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Interaction of Flavivirus with their mosquito vectors and their impact on the human health in the Americas

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ABSTRACT

Some of the major arboviruses with public health importance, such as dengue, yellow fever, Zika and West Nile virus are mosquito-borne or mosquito-transmitted Flavivirus. Their principal vectors are from the family *Culicidae*, *Aedes aegypti* and *Aedes albopictus* being responsible of the urban cycles of dengue, Zika and yellow fever virus. These vectors are highly competent for transmission of many arboviruses. The genetic variability of the vectors, the environment and the viral diversity modulate the vector competence, in this context, it is important to determine which vector species is responsible of an outbreak in areas where many vectors coexist. As some vectors can transmit several flaviviruses and some flaviviruses can be transmitted by different species of vectors, through this review we expose importance of yellow fever, dengue and Zika virus in the world and the Americas, as well as the updated knowledge about these flaviviruses in their interaction with their mosquito vectors, guiding us on what is probably the beginning of a new stage in which the simultaneity of outbreaks will occur more frequently.

1. Yellow fever, dengue and Zika history of transmission in the Americas

The arboviruses (ARthropod-BOrne virus) with the greatest impact on public health are from Flavivirus genus and include dengue virus (DENV), yellow fever virus (YFV) and Zika virus (ZIKV). *Flavivirus* is a member of the *Flaviviridae* family, and is the only arbovirus in this group which utilizes mosquitoes and ticks as primary vectors.

The term yellow fever appeared in 1750, however the disease was described in 6th century Europe. Yellow fever outbreaks were notorious in the Americas, killing 10% of Caribbean populations annually from 1750 to 1900 [1]. The European arrival to the Americas was accompanied by the introduction of YFV and of *Aedes aegypti* [2]. *Ae.* aegypti was described as the vector of yellow fever in 1881 [3]. Yellow fever played an important role in Panama's Canal construction history in the 19th and 20th century, in part causing the French Panama Canal failure [4]. Dr. William C. Gorgas carried out sanitation measures in Cuba and Panama leading to the eradication of urban cases of yellow fever and dengue in November 1905. These measures were partially responsible for the successful construction of the Panama Canal by the United States of America [5] (Fig. 1). Many eradications and reintroductions of YFV were reported during this time, with the last sylvatic case reported in 1974. Unfortunately, the number of cases of yellow fever has been increasing over the past years in South America, mainly in Brazil, Peru, and Colombia (PAHO/WHO 2017). These outbreaks are mainly sylvatic. The most recent urban yellow fever outbreak occurred in 1997 in Santa Cruz, Bolivia [6]. The current disease containment in the Americas is precarious and yellow fever remains a serious threat to Panama and Central America, especially given the large amount of immigrants from South American countries.

In contrast to yellow fever, dengue has been more difficult to eliminate with vector control measures. Dengue was first described in the Americas in 1635 in Martinique and Guadeloupe and then in 1699 in Panama [7,8] (Fig. 1). In the 1940's, the Americas instituted a vector control campaign resulting in elimination of *Ae. aegypti*. By 1958, many countries were declared *Ae. aegypti* free; however, from 1969 to 1985 intermittent reinfection and eradication cycles occurred with establishment of *Ae. aegypti* population in the 1970s-1980's. Panama was reinfested with *Ae. aegypti* in 1985, and dengue was reintroduced in 1993 after large outbreaks in South America and the Caribbean [9]. DENV has continued to cause annual outbreaks throughout Central/South America despite the introduction

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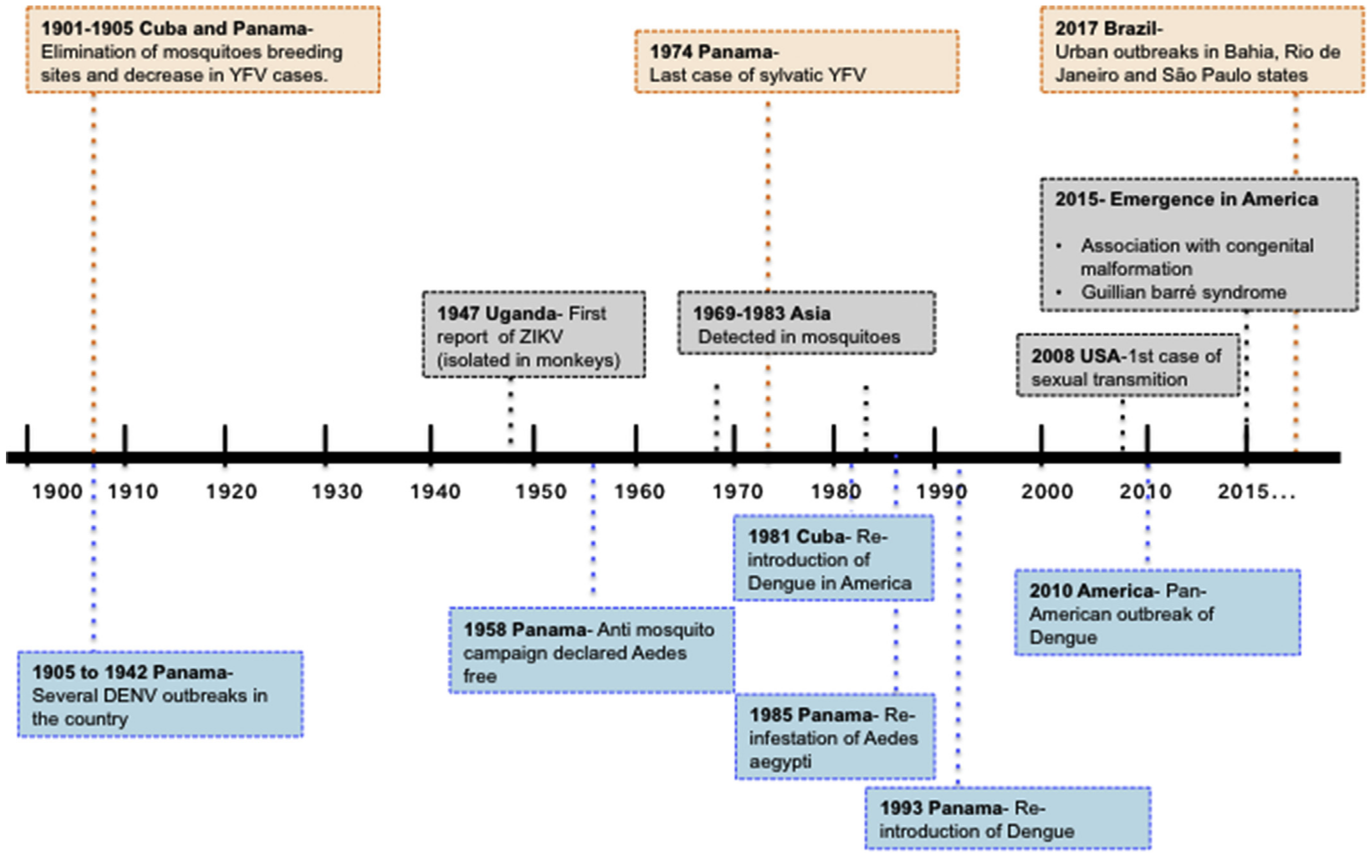

