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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.

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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 occured 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 costal 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*