THE EMERGENCE OF ARTHROPOD-BORNE VIRAL DISEASES:
A GLOBAL PROSPECTIVE ON DENGUE, CHIKUNGUNYA AND ZIKA FEVERS

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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.

Keywords
Arboviruses; dengue; Zika; chikungunya; human transmission; emergence

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.

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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, Shaw et al. 2000; May, Gupta 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, Latham et al. 2001; Jones, Patel et al. 2008).

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, George 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, Patel et al. 2008; Newcomb, Harrington et al. 2011; Karesh, Dobson 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 (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, Epstein et al. 1993; Morse 1994). For example, bats represent a major source of zoonotic viruses (Calisher, Childs et al. 2006), including rabies, Nipah (NiV), SARS (SARS-CoV) and Ebola (EBOV) viruses (Taylor, Latham et al. 2001; Woolhouse, Haydon 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; Weaver 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, Suarez et al. 2012; Bisset, Marin et al. 2013).

**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, Lefkowitz 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, Brault et al. 2000; Volk, Chen 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* (Diaallo, Thonnnon et al. 1999; Volk, Chen et al. 2010; Diaallo, Sall et al. 2012). In 2004, CHIKV emergence was reported in the coastal area of Kenya (Chretien, Anyamba et al. 2007) following a global expansion to different regions of Africa, Asia, several islands in the Indian Ocean (Hochedez, Jaureguiberry et al. 2006; Lanciotti, Kosoy et al. 2007; Taubitz, Cramer et al. 2007) and temperate areas in Europe (Rezza, Nicoletti et al. 2007; Grandadam, Caro 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, Jaureguiberry et al. 2006; Lanciotti, Kosoy et al. 2007; Taubitz, Cramer 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, Brault et al. 2000; Volk, Chen et al. 2010). The different CHIKV lineages can exhibit distinct patterns of infectivity and transmissibility in the mosquito vectors (Arias-Goeta, Mousson et al. 2013; Vega-Rua, Zouache et al. 2013). The acquisition of specific mutations in the E1 (Tsetsarkin, Vanlandingham et al. 2007; Vazeille, Moutailler et al. 2007) and E2 (Tsetsarkin and Weaver 2011; Tsetsarkin, Chen 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, LaDeau 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, Kosoy 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, Nougairede 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, Faria 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, Faria 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, Ksiazek et al. 1981; Duffy, Chen et al. 2009; Foy, Kobyliński et al. 2011; Kutsuna, Kato et al. 2014). ZIKV was first isolated in 1947 from the blood of a sentinel rhesus monkey exposed in the canopy of Zika Forest in Uganda during epidemiologic studies of yellow fever (Dick, Kitchen et al. 1952). Subsequent isolations of the virus were made from *Aedes africanus*, *Ae. luteocephalus* and *Ae. furcifer* (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, Schuh 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, Garcia et al. 1969); and in 1977, the first human case was described in Indonesia (Olson, Ksiazek 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, Rosen et al. 1967; Cao-Lormeau, Roche et al. 2011; Musso, Roche 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, Teissier 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, Roche et al. 2014; Musso, Nilles 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-Rouzyrol, O'Connor 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 2015a).

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 6,000 people in Northeast region of that country (ECDC 2015b; ProMEDmail 2015; Zanluca, de Melo 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 2015a; WHO 2015a). 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 2015). Since ZIKV introduction in Brazil, autochthonous transmission has been reported in 31 countries/territories in the Americas (PAHO/WHO 2016).

**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* 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, Rudnick 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, Couteville et al. 2011).

### 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, Cardosa 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, Nalim 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, Mousson et al. 1999; Bennett, Olson 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, Lee et al. 2013).

**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, Ni 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, Hanley et al. 2010; Vasilakis, Cardosa et al. 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, Harrison et al. 1997; Carrington, Foster et al. 2005; Myat Thu, Lowry et al. 2005; Diaz, Black 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, Daszak et al. 2004). In regions of Asia and Africa, where rapid and uncontrolled urbanization takes place, the risk of sylvatic dengue emergence is high.

**Antigenic relationship of dengue viruses**

Historically, flaviviruses were classified into serocomplexes based on serologic relationships, such as the virus neutralization profile (Calisher, Karabatsos 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).

