>Anopheles</i> , <i>Mansonia</i> , <i>Psorophora</i> , <i>Aedes</i> spp. and others	Horses, Rodents, Other mammals, Birds	Americas	CFSPH (2015), Weaver and Reisen (2010), Zacks and Paessler, (2010)
Dengue	<i>Flaviviridae</i>	Mosquitoes: <i>Aedes</i> spp	Primates	Asia, Americas, Africa, Europe, Oceania	CDC (2016a), Vasilakis and Cardosa et al. (2011)
Yellow Fever	<i>Flaviviridae</i>	Mosquitoes: <i>Aedes</i> and <i>Haemagogus</i> spp.	Primates	South America, Africa	Gershman and Staples (2015), Yactayo et al. (2015)
West Nile	<i>Flaviviridae</i>	Mosquitoes: <i>Culex</i> spp	Birds, Horses, Other Mammals	Africa, Asia, Europe, Oceania, Americas	CDC (2015c), Lanciotti et al. (1999), Mackenzie et al. (2004), Sambri et al. (2013)
Japanese encephalitis	<i>Flaviviridae</i>	Mosquitoes: <i>Culex</i> spp	Birds, Pigs	Asia, Oceania	Erlanger et al. (2009), Han et al. (2014), Huang et al. (2015), Mackenzie et al. (2004)
Murray Valley encephalitis	<i>Flaviviridae</i>	Mosquitoes: <i>Culex</i> spp	Birds	Oceania	CDC (2013a), Mackenzie et al. (2004), Selvey et al. (2014)
Zika virus	<i>Flaviviridae</i>	Mosquitoes: <i>Aedes</i> spp	Primates	Africa, Asia, Oceania, Central and South America	Campos et al. (2015), CDC (2016b); Hayes, (2009), WHO (2015)
Rocio	<i>Flaviviridae</i>	Mosquitoes: <i>Psorophora</i> and <i>Aedes</i> spp	Birds	South America	Medeiros et al. (2007), Mitchell et al. (1986), Silva et al. (2014)
St. Louis encephalitis	<i>Flaviviridae</i>	Mosquitoes: <i>Culex</i> spp	Birds, Bats, Other Mammals	Americas	CDC, (2010), Kopp et al., (2013), Reisen (2003)
Kyasanur Forest disease	<i>Flaviviridae</i>	Ticks: <i>Hemaphysalis</i> spp.	Primates, Rodents, Other Mammals	Asia	CDC (2014), Holbrook (2012)
Omsk hemorrhagic fever	<i>Flaviviridae</i>	Ticks: <i>Dermacentor</i> and <i>Ixodes</i> spp Mosquitoes:?	Rodents, Voles, Other Mammals	Europe	CDC (2013b), Ruzek et al. (2010)
Tick-borne encephalitis	<i>Flaviviridae</i>	Ticks: <i>Ixodes</i> spp	Rodents, Goats, Sheep, Cows, Other Mammals, Birds?	Europe, Asia	Bogovic and Strle (2015), Fischer et al. (2015)
Sandfly fever	<i>Bunyaviridae</i>	Sandflies: <i>Phlebotomus</i> spp.	Birds? Mammals?	Europe, Asia, Africa	Guler et al. (2012), Tufan and Tasyaran (2013)
Rift Valley fever	<i>Bunyaviridae</i>	Mosquitoes: <i>Aedes</i> , <i>Ochlerotatus</i> , <i>Stegomyia</i> , <i>Anopheles</i> , <i>Culex</i> , <i>Neomelanimonion</i> , <i>Eretmapodites</i> and others	Cows, Sheep, Camels, Goats and Other Mammals	Africa, Asia	Nanyingi et al. (2015), Olive et al., (2012), Tantely et al. (2015)
La Crosse encephalitis	<i>Bunyaviridae</i>	Mosquitoes: <i>Aedes</i> spp	Rodents	North America	CDC (2015b), Harris et al., (2015)
Crimean-Congo hemorrhagic fever	<i>Bunyaviridae</i>	Ticks: <i>Hyalomma</i> spp	Cows, Sheep, Goats, Hares and Other Mammals	Europe, Asia, Africa	Chinikar et al. (2008), Shayan et al., (2015), Tuncer et al. (2014), Whitehouse (2004)
Oropouche	<i>Bunyaviridae</i>	Midges: <i>Culicoides</i> sp	Primates? Sloths? Birds?	Central and South America	Anderson et al. (1961), Mourao et al. (2009), Nunes et al., (2005), Vasconcelos et al. (2011)
Severe febrile thrombocytopenia syndrome	<i>Bunyaviridae</i>	Ticks: <i>Haemaphysalis</i> sp	?	Asia	Takahashi et al. (2014), Yu et al. (2011), Yun et al. (2013)
Chandipura	<i>Rhabdoviridae</i>	Sandflies: <i>Phlebotomus</i> and <i>Sergentomyia</i> spp.	Hedgehogs, Others?	Asia and Africa	Fontenille et al. (1994), Maiti et al. (2014), Menghani et al. (2012), Rao et al. (2004), Tesh, (1988), Tesh and Modi, (1983)
Bluetongue	<i>Reoviridae</i>	Midges: <i>Culicoides</i> spp	Sheep, Cows, Other Mammals	Africa, Asia, Europe, Oceania, Americas (all except Antarctica)	Maclachlan (2011), OIE (2013)

