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Prediction and prevention of urban arbovirus epidemics: A challenge for the global virology community

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A B S T R A C T

The recent emergence and rapid spread of Zika virus in tropical regions of the Western Hemisphere took arbovirologists and public health officials by surprise, and the earlier transfers of West Nile and chikungunya viruses from the Old to the New World were also unexpected.

These pandemics underscore the increasing threat of zoonotic arboviruses, especially those that are capable of entering into human-amplified, urban transmission cycles transmitted by *Aedes* (*Stegomyia*) *aegypti* and sometimes other *Aedes* (*Stegomyia*) spp. mosquitoes. This review serves as an introduction to a World Health Organization-sponsored conference to be held on June 18–19, 2018 in Geneva, titled "From obscurity to urban epidemics: what are the next urban arboviruses?" It is intended to set the stage and fuel discussions of future urban arbovirus threats, how we can predict these risks from known and unknown viruses, and what factors may change these risks over time.

1. Introduction

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2. Arbovirus transmission cycles and history of urbanization

Arthropod-borne viruses (arboviruses) are transmitted biologically (requiring replication in the arthropod) among vertebrate hosts by a wide variety of vectors, including mosquitoes, ticks and others. All arboviruses that affect human health are zoonotic pathogens that originate in enzootic transmission cycles involving wild animals that serve as amplification and/or reservoir hosts (Weaver and Reisen, 2010). Those viruses that cause large epidemics, typically based in cities, are transmitted by mosquitoes and occasionally other arthropods such as *Culicoides* spp, midges (Oropouche virus).

Cycles and mechanisms of maintenance and transmission to humans of mosquito-borne pathogens can be grouped into three categories:

1. The vast majority of arboviruses infect people "accidentally" via spillover, when a vector first bites a viremic enzootic (wild animal) host and then, following extrinsic incubation, with replication and dissemination to the saliva, transmits during a subsequent feeding on a human (Fig. 1). Examples of arboviruses that cause a significant human disease burden only via enzootic spillover include West Nile (WNV) and tick-borne encephalitis viruses.
2. A few arboviruses are able to undergo secondary amplification in domesticated animals to increase levels of circulation and consequently human spillover infections (Fig. 2). Examples include Rift Valley fever virus (RVFV, amplification in livestock), Japanese encephalitis (JEV, swine) and epizootic/epidemic strains of Venezuelan equine encephalitis virus (VEEV; equids).
3. Arboviruses that can undergo direct human amplification and bypass enzootic hosts altogether have the potential to infect even more people and to spread rapidly and widely via infected travelers, with air travel of an unknowing, incubating person allowing for intercontinental spread within hours (Wilder-Smith et al., 2016). This transfer from an enzootic to an endemic/epidemic transmission cycle can be temporary, lasting months or a few years, as with

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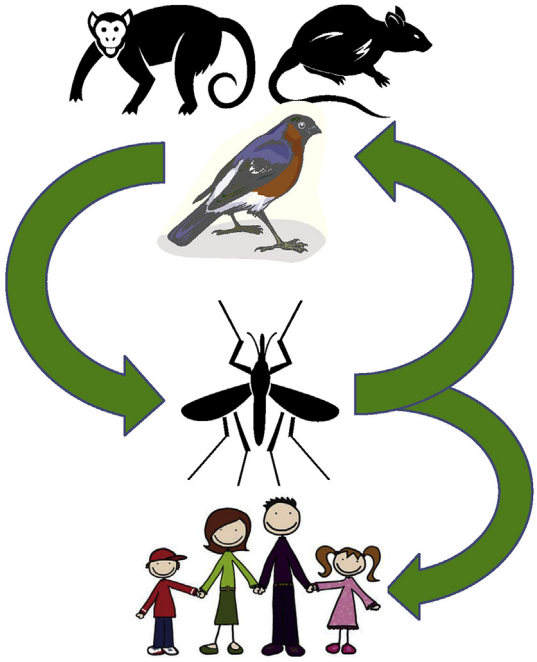

Fig. 1. The most common mechanism of human infection by most arboviruses is direct spillover from enzootic transmission cycles (involving various wildlife as amplification hosts). This occurs when enzootic vectors, or bridge vectors that bite both wild animals and humans, transmit. An example is West Nile virus, which emerged in the Americas after its introduction into New York in 1999, and which uses birds as amplification hosts and *Culex* spp. mosquitoes as vectors (Roehrig, 2013).

