



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

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ABSTRACT

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

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.

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 inter-continental 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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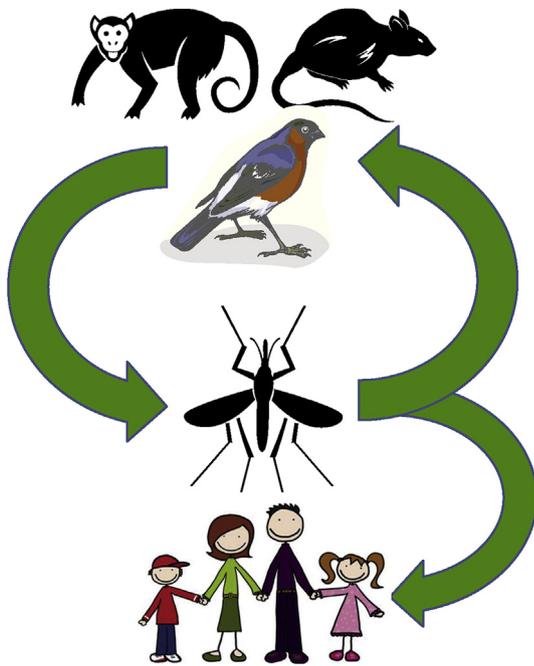


Fig. 1. The most common mechanism of human infection by most arboviruses is direct spillover from enzootic transmission cycles (involving various wildlife as amplification hosts). This occurs when enzootic vectors, or bridge vectors that bite both wild animals and humans, transmit. An example is West 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).

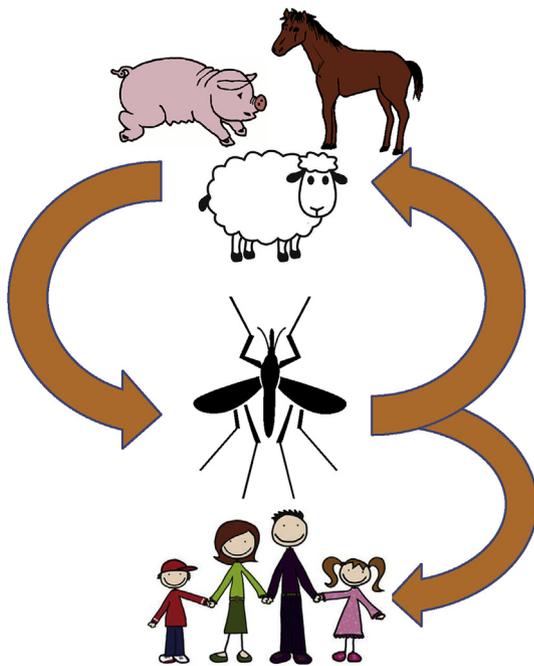


Fig. 2. Some arboviruses undergo secondary amplification in domesticated animals with spillover to humans, resulting in increased exposure and disease. Examples include epizootic strains of Venezuelan equine encephalitis virus, which amplify in equids as during the last major epizootic/epidemic in Venezuela and Colombia in 1995 (Weaver et al., 1996); another is Japanese encephalitis virus, which amplifies in swine and causes endemic disease in the Asian tropics 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

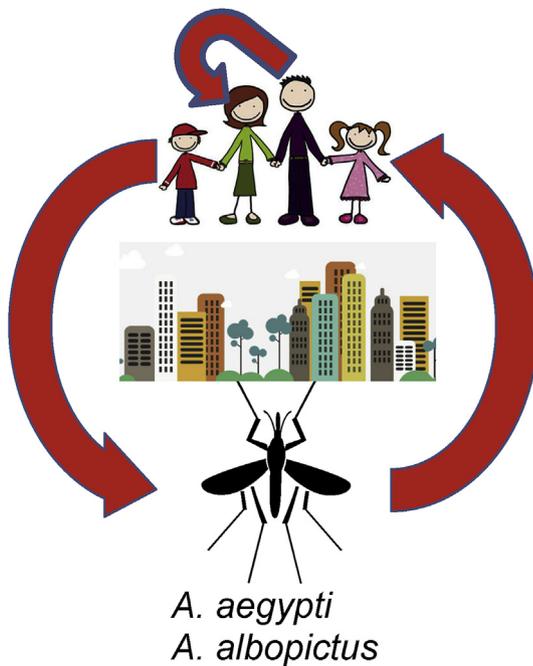


Fig. 3. The most important human arboviral pathogens undergo human-amplified, typically urban transmission cycles, which evolve from primate-amplified, ancestral enzootic cycles (see Fig. 1). These include dengue, yellow fever, chikungunya and Zika viruses (Wilder-Smith et al., 2016). Direct human-human transmission, which can be vertical or sexual (arrow at top), has only been documented for Zika virus (Aliota et al., 2017).