Fig. 1. Time-line frame of Yellow fever (in orange), Dengue (in blue) and Zika (in grey) viruses circulation in the Americas during the 20th and 21st century.

of other emerging arboviral diseases such as Chikungunya and Zika [10–13].

Zika virus was introduced into Brazil in 2014 via Southeast Asia causing a large outbreak, which was associated with neonatal microcephaly due to maternal infection. The rates of Guillain-Barré syndrome also rose dramatically and were associated with the Zika virus outbreak [14]. ZIKV has established itself and continues to circulate throughout the Caribbean, Central and South American countries.

The current epidemiologic situation in the Americas is of great concern as DENV, ZIKV and chikungunya virus (CHIKV) are currently circulating together. Furthermore, YFV is currently circulating in Brazil, Peru, and Colombia.

2. The vectors and transmission cycles of Yellow fever, dengue and Zika viruses

Flaviviruses have three overlapping transmission cycles: a sylvatic cycle, a rural cycle that occurs in “emergence zones”, and an urban cycle. The sylvatic Flavivirus transmission cycle involves an arthropod vector and a non-human vertebrate reservoir (birds, rodents, bats, or primates). Humans are infected by mosquito vectors in emergence zones where human activity overlaps with sylvatic cycles (Fig. 2). The urban cycle utilizes domesticated mosquitoes and humans as hosts.

For Flaviviruses, relevant mosquitoes are from family *Culicidae*, with *Aedes* (*Ae. albopictus* and *Ae. aegypti*) transmitting Dengue, Yellow Fever and Zika; and *Culex*, transmitting West Nile, Japanese Encephalitis, and St. Louis encephalitis. Other genera such as *Haemagogus*, *Sabethes*, *Mansonia*, *Deinocerites* are implicated in sylvatic transmissions of arboviruses. The *Culicidae* are a group of insects with bloodsucking feeding behavior [15,16]. This behavior has facilitated the inoculation of arboviruses in various species of vertebrates [17].

The mosquitoes involved in the sylvatic transmission cycles of DENV and ZIKV are various *Aedes spp.* in Africa and Asia, as no sylvatic cycle has been reported in the Americas. Vectors in emergence zones for DENV are *Ae. furcifer* in Africa and *Ae. albopictus* in Asia whereas for ZIKV it is *Ae. vittatus* in Africa (Fig. 2). The Yellow Fever virus sylvatic cycle is transmitted by the genera *Haemagogus* and *Sabethes* in the Americas [18,19], and by the genus *Aedes* in Africa. In the emergence zone different *Aedes spp* are implicated in both continents. Sylvatic mosquitoes have adapted to urban environments and utilize humans as amplifying hosts. *Ae. albopictus* is more abundant than *Ae. aegypti* in regions of Brazil where the sylvatic YFV outbreak is occurring, raising concern that it may enter an urban cycle. However, *Ae. albopictus* is less susceptible to YFV than *Ae. aegypti* [20], thus the presence of *Ae. aegypti* makes re-urbanization of yellow fever possible [6,21]. The urban cycles of *Ae. aegypti* and *Ae. albopictus* [22,23] have contributed to the increase in incidence of chikungunya, dengue, and Zika worldwide [24–29] (Fig. 2). In addition there is recent, albeit controversial evidence that mosquitoes of the genus *Culex* may also be able to transmit Zika virus [30]. Future investigations should attempt to determine which animal species are competent reservoirs for DENV and ZIKV and could support a sylvatic cycle, and which vectors could be active in the emergence zone for YFV, DENV, and ZIKV. Further studies exploring the role of *Culex* versus *Aedes* vectors for ZIKV are also needed, as *Culex* is widespread throughout the Americas.

Ae. aegypti is originally from Africa but is now found in tropical and subtropical regions all around the world [31]. In the Americas,