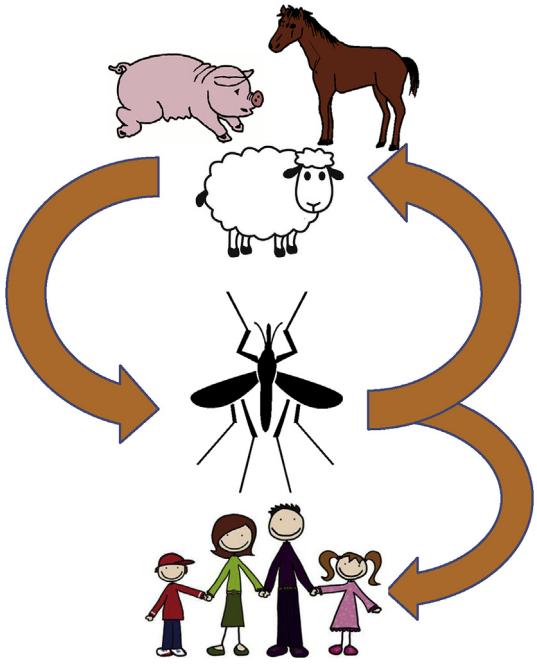

Fig. 2. Some arboviruses undergo secondary amplification in domesticated animals with spillover to humans, resulting in increased exposure and disease. Examples include epizootic strains of Venezuelan equine encephalitis virus, which amplify in equids as during the last major epizootic/epidemic in Venezuela and Colombia in 1995 (Weaver et al., 1996); another is Japanese encephalitis virus, which amplifies in swine and causes endemic disease in the Asian topics and summer epidemics in temperate climates (Pearce et al., 2018); and another is Rift Valley fever virus, which amplifies in ruminants, with several epizootics/epidemics since 2000 (Kenawy et al., 2018).

yellow fever virus (YFV), which evolved enzootically in Africa and was transferred centuries ago to the Americas, where both epidemic transmission and enzootic spillback (from human-to-mosquito-to-wild primates) has occurred.

YFV continues to cause urban, human-amplified epidemic outbreaks in Africa (Beasley et al., 2015; Paules and Fauci, 2017), as well as high levels of enzootic spillover infections in Brazil during epizootics in wild primates. Epidemic arbovirus transmission cycles can also become permanent (endemic), as with the four serotypes of dengue virus (DENV) that diverged from extant Asian enzootic lineages on the order of hundreds-to-thousands of years ago (Vasilakis et al., 2011; Wang et al., 2000), and the Asian genetic lineage of chikungunya virus (CHIKV), which diverged from a progenitor East/Central/South African enzootic lineage about a century ago and was introduced into Asia, followed by endemic/epidemic circulation in Southeast Asia for many decades before its more recent spread to the Americas (Cassadou et al., 2014; Chen et al., 2016).

The most recent new urban arbovirus to emerge, Zika virus (ZIKV), began amplifying in humans and spreading rapidly in the South Pacific and the Americas in 2013 to infect millions of persons. With this major epidemic came newly recognized disease manifestations including Guillain-Barré syndrome and, following infection of pregnant women, congenital Zika syndrome (CZS) with microcephaly as the most severe outcome of this disease spectrum (Aliota et al., 2017; Musso and Gubler, 2016; Weaver et al., 2018). Although ZIKV was discovered in an African enzootic transmission cycle in 1947, prior to 2007 it was believed to cause only sporadic spillover infections from its mosquito-NHP sylvatic cycle with very mild, undifferentiated febrile disease outcomes. Then, small outbreaks involving hundreds-to-thousands of human infections in Gabon (Grard et al., 2014) and Yap Island in Pacific Micronesia (Duffy et al., 2009) in 2007 were apparently the result of interhuman transmission by *Aedes* (*Stegomyia*) *albopictus* and *A.* (*Stegomyia*) *hensilli*, respectively. These outbreaks presented the first evidence of urban transmission other than the 1966 isolation of ZIKV from the peridomestic mosquito *A. aegypti* in Malaysia (Marchette et al., 1969), suggesting the possibility of interhuman transmission at that earlier time. With the renewed spotlight on ZIKV, past human exposure inferred from seroprevalence data suggest frequent or continuous exposure in Southeast Asia. Ongoing transmission in the Americas two years after the 2016 peak of the epidemic, also suggests current endemicity.

3. Determinants of arbovirus urbanization via interhuman transmission

Although enzootic arbovirus transmission can occur at high levels in urban environments, such as WNV circulation in birds, the highest levels of human exposure in urban areas generally occur with interhuman transmission via anthropophilic mosquito vectors, especially *A. aegypti* (Fig. 3). The efficiency of this kind of human-amplified urban cycle depends on several key factors, including but not limited to: 1) the ability of the arbovirus to generate a sufficiently high level of human viremia to infect potential mosquito vectors, and; 2) the availability of mosquitoes with adequate vectorial capacity for interhuman transmission.

Of the four arboviruses (YFV, DENV, CHIKV and ZIKV) with evidence of sustained interhuman transmission, all generate viremia titers sufficient to infect at least some mosquito species including urban *A. aegypti*. The level of ZIKV viremia is generally lower than that of DENV, for which peak titers typically exceed 10^8 infectious units/ml blood (Vaughn et al., 2000), and is also lower than for CHIKV, with peak titers typically 10^7 infectious units/ml (Thiberville et al., 2013), and YFV, with titers up to 10^{5-6}/ml. (Monath, 2001). Human viremia data for ZIKV are quite limited because many patients with apparent infection may seek medical care and be sampled only after peak viremia, and