asymptomatic infections (the majority) are rarely sampled at all. However, even the peak titers of infectious ZIKV or viral RNA measured in infected patients without complications, typically on the order of 10^5 RNA copies/ml, roughly extrapolated to 10^3 infectious units/ml of blood (Musso et al., 2017), are only marginally infectious for most mosquitoes tested experimentally, including *A. aegypti* (Ciota et al., 2017; Roundy et al., 2017). This has led to questions about the possible involvement of other common tropical urban mosquitoes such as *Culex quinquefasciatus* (see below).

Although some arboviruses such as WNV generate only low levels of human viremia (Barzon et al., 2015), which may in part explain the absence of interhuman transmission, others such as VEEV (Aguilar et al., 2011) and Mayaro virus (MAYV) (Long et al., 2011) produce relatively high human viremia titers, but without evidence of interhuman transmission. These examples suggest that other factors also determine urban epidemic potential and underscore our limited understanding of this mechanism of arboviral emergence.

In addition to vector competence (the intrinsic susceptibility to infection of a given arthropod species and its ability to transmit following extrinsic incubation), the more comprehensive vectorial capacity includes other critical factors that are in some cases more important (MacDonald, 1957). The formula, which attempts to quantify the daily rate at which new infections arise from an infective case (C , or R_0), is:

$$C = ma^2bp^n / -\ln p$$

in which

- m = vector population size, specifically the number of vectors per amplification host,
- a = daily biting rate of an individual female on humans,
- b = fraction of vectors that transmit virus to an uninfected host during feeding,
- p = daily survival rate of the vector (survival must be adequate to bite an infected host, undergo extrinsic incubation what can be up to 14 days), then bite a susceptible host for transmission, for

amplification, multiple susceptible hosts must be bitten at least occasionally.

- n = number of days between vector infection and its first ability to transmit (extrinsic incubation period), and

The factors with the greatest impact include vector density relative to potential amplification hosts, such as humans in urban cycles, and the biting rate of the vector on the amplification host (often reflected in host preference or a high degree of access). These determine whether an adequate frequency of sequential feeding on these hosts occurs for transmission and amplification. Also critical is sufficient longevity for infection and extrinsic incubation (the period between initial oral infection and appearance of virus in the saliva), and the minimum duration of the extrinsic incubation period or time between feedings. For arboviruses, infection and transmission competence are generally life-long so the final factor, the daily recovery rate from infection, is irrelevant.

4. Role of *Aedes* species mosquitoes in arbovirus urbanization

Aedes aegypti epitomizes many of the ecological and behavioral factors described above that maximize vectorial capacity for human-amplified arboviruses. Many of these are the result of its evolutionary history of adapting to exploit humans over thousands of years in sub-Saharan Africa by living in close association to exploit a stable supply of artificial larval habitats (water storage) and human blood (Gubler, 2011). This species, which centuries ago spread around the world in the tropics and subtropics (Powell and Tabachnick, 2013; Powell et al., 1980), typically exhibits high rates of biting humans rather than other animals, including multiple, partial human bloodmeals within a reproductive cycle to increase its chances of oral infection and, when infected, to transmit to multiple people for amplification (Harrington et al., 2001, 2014). These behaviors are consequences of its preference for artificial containers as oviposition sites for larval development (Harrington et al., 2008), and the tendency of adult females to enter and remain in homes and other buildings (endophilic) with ready access to human bloodmeals (Dzul-Manzanilla et al., 2017).

Aedes albopictus exhibits more variable rates of human feeding and multiple host contacts within a reproductive cycles (host-seeking, feeding, blood digestion, oogenesis, oviposition), use of artificial containers, and endophilic behavior (Delatte et al., 2010) that may account for its typically secondary role in DENV, CHIKV and ZIKV transmission. The involvement of other *Aedes* (*Stegomyia*) spp. mosquitoes as urban vectors for DENV, CHIKV and ZIKV suggests that additional members of this critical subgenus should be evaluated for their potential to adapt for increasing their populations in urban and other peridomestic environments. Also, the impact of climate change on the distribution of *Aedes* (*Stegomyia*) spp. mosquitoes, especially *A. aegypti* that cannot survive cold climates, will be critical to predicting future trends in urban arbovirus ranges. Furthermore, could this species evolve diapause mechanisms (developmental dormancy, in the case of *Aedes* spp. embryogenesis in the egg) that would allow it to invade temperate climates?