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, Durbin 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, Durbin et al. 2008). However, many times these analyses are difficult to interpret due to the intrinsic variability among samples derived from different hosts or infection histories (Thomas, Nisalak et al. 2009; van Panhuis, Gibbons et al. 2010). More recently, the antigenic relationships of DENV have been studied using antigenic cartography to reduce some measurements errors of neutralization against multiple serotypes (Katzelnick, Fonville et al. 2015). The analyses of a panel of human and non-human primate sera derived from experimental infection, as well 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, Fonville et al. 2015).

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, Ni 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, Shell 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, Shell 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, Fokam 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.

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.

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, Meltzer et al. 2004; Zohrabian, Hayes et al. 2006; Barber, Schleier 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 8,098 people resulting in 774 deaths (CDC 2003). Its economic impact was estimated between 50 to 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, Meltzer et al. 2004; Zohrabian, Hayes et al. 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, Schleier 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, Skerratt et al. 2012). A study on the next influenza pandemic in the United States, estimated 89,000 to 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, Cox 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.

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 knowledge, 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 being 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.

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Highlights

Arboviruses are still expanding their geographic distribution and causing significant public health impact around the world.

Dengue, chikungunya and Zika viruses are mosquito-transmitted pathogens threatening the human population in many tropical and subtropical regions of the world.

Global travel and trade have facilitated the emergence of vector-borne diseases.