To determine the antigenic relationships among the DENV, it is common to represent their neutralization profile against a panel of several different sera known to react with specific DENV types (Vasilakis et al., 2008a). It has been demonstrated that sera obtained from humans during a primary infection or immunized with DENV exhibit strong homotypic neutralization against different urban and sylvatic DENV, where the heterotypic neutralization is absent or last for a short period of time (Vasilakis et al., 2008a,b). However, many times these analyses are difficult to interpret due to the intrinsic variability among samples derived from different hosts or infection histories (Thomas et al., 2009; van Panhuis et al., 2010). More recently, the antigenic relationships of DENV have been studied using antigenic cartography to reduce some measurement errors of neutralization against multiple serotypes (Katzelnick et al., 2015). The analyses of a panel of human and non-human primate sera derived from experimental infection, as well as vaccination and natural infection demonstrated that the majority of DENV isolates were clustered into each DENV type classification. However, a number of viruses were located more adjacent to another DENV type than its own type and the distance within and between types was similar. The neutralization profile of antisera demonstrated similar trend, with groups close to the homologous virus type, but also close to a heterologous DENV (Katzelnick et al., 2015).

### 1.6. Requirements for dengue emergence

Vector switching from arboreal primatophilic mosquito species to peridomestic mosquito vectors (*Ae. aegypti* and *Ae. albopictus*) may have facilitated the emergence of sylvatic strains into the urban transmission cycle (Wang et al., 2000). The expansion of non-human primates and human populations in different geographic areas allowed the sustained transmission of DENV into the major tropical regions of the world.

The possibility of sylvatic strains to enter the human transmission cycle was evaluated by both *in vitro* and *in vivo* human models of DENV replication. The purpose of those studies was to verify if any adaptation is required to sylvatic DENV strains been established in a new transmission cycle (Vasilakis et al., 2007). Replication of sylvatic DENV-2 in human monocytes-derived dendritic cells (moDCs) was comparable with human DENV-2 strains, suggesting they can promptly infect human hosts (Vasilakis et al., 2007). Other study using cell lines representing human (Huh-7), monkey (Vero) and mosquito (C6/36) hosts demonstrated that the human strains only have higher level of viral replication in the human cell, but virus titer were similar in the monkey and mosquito cell lines (Vasilakis et al., 2008b). Collectively, these studies demonstrate the ability of sylvatic DENV strains to replicate in a range of host cells, suggesting that their emergence in the human population is not dependent on adaptation to new hosts, but most dependent on the opportunity of the sylvatic virus to infect a wide range of hosts and eventually emerge into a human transmission cycle (Fig. 1).

### 1.7. The impact of emerging infectious diseases

The impact of emerging infectious diseases (EIDs) is not only a public health threat, but also an economic burden, and has both direct and indirect consequences. The total investment for the development of tools for early detection of pathogens, as well as, sustainable surveillance for potential pathogens emerging into a population, are costs that must be considered as a direct consequence of EIDs economic impact (Fig. 2). These costs are incurred not only in diagnostic laboratory settings, but also directly in the field, in hospitals or other point-of-care (POC) health care facilities. Examples of indirect costs accountable for the economic burden of EIDs are productivity losses from work absence, short-term disability and impairment of patient quality of life (Fig. 2). Further steps

following the introduction of an EID should be considered such as, training of health care and other professionals dealing with the emerging pathogen, reducing the possibility of transmission to a larger population, and treatment responses, if available (Table 1).

The World Economic Forum has listed the spread of EIDs as one of the top risk factors to cause potential economic loss to the world population (WEF, 2015). Although the economic impact of EIDs is difficult to be accurately determined, several studies have been conducted to estimate their economic burden to society (Newcomb, 2003; Zohrabian et al., 2004, 2006; Barber et al., 2010). For example, during the emergence of severe acute respiratory syndrome (SARS) in 2003 in China, the virus rapidly spread to several countries in Asia, Europe and South and North America, in only a few months, affecting 8098 people resulting in 774 deaths (CDC, 2003). Its economic impact was estimated between 50 and 100 billion U.S. dollars (Newcomb, 2003). The economic impact of the 2002 outbreak of West Nile virus (WNV) in Louisiana, which resulted in 24 deaths of the total 329 reported cases, was estimated to cost approximately 20 million U.S. dollars. These costs included inpatient and outpatient visits, loss of work productivity, costs incurred by public health departments and mosquito control agencies (Zohrabian et al., 2004, 2006). The spread of WNV in California and an outbreak in Sacramento County in 2005 resulted in 163 human cases, whose economic impact was estimated to be near 3 million U.S. dollars, which included medical visits and treatment, job productivity loss and mosquito control (Barber et al., 2010).

Additional studies have also attempted to anticipate the cost of potential outbreaks. In Australia, as one example of an isolated geographic area, the introduction of exotic diseases, as well as, pests and weeds could have a potential cost of over \$1 billion Australian dollars (Murray et al., 2012). A study on the next influenza pandemic in the United States, estimated 89,000–207,000 deaths and an economic loss of 71.3–166.5 billion U.S. dollars. The cost was based on estimations for patient hospitalizations, outpatient visits and expenses for drug treatment and did not account for indirect costs interfering with commerce and community activities in affected areas (Meltzer et al., 1999). Overall, these examples highlight the impact EIDs can create for human populations and demonstrate the importance of controlling these diseases. One example would be the use of immunizations, when a vaccine is available.

## 2. Conclusions

The majority of viruses with potential to produce important epidemics are zoonotic, which means that they are originated in an animal hosts and are driven by several emergence forces, including changes in ecological and social behaviors, supporting the possibility to spill over into the human population. The understanding of the potential for spread of emerging infectious diseases is essential in the prevention and control of large-scale outbreaks and effective use of resources to combat them. Knowing the source and modes to human transmission allows the prediction of disease appearance and implementation of global measures to eliminate the risk. As example, the eradication campaigns initiated in the late 40's to eliminate *Ae. aegypti* from Central and South America were effective during the time they were in effect because of government support, rigorous compliance and population support, which demonstrates the importance and effectiveness of coordinated global measures to combat diseases. Isolated prevention measures won't have the same results, or even been completely unsuccessful. Nowadays, with the advance of new technologies for detection, treatment and control of diseases and quick and easy dissemination of information, prevention measures should be more effective and time of response should be much shorter. Based on the current knowl-

edge, it seems that a successful program will require the integration of different segments involved in the detection, treatment and prevention of diseases including diagnostic labs, hospitals, and government agencies, among others.

In the case of dengue as one example of global human threat, to clearly comprehend and anticipate the occurrence of sylvatic DENV emergence is fundamental to clarify the ecological and epidemiological aspects related to this virus cycle. There is enough evidence to support the existence of endemic serotypes as a result of independent events through cross-species transmission of sylvatic DENV. However, there is clear indication that sylvatic DENV come into close contact with humans in Asia and Africa, and possibly in other parts of the world, originating sporadic severe dengue disease that can spillover in the urban environment. The sylvatic cycle of DENV has not been intensively explored and not considerable attention is given to the consequences involved in viruses coming from unexplored habitats. Additionally, different of what was proposed in the past, recent studies indicated that the emergence of sylvatic DENV represent a real threat to people considering the inexistence of an adaptation barrier to sylvatic viruses emerge into the human population. Moreover, the diversity of DENV strains and the emergence of new isolates have important consequences in the development of therapeutics, including vaccines currently in the developmental and clinical trial phases.

The establishment of preventive measures and surveillance of current and newly identified infectious diseases should be based on several factors, many of them discussed in this review, starting with the knowledge of the disease ecology, human behavior, socio-economic factors of a target population or area, among others. Policy-makers and the distribution of resources must consider not only short-term measures, but also long-term goals to maintain the infrastructure and research programs, from basic science through translational research. Nowadays, human travel and rapid transportation of products, live animals, insects, and so forth, not only locally, but around the world have the potential for quick dissemination or re-emergence of diseases. Anthropogenic land-use changes, especially intensification of agriculture and livestock production, increase the risk of pathogen spillover from wildlife hosts to the human population. Knowing the dynamic of diseases allows more effective surveillance and implementation of strategies that are critical for their control as well for the allocation of scarce financial resources.

## Acknowledgements

This work was supported by grant 1U01AI115577 from the U.S. National Institutes of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have no conflicting financial interests.

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