Culex quinquefasciatus is often even more abundant than these *Aedes* mosquitoes in tropical urban habitats, frequently exploiting storm sewers and other artificial larval habitats, and can be found at high densities within houses (Kohn, 1990). Estimated frequencies of human feeding by *C. quinquefasciatus* vary widely but are generally low (Garcia-Rejon et al., 2010; Molaei et al., 2007). This may reflect the availability of birds, which appear to be favored according to some studies (Guo et al., 2014). However, one study in two southern Mexican cities reported high rates of mammal and especially human feeding (Janssen et al., 2015). With increasing urbanization and human population growth in the tropics, could *C. quinquefasciatus* undergo selection for some of the same ecological and behavioral characteristics that contribute to the high vectorial capacity of *A. aegypti*? The genetic and

physiologic basis of host preference as well as on climate limits of urban mosquitoes with the potential for interhuman arbovirus transmission should be research priorities.

5. Assessing the potential for additional urban arboviral emergences

The unanticipated Zika pandemic and its major public health impacts underscore the need not only to develop interventions for DENV, CHIKV and YFV, with long histories of this risk, but also to identify other arboviruses with unrecognized potential for urbanization, and to develop proactive interventions for the latter. With ZIKV as an example, based on knowledge prior to 2007, these could include both known viruses with poorly understood emergence potential and unknown viruses that also have such potential. Interventions could be virus- or virus group-specific, such as vaccines or antivirals, or transmission-specific, such as improved methods of vector control or modifications of vector populations to reduce transmission competence (Wilder-Smith et al., 2016).

A systematic and comprehensive evaluation of all known arboviruses, which number in the thousands, for the key phenotypic characteristics discussed above would comprise an impossibly complex and expensive undertaking. However, targeted studies to partially undertake this evaluation could include additional assessments of human feeding rates and vector competence by mosquitoes already inhabiting urban environments, and surveillance for arbovirus activity at the interfaces between sylvatic habitats and urban areas. Commonalities among DENV, YFV, CHIKV and ZIKV that probably offer additional predictive value include their use of wild primates as enzootic hosts and arboreal *Aedes* spp. mosquitoes as sylvatic vectors. These suggest the value of additional field surveys of these hosts and vectors for arbovirus infection, or wild primate exposure via serology combined with experimental laboratory infection of monkeys for viremia competence.

In addition to current vector competence of widespread vector populations, the possibility of vector-adaptive mutations by arboviruses to increase their use of peridomestic mosquitoes, best exemplified by the adaptation of the Indian Ocean Lineage of CHIKV for transmission by *A. albopictus* in temperate climates such as Italy and France (Weaver et al., 2018), must also be considered. Understanding these examples of vector-adaptive evolution will require extensive experimental vector competence studies in the laboratory, with multiple virus strains collected longitudinally combined with reverse genetic approaches to test the effects of mutations associated with new outbreaks. Such data have been shown to have some predictive value to inform surveillance for the potential use by a virus of new mosquito vectors (Tsatsarkin et al., 2014).

Additional arbovirus and vector surveillance, especially in sylvatic, tropical regions of Africa and Asia where most urban arboviruses circulate enzootically, is clearly needed to identify potential future arbovirus threats. However, such field studies have declined over many decades. To minimize costs and capitalize on ongoing studies, field projects that involve wild primates and other wild animals, but are not necessarily related to arbovirus research, should be leveraged to inexpensively collect or share blood samples for identifying new urban arbovirus threats. Another approach to limiting the scope and cost of work required to assess urbanization potential is to focus on close relatives of the four viruses with proven emergence potential discussed above. An example is the evaluation of vector competence for *A. aegypti*, *A. albopictus* and *C. quinquefasciatus* of Spondweni virus, the closest relative of Zika and known to infect humans in Africa (Haddow et al., 2016). The results of this work demonstrated the refractoriness of all of these peridomestic species to infection, suggesting that Spondweni virus has a low immediate potential for urbanization.

The identification of previously unrecognized arboviruses with urbanization potential represents an equally challenging approach to determining and mitigating the risk of new epidemics. However, high-

throughput sequencing methods now make it possible to identify viruses in sylvatic mosquitoes, wild primates and other likely enzootic hosts without prior knowledge of the virus taxon and without taxon-specific reagents. These methods can succeed even for agents that are too divergent from known arboviruses to allow detection using PCR-based methods, or which cannot be detected or isolated using traditional cell culture or *in vivo* methods.

Conflicts of interest

Scott Weaver holds patents for alphavirus vaccine development, including chikungunya.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.antiviral.2018.06.009>.

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