Surveillance of areas close to the forest is important to monitor the emergence of pathogens from their sylvatic cycle into the urban transmission cycle.
Figure 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.
Figure 2. Economic impact of emerging infectious diseases
Representation of direct and indirect costs accounted for the total expenses of infectious diseases.
Table 1
Examples of important arboviruses affecting humans.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Family</th>
<th>Vector</th>
<th>Vertebrate hosts</th>
<th>Geographic distribution</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chikungunya</td>
<td>Togaviridae</td>
<td>Mosquitoes: Aedes and Culex spp.</td>
<td>Primates, birds, cattle, and rodents</td>
<td>Africa, Asia, Europe, Americas, Oceania</td>
<td>8, 144, 159</td>
</tr>
<tr>
<td>Mayaro</td>
<td>Togaviridae</td>
<td>Mosquitoes: Haemagogus spp.</td>
<td>Primates, other mammals, birds</td>
<td>South and Central America</td>
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</tr>
<tr>
<td>Ross River</td>
<td>Togaviridae</td>
<td>Mosquitoes: Aedes and Culex spp.</td>
<td>Marsupials, other mammals, birds</td>
<td>Oceania and Asia</td>
<td>76, 123</td>
</tr>
<tr>
<td>O'nyong-nyong</td>
<td>Togaviridae</td>
<td>Mosquitoes: Anopheles spp.</td>
<td></td>
<td>Africa</td>
<td>122, 159</td>
</tr>
<tr>
<td>Sindbis</td>
<td>Togaviridae</td>
<td>Mosquitoes: Aedes, Culex, and Culiseta spp.</td>
<td>Birds</td>
<td>Europe, Africa, Oceania, Asia</td>
<td>38, 78</td>
</tr>
<tr>
<td>Eastern equine encephalitis</td>
<td>Togaviridae</td>
<td>Mosquitoes: Culiseta, Aedes, Coquillettidia, and Culex spp.</td>
<td>Birds, horses, other mammals</td>
<td>Americas</td>
<td>22, 27, 174, 185</td>
</tr>
<tr>
<td>Western equine encephalitis</td>
<td>Togaviridae</td>
<td>Mosquitoes: Culex, Aedes, Ochlerotatus, and Coquillettidia spp.</td>
<td>Birds, horses, other mammals</td>
<td>Americas</td>
<td>27, 174, 185</td>
</tr>
<tr>
<td>Venezuelan equine encephalitis</td>
<td>Togaviridae</td>
<td>Mosquitoes: Culex, Ochlerotatus, Anopheles, Mansonia, Psorophora, Aedes spp. and others</td>
<td>Horses, Rodents, Other mammals, Birds</td>
<td>Americas</td>
<td>27, 174, 185</td>
</tr>
<tr>
<td>Dengue</td>
<td>Flaviviridae</td>
<td>Mosquitoes: Aedes spp</td>
<td>Primates</td>
<td>Asia, Americas, Africa, Europe, Oceania</td>
<td>25, 165</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Flaviviridae</td>
<td>Mosquitoes: Aedes and Haemagogus spp.</td>
<td>Primates</td>
<td>South America, Africa</td>
<td>45, 182</td>
</tr>
<tr>
<td>West Nile</td>
<td>Flaviviridae</td>
<td>Mosquitoes: Culex spp</td>
<td>Birds, Horses, Other Mammals</td>
<td>Africa, Asia, Europe, Oceania, Americas</td>
<td>24, 81, 88, 137</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Flaviviridae</td>
<td>Mosquitoes: Culex spp</td>
<td>Birds, Pigs</td>
<td>Asia, Oceania</td>
<td>41, 60, 68, 88</td>
</tr>
<tr>
<td>Murray Valley encephalitis</td>
<td>Flaviviridae</td>
<td>Mosquitoes: Culex spp</td>
<td>Birds</td>
<td>Oceania</td>
<td>19, 88, 139</td>
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<tr>
<td>Zika virus</td>
<td>Flaviviridae</td>
<td>Mosquitoes: Aedes spp</td>
<td>Primates</td>
<td>Africa, Asia, Oceania, Central and South America</td>
<td>13, 26, 62, 176</td>
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<tr>
<td>Rocio</td>
<td>Flaviviridae</td>
<td>Mosquitoes: Psorophora and Aedes spp</td>
<td>Birds</td>
<td>South America</td>
<td>95, 98, 142</td>
</tr>
<tr>
<td>St. Louis encephalitis</td>
<td>Flaviviridae</td>
<td>Mosquitoes: Culex spp</td>
<td>Birds, Bats, Other Mammals</td>
<td>Americas</td>
<td>18, 77, 129</td>
</tr>
<tr>
<td>Kyasanur Forest disease</td>
<td>Flaviviridae</td>
<td>Ticks: Hemaphysals spp.</td>
<td>Primates, Rodents, Other Mammals</td>
<td>Asia</td>
<td>21, 66</td>
</tr>
<tr>
<td>Omuk hemorrhagic fever</td>
<td>Flaviviridae</td>
<td>Ticks: Dermacentor and Ixodes spp Mosquitoes?</td>
<td>Rodents, Volves, Other Mammals</td>
<td>Europe</td>
<td>20, 133</td>
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<tr>
<td>Tick-borne encephalitis</td>
<td>Flaviviridae</td>
<td>Ticks: Ixodes spp</td>
<td>Rodents, Goats, Sheep, Cows, Other Mammals, Birds?</td>
<td>Europe, Asia</td>
<td>7, 42</td>
</tr>
<tr>
<td>Virus</td>
<td>Family</td>
<td>Vector</td>
<td>Vertebrate hosts</td>
<td>Geographic distribution</td>
<td>References</td>
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<tr>
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<tr>
<td>La Crosse encephalitis</td>
<td>Bunyaviridae</td>
<td>Mosquitoes: Aedes spp</td>
<td>Rodents</td>
<td>North America</td>
<td>23, 61</td>
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<tr>
<td>Crimean-Congo hemorrhagic fever</td>
<td>Bunyaviridae</td>
<td>Ticks: Hyalomma spp</td>
<td>Cows, Sheep, Goats, Hares and Other Mammals</td>
<td>Europe, Asia, Africa</td>
<td>28, 140, 157, 175</td>
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<tr>
<td>Severe febrile thrombocytopenia syndrome</td>
<td>Bunyaviridae</td>
<td>Ticks: Haemaphysalis sp</td>
<td>?</td>
<td>Asia</td>
<td>145, 183, 184</td>
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<tr>
<td>Chandipura</td>
<td>Rhabdoviridae</td>
<td>Sandflies: Phlebotomus and Sergentomyia spp.</td>
<td>Hedgehogs, Others?</td>
<td>Asia and Africa</td>
<td>43, 91, 97, 128, 149, 150</td>
</tr>
<tr>
<td>Bluetongue</td>
<td>Reoviridae</td>
<td>Midges: Culicoides spp</td>
<td>Sheep, Cows, Other Mammals</td>
<td>Africa, Asia, Europe, Oceania, Americas (all except Antarctica)</td>
<td>89, 115</td>
</tr>
</tbody>